The Efficacy of Curcuma Longa L. Extract as an Adjuvant Therapy in Primary Knee Osteoarthritis: A Randomized Control Trial

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Nonsteroidal Anti-inflammatory Drugs (NSAIDs) is one of the most commonly use medication for treatment of knee osteoarthritis which has the analgesic and anti-inflammation by inhibition of prostaglandin synthesis via COX-1 and COX-2 isoenzyme. The problem of prolong using NSAIDs has side effect on kidney, liver and GI system. Curcumin longa extract (Curcumin) is the Asian herbal medicine that has the anti-inflammatory effect by down regulate activation of NF-κB and proinflammatory cytokines such as Tumor Necrotic Factor-α, Interleukin-1, Interleukin-8, and Nitric Oxide Syntase. Many research data had advocate for the combination therapy which can increase safety and efficacy with less side effect compare with monotherapy regimen especially when the medicine has the different mechanism of action.

The present study is the double blind prospective randomized control trial to evaluate the efficacy of curcumin as an adjuvant therapy of diclofenac in primary knee osteoarthritis. 44 patients were randomized to take NSAIDs (diclofenac) 75 mg/d with placebo and the other 44 took NSAIDs (diclofenac) 75 mg/d with curcumin 1,000 mg/d for 3 months. The authors evaluated the Visual Analog Scale (VAS) for pain and Knee Injury and Osteoarthritis Outcome Score (KOOS) every month for 3 months. At the end of study 36 patients were completed for the first group and 37 for the study group. There was no difference in VAS [p-value = 0.923 (F = 0.009)]. The KOOS was analyzed in 5 categories symptom, pain, function in daily living, function in sport and recreation and knee related quality of life. The curcumin with diclofenac group had tendency to be better in Pain and Function in daily living, but there were no statistic different in all group [p-value = 0.412 (F = 0.683), p-value = 0.814 (F = 0.056), p-value = 0.446 (F = 0.589), p-value = 0.224 (F = 1.511) and p-value = 0.938 (F = 0.006)].

In conclusion, the adjuvant therapy of curcumin with diclofenac has the potential beneficial effect in comparison with diclofenac alone, but no statistical significance.

Keywords: *Curcuma Longa L, Knee osteoarthritis, Anti-inflammatory effect*

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Nowadays, the life expectancy of Thai population is longer than in the past. The prevalence of knee osteoarthritis is more common and the disease is chronic. This problem spends a lot of budget to take care for the national health care system.

The standard medical treatment for knee osteoarthritis is acetaminophen and NSAIDs (Nonsteroidal Anti Inflammatory Drugs). NSAIDs have the effect both on analgesia and anti-inflammation by inhibition of prostaglandin synthesis via COX-1 and COX-2 isoenzyme. The prolonged usage of NSAIDs has a lot of side effect including peptic ulcer, liver, kidney impairment and sometimes life threatening condition.

Currently the usage of Thai traditional medicine as the alternative treatment gets more popularity because of its safety. Curcumin (diferuloymethane) is a yellow coloring agent which is found in the turmeric (curcumin longa). Curcumin has the effect of potent antioxidant, anti-inflammation[1-4], antimicrobial and anticarcinogenic[5-9] property. Curcumin longa has been used in East Asia for a long time as a herbal therapy. This medicine has been proved for its safety in phase 1 clinical trials with a very high dose up to 12 g per days[10-12]. The anti-inflammatory effect was proved *in vitro* and animal model. In the

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arthritic rat, usage of oral curcumin 30 mg/kg/d for 15 days can reduce the inflammation of the paw[13].

The pharmacological effect of curcumin which shown both *in vitro* and *in vivo* is the anti-inflammation by down regulate activation of NF-kB[14]. Inhibition of NF-kB has the effect on down regulation of the inflammatory mediator including cyclooxygenase-2 (COX-2)[15], 5-Lypooxygenase (LOX)[16], adhesive molecule[17] and MMPs[15]. Also, curcumin was shown to suppress many pro-inflammatory cytokines such as tumor necrotic factor-α (TNF-α), interleukin (IL)-1, IL-8 and nitric oxide synthase (NOS)[18-20]

Many research data had advocate for the combination therapy which can increase safety and efficacy with less side effect comparing with monotherapy regimen. Lev-Ari et al show the synergistic effect in inhibition of the OA synovial adherent cell growth, when the cells were exposed with celecoxib combined with curcumin[21].

Curcumin has the additive effect on NSAIDs to reduce the inflammation with the different mechanism of action. Curcumin can down regulate COX-2 mRNA and protein level but diclofenac has the inhibitory effect on COX-1 and COX-2 enzyme at the active site. The combination therapy should increase the effect on reduction of the inflammation without increasing the side effect.

Material and Method

The authors did the double blind prospective randomized control trial by dividing patients into 2 groups. The first group (44 patients) was assigned for receiving placebo (with identical to the curcuminoid capsule) 2 caps per oral bid pc and diclofenac 25 mg per oral tid pc for 3 months (group 1 = control group). The latter group was assigned to take curcuminoids capsules (250 mg) 2 caps per oral bid pc (manufactured by the Government Pharmaceutical Organization, each capsule contain tumeric extract equivalent to curcuminoids 250 mg) and diclofenac 25 mg per oral tid pc for 3 months (group 2 = experimental group).

The evaluation was done by the research assistant who was blinded for the medication patients take. The pain visual analog score (0 representing no pain and 10 representing severe pain) and Knee injury and Osteoarthritis Outcome Score (KOOS)[22] were used for evaluation at premedication, 1 month, 2 months and 3 months after medication.

The KOOS is knee-specific instrument, developed to assess the patients' opinion about their knees and associated problems. The purpose of score is to evaluate short-term and long-term symptom and function of the patients with knee injury and osteoarthritis. KOOS has 42 items with 5 seperated scores subscales; Pain, other symptoms, Activity of Daily Living(ADL), Function in Sport and Recreation (Sport/Rec) and knee-related Quality of life (QOL). It is an extension of the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) and validated for several cohorts of patients. The scores are 0-100 scale, with zero manifesting the extreme knee problem and 100 representing no problem.

The present study was permitted by Ethic committee of faculty of medicine, Thammasat University. All patients were informed the experimental protocol and signed consent. All complications and side effect of the medicine were advised.

The patients age between 38-80 who met the diagnostic criteria for knee osteoarthritis according to American College of Rheumatology (by history and physical examination) were enrolled[23]. Patient with the history of knee pain who had 3 of the following criteria, 1) over 38 years of age, 2) less than 30 minutes of joint morning stiffness, 3) crepitus on active motion, 4) bony tenderness, 5) bony enlargement and 6) no palpable warmth of synovium would diagnose of osteoarthritis.

The patients who diagnosed of inflammatory arthritis (rheumatiod arthritis, gouty arthritis, CPPD etc) or who had the contraindication for using NSAIDs such as history of peptic or gastric ulcer, renal insufficiency were excluded from the present study.

The discontinuation criteria of the program is 1) The patients who could not make the follow-up appointment monthly for 3 months 2) the patient who did not continue taking the medicine as prescribed 3) The patients who could not tolerate the side effect of the NSIADs or curcumin and 4) the patient who is unwilling to continue the present study.

Statistical analyses general linear model repeated measures, descriptive t-test and ANOVA were used to categorical continuous the different outcome between 2 groups. Results were considered significant at $p < 0.05$.

Results

The present study started from October 2008 to October 2010. 7/44 patients quit the protocol in group 1 (control group) because of loss follow-up (4 patients), renal function problem (2 patients with BUN/Cr rising after taking the medicine) and drug allergy (1 patient with facial swelling). 6/44 patients in group 2 (experimental group) were discontinued from the study

because of loss follow-up (4 patients), do not want to continue the medicine (1 patient), and hair falling (1 patient).

The demographic data of the patients were showed in Table 1 and 2.

Comparing the efficacy of diclofenac alone and Curcumin with diclofenac in VAS, the authors found that both groups had significant improvement in pain when compared with the first visit. Pain scale reduction tended to be better in group 2 at the end of the present study (Fig. 1). But when using the repeated ANOVA of statistically analysis, there was no statistic significant (F = 0.009, p-value = 0.923) (Table 3).

The KOOS categorized in 5 aspects. More improvement in symptom was seen in group 2 (Fig. 2), but comparing between groups in the repeated ANOVA test showed no statistic significant (F = 0.683, p-value = 0.412) (Table 4). The pain improvement was also tended to be better in group 2 at the first, second and third month after medication (Fig. 3), but no statistic significant (F = 0.056, p-value = 0.814) (Table 5). The function in daily living, at the beginning was worse in group 2 (p-value = 0.022). After medication, the score was improved to the same level as group 1 at the first and second month and better at the end of the present study (Fig. 4), but the comparison between group had no statistic significant (F = 0.589, p-value = 0.446)

Table 1. Sex distribution of the patients

Sex	Number	Percent
Male	13	17
Female	62	83
Total	75	100.00

Table 2. Age distribution of the patients

Age (years)	Number	Percent
35-44	0	0
45-54	16	21.5
55-64	24	32.3
65-74	30	40
≥ 75	5	6.2
Total	75	100

Table 3. The mean of Visual Analog Score at 0, 1, 2, and 3 month after medication

Time	Day 0(D0) At screening	Month 1	Month 2	Month 3
Group1	5.31	4.48	3.83	3.55
Group2	5.50	4.53	3.81	3.19
p-value[1]	0.662	0.910	0.958	0.441
p-value[2]	-	< 0.001*	< 0.001*	< 0.001*
p-value[3]	-	< 0.001*	< 0.001*	< 0.001*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.009
p-value = 0.923

p-value[1]: Comparison between Group1 and Group2 at the same period of time
p-value[2]: Comparison in Group1 from D0 at screening with the 1st, 2nd and 3rd month
p-value[3]: Comparison in Group2 from D0 at screening with the 1st, 2nd and 3rd month

Table 4. Shows the mean of Symptoms at 0, 1, 2, and 3 month after medication

Time	D0At screening	Month 1	Month 2	Month 3
Group1	72.91	81.77	81.77	83.74
Group2	68.55	78.77	81.95	83.04
p-value[1]	0.0242	0.379	0.950	0.822
p-value[2]	-	<0.001*	0.002	0.002*
p-value[3]	-	<0.001*	<0.001*	<0.001*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.683 P-Value = 0.412

p-value[1]: Comparison between Group 1 and Group 2 at the same period of time
p-value[2]: Comparison in Group 1 from D0 at screening with the 1st, 2nd, and 3rd month
p-value[3]: Comparison in Group 2 from D0 at screening with the 1st, 2nd, and 3rd month

Table 5. The mean of pain at 0, 1, 2 and 3 month after medication

Time	D0At screening	Month 1	Month 2	Month 3
Group 1	70.40	75.77	83.24	81.99
Group 2	66.43	79.32	83.72	84.49
p-value[1]	0.404	0.364	0.878	0.474
p-value[2]	-	0.086	< 0.001*	0.006*
p-value[3]	-	< 0.001*	< 0.001*	< 0.001*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.056, p-value = 0.814

p-value[1]: Comparison between Group 1 and Group 2 at the same period of time
p-value[2]: Comparison in Group 1 from D0 at screening with the 1st, 2nd, and 3rd month
p-value[3]: Comparison in Group 2 from D0 at screening with the 1st, 2nd, and 3rd month

(Table 6). The function in sport and recreation showed sequentially improve in both groups (Fig. 5) but no statistic significant (F = 1.511, p-value = 0.224) (Table 7) different in between group comparison. The knee related quality of life in both groups were also better after medication, and at the end of the study (Fig. 6), but had no statistic significant difference when compared between groups in the same period of time (F = 0.006, p-value = 0.936) (Table 8).

Discussion

To the authors knowledge, this is the first double blind randomize control trial study to evaluate the efficacy of curcumin for adjuvant therapy of diclofenac in treatment of primary knee osteoarthritis. From our study, both groups had clinical improvement after medication. The VAS decreased more in the experimental group which implied the additive effect in pain reduction using curcumin with the NSAIDs even no statistic significant (Fig. 1). In the KOOS, when looking at the improvement of all 5 aspects, the experimental group seems to have superior or equal improvement at the end of study, especially in pain and the function in daily living (Fig. 3 and 4). In the function in daily living, the control group had no statistic significant improvement comparing with the beginning of study, but the experimental group showed better outcome in every period of time ($p < 0.05$) (Table 6).

From the present study the authors found the complication of renal function deterioration (2/37), and facial swelling (1/37) in control group. 1/36 hair fall was seen in the experimental group, which has not be found in the literature. The present study show low complication rate and high safety margin for using combination therapy in the clinical practice.

There are some weak points in the present study. The first one is high number of drop out because of some patients living in the remote area and difficulty transportation. The second problem is the optimal dose of curcumin for combination therapy with diclofenac. As the authors know, this is the first clinical trial for the combination treatment, and the authors do not know the appropriate dose for this. Kuptniratsaikul et al reported the efficacy and safety of curcumin extract 2,000 mg/day equivalent to ibuprofen 800 mg/day for 6 weeks therapy[24]. Because of high safety margin of

Table 6. The mean of function in daily living at 0, 1, 2 and 3 month after medication

Time	D0At screening	Month 1	Month 2	Month 3
Group 1	76.93	77.89	81.79	81.49
Group 2	67.00	77.45	81.43	83.91
p-value[1]	0.022*	0.900	0.905	0.496
p-value[2]	-	0.637	0.080	0.191
p-value[3]	-	0.005*	< 0.001*	< 0.001*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.589 p-value = 0.446

p-value[1]: Comparison between Group 1 and Group 2 at the same period of time
p-value[2]: Comparison in Group1 from D0 at screening with the 1st, 2nd and 3rd month
p-value[3]: Comparison in Group 2 from D0 at screening with the 1st, 2nd and 3rd month

Table 7. The mean of function in sport and recreation at 0, 1, 2 and 3 month after medication

Time	D0At screening	Month 1	Month 2	Month 3
Group1	28.79	31.72	37.07	38.97
Group2	32.08	37.64	41.11	43.75
p-value[1]	0.485	0.201	0.330	0.321
p-value[2]	-	0.353	0.015*	0.023*
p-value[3]	-	0.037*	0.009*	0.002*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 1.511 P-Value = 0.224

p-value[1]: Comparison between Group 1 and Group 2 at the same period of time
p-value[2]: Comparison in Group1 from D0 at screening with the 1st, 2nd and 3rd month
p-value[3]: Comparison in Group2 from D0 at screening with the 1st, 2nd, and 3rd month

Table 8. The mean of Knee related quality of life at 0, 1, 2, and 3 month after medication

Time	D0At screening	Month 1	Month 2	Month 3
Group1	46.55	47.63	54.53	59.27
Group2	43.75	53.30	54.69	57.29
p-value[1]	0.556	0.254	0.972	0.662
p-value[2]	-	0.775	0.020*	0.005*
p-value[3]	-	0.005*	0.007*	< 0.001*

F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.006 p-value = 0.936

p-value[1]: Comparison between Group 1 and Group 2 at the same period of time
p-value[2]: Comparison in Group1 from D0 at screening with the 1st, 2nd, and 3rd month
p-value[3]: Comparison in Group2 from D0 at screening with the 1st, 2nd, and 3rd month

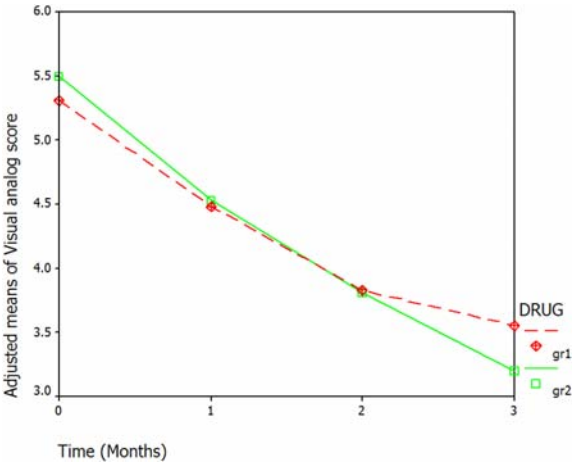

Fig.1 Comparison of Visual Analog Scale at 0, 1, 2, and 3 months after medication

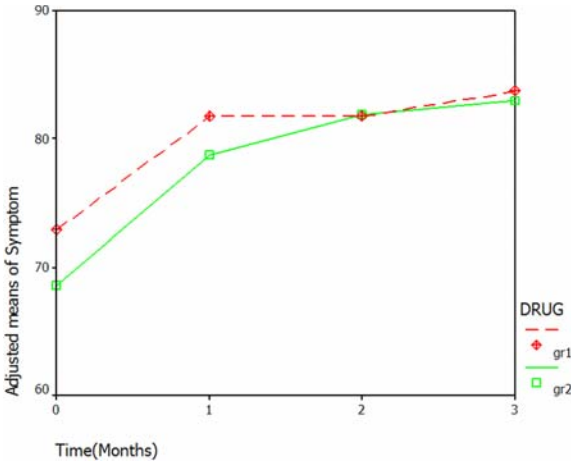

Fig. 2 Comparison of Symptoms at 0, 1, 2, and 3 months after medication

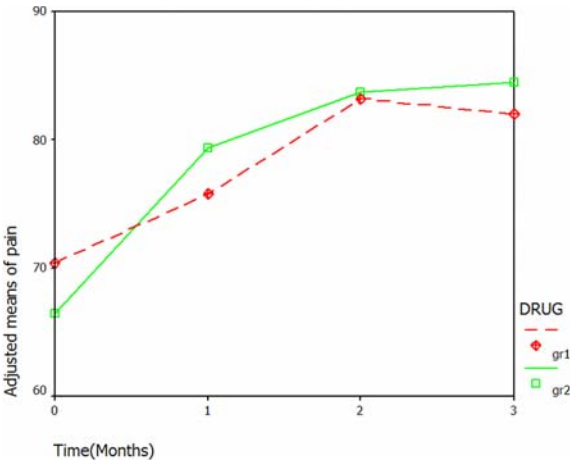

Fig. 3 Comparison of pain at 0, 1, 2, and 3 months after medication

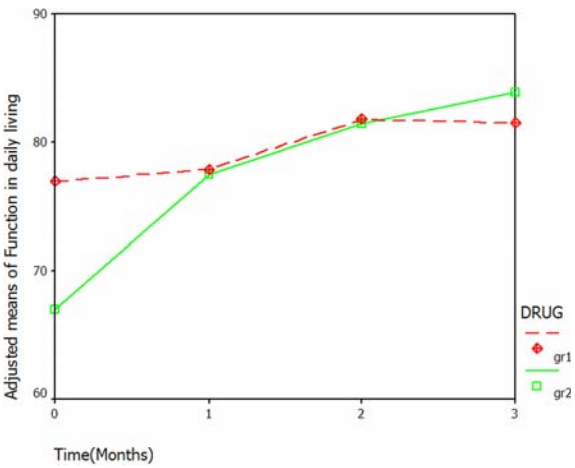

Fig. 4 Comparison of function in daily living at 0, 1, 2, and 3 months after medication

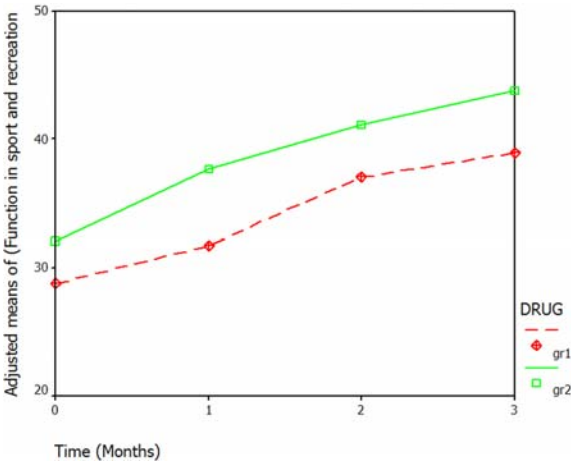

Fig. 5 Comparison of function in sport and recreation at 0, 1, 2, and 3 months after medication

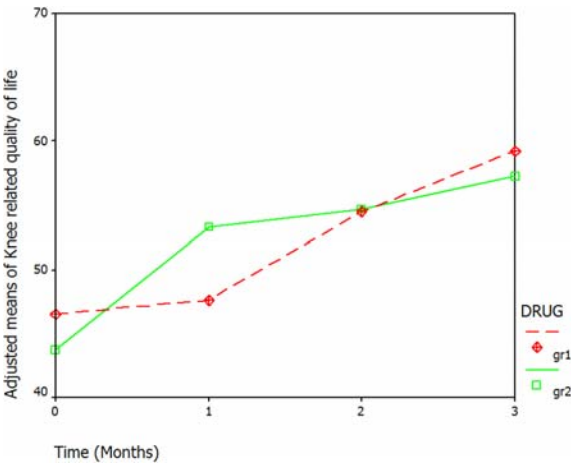

Fig. 6 Comparison of knee related quality of life at 0, 1, 2, and 3 months after medication

curcumin, in the near future the authors hope to use the higher dose of curcumin combination with lower dose of diclofenac for treatment of osteoarthritis patient to lessen the gastrointestinal, and renal complications of NSAIDs.

In conclusion the combination therapy of curcumin with diclofenac has the additive improvement in decreasing pain and improving KOOS, but from the limitation of drop out cases and inadequate dose of curcumin, the statistic analysis found no significant different.

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Potential conflicts of interest

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ประสิทธิภาพของขมิ้นชันในการรักษาผู้ป่วยข้อเข่าเสื่อมปฐมภูมิ

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ยากลุ่ม Nonsteroidal Anti-inflammatory Drugs(NSAIDs) เป็นยามาตรฐานในปัจจุบันที่ใช้ในการรักษาการอักเสบจากข้อเข่าเสื่อม ซึ่งตัวยามีผลทั้งการลดอาการปวดและลดการอักเสบ โดยการยับยั้งการสร้างสารของ prostaglandin ผ่านทาง COX-1 และCOX-2 isoenzyme แต่การใช้ NSAIDs เป็นเวลานานมักมีผลข้างเคียงต่อกระเพาะอาหาร ไต และตับ Curcuminเป็นสารสกัดที่ได้มาจากสมุนไพรขมิ้นชันที่มีใช้กันมานานในแถบเอเชีย ซึ่งมีฤทธิ์ลดการอักเสบผ่านการ down regulation ของ NF-kB และ proinflammatory cytokines เช่น Tumor Necrotic Factor-α, Interleukin-1, Interleukin-8 และ Nitric Oxide Synthase มีการทดลองทางคลินิคมากมายที่สนับสนุนการรักษาแบบ combination therapy เพื่อเพิ่มประสิทธิภาพและลดภาวะแทรกซ้อนจากการใช้ยาเมื่อเทียบกับการใช้ยาเพียงชนิดเดียวในการรักษาโรคโดยเฉพาะยาที่มี mechanism of action ที่แตกต่างกัน

การทดลองนี้เป็น Double blind prospective randomize control trial เปรียบเทียบถึงการรักษาอาการข้อเข่าอักเสบจากข้อเข่าเสื่อมโดยใช้ยา NSAIDs(diclofenac) 75 mg/d ร่วมกับ placebo จำนวน 44 คน เปรียบเทียบกับผู้ป่วยที่ได้รับยา NSAIDs(diclofenac) 75 mg/d ร่วมกับ Curcumin 1000 mg/d จำนวน 44 คน ติดตามการรักษาทุกเดือนเป็นเวลา 3 เดือน โดยทำการประเมินด้วย Visual Analog Scale(VAS) for pain และKnee injury and Osteoarthritis Outcome Score (KOOS) เมื่อติดตามจนสิ้นสุดการรักษามีผู้ป่วยเข้ารับการรักษาครบในกลุ่มแรกจำนวน 37 คน และในกลุ่มทดลอง 38 คน ผลการเปรียบเทียบค่าเฉลี่ยการประเมินความเจ็บปวดจาก VAS ระหว่างกลุ่มทดลองและกลุ่มเปรียบเทียบ พบว่าไม่มีความแตกต่างกันทางสถิติในทุกช่วงเวลา p-value = 0.923 (F = 0.009) ผลการเปรียบเทียบค่า KOOS ระหว่างกลุ่มเปรียบเทียบและกลุ่มทดลองแบ่งเป็นออกเป็น 5 หัวข้อ ได้แก่ อาการ (Symptoms) อาการปวด (Pain) การเคลื่อนไหวในกิจวัตรประจำวัน (Function in daily living) การเคลื่อนไหวในการออกกำลังกาย หรือทำกิจกรรมอื่นๆ (Function in sport and recreation) และคุณภาพชีวิตที่เกี่ยวข้องกับการใช้เข่า (Knee related quality of life) พบว่าในกลุ่มที่ได้รับการรักษาด้วย diclofenac ร่วมกับ curcumin มีแนวโน้มที่ได้ผลดีกว่าในเรื่องการลดอาการปวดและการทำกิจวัตรประจำวัน แต่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ส่วนในแง่อื่นๆ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ Symptoms p-value = 0.412 (F = 0.683), Pain p-value = 0.814 (F = 0.056), Function in daily living p-value = 0.446 (F = 0.589), Function in sport and recreation p-value = 0.224 (F = 1.511), Knee related quality of life p-value = 0.938 (F = 0.006) ตามลำดับ

สรุปว่าผลของการใช้ Curcumin ร่วมกับ NSAIDs (diclofenac) มาใช้ร่วมกันในการรักษา osteoarthritis มีแนวโน้มที่จะได้ผลดีกว่าใช้ diclofenac เพียงอย่างเดียวแต่ไม่มีนัยสำคัญทางสถิติ