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 (diferuloy-methane) 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
arthritic rat, usage of oral curcumin 30 mg/kg/d for 15
days can reduce the inflammation of the paw\textsuperscript{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\textsuperscript{14}. Inhibition of
NF-kB has the effect on down regulation of the
inflammatory mediator including cyclooxygenase-2
(COX-2)\textsuperscript{15}, 5-Lypoxygenase (LOX)\textsuperscript{16}, adhesives
molecule\textsuperscript{17} and MMPs\textsuperscript{15}. Also, curcumin was shown
to suppress many pro-inflammatory cytokines such as
tumor necrotic factor-\(\alpha\) (TNF-\(\alpha\)), interleukin (IL)-1, IL-
8 and nitric oxide synthase (NOS)\textsuperscript{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\textsuperscript{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)\textsuperscript{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 facultly 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\textsuperscript{21}. 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>
<thead>
<tr>
<th>Table 1. Sex distribution of the patients</th>
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<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
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<tr>
<td>Female</td>
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<td>Total</td>
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<th>Table 2. Age distribution of the patients</th>
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<td>Age (years)</td>
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<tr>
<th>Table 3. The mean of Visual Analog Score at 0, 1, 2, and 3 month after medication</th>
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<tr>
<td>Time</td>
</tr>
<tr>
<td>Group 1</td>
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<td>Group 2</td>
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<tr>
<td>p-value1</td>
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<tr>
<td>p-value2</td>
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<tr>
<td>p-value3</td>
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<tr>
<td>F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.009</td>
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<td>p-value2</td>
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<tr>
<th>Table 4. Shows the mean of Symptoms at 0, 1, 2, and 3 month after medication</th>
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<tbody>
<tr>
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<td>Group 2</td>
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<td>p-value1</td>
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<tr>
<td>p-value2</td>
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<tr>
<td>p-value3</td>
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<tr>
<td>F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.683 P-Value = 0.412</td>
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<tr>
<th>Table 5. The mean of pain at 0, 1, 2 and 3 month after medication</th>
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<tr>
<td>Time</td>
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<tr>
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<tr>
<td>Group 2</td>
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<tr>
<td>p-value1</td>
</tr>
<tr>
<td>p-value2</td>
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<tr>
<td>p-value3</td>
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<tr>
<td>F value between Group 1 and Group 2 calculating by Repeated Measures ANOVA = 0.056, p-value = 0.814</td>
</tr>
</tbody>
</table>

p-value1: Comparison between Group 1 and Group 2 at the same period of time
p-value2: Comparison in Group 1 from D0 at screening with the 1st, 2nd, and 3rd month
p-value3: Comparison in Group 2 from D0 at screening with the 1st, 2nd, and 3rd month
Table 6. The mean of function in daily living at 0, 1, 2 and 3 month after medication

<table>
<thead>
<tr>
<th>Time</th>
<th>D0At screening</th>
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<th>Month 2</th>
<th>Month 3</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>76.93</td>
<td>77.89</td>
<td>81.79</td>
<td>81.49</td>
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<tr>
<td>Group 2</td>
<td>67.00</td>
<td>77.45</td>
<td>81.43</td>
<td>83.91</td>
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<tr>
<td>p-value¹</td>
<td>0.022*</td>
<td>0.900</td>
<td>0.905</td>
<td>0.496</td>
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<tr>
<td>p-value²</td>
<td>-</td>
<td>0.637</td>
<td>0.080</td>
<td>0.191</td>
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<tr>
<td>F value</td>
<td></td>
<td>0.005*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

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

p-value¹: Comparison between Group 1 and Group 2 at the same period of time
p-value²: Comparison in Group 1 from D0 at screening with the 1st, 2nd and 3rd month
p-value³: Comparison in Group 2 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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References

19. Singh BB, Mishra LC, Vinjamury SP, Aquilina N,


ประสิทธิภาพของขมิ้นชันในการรักษาผู้ป่วยข้อเข่าเสื่อมปฐมภูมิ

ปิยะ ปิ่นศรศักดิ์, สัญญาณ เนียมปุก

ยากลุ่ม Nonsteroidal Anti-inflammatory Drugs (NSAIDs) เป็นยาที่มาตรฐานในการรักษาการข้อเข่าเสื่อมหัวใจชนิดหล่มสลาย ซึ่งมีผลทั้งการลดอาการปวดและลดการอักเสบ โดยการยับยั้งการสร้างสารของ prostaglandin ผ่านทาง COX-1 แต่ละ COX-2 isoenzyme แต่การใช้ NSAIDs เป็นยาที่มีผลข้างเคียงต่อกระเพาะอาหาร ไต และตับ Curcuminเป็นสารสกัดที่ได้มาจากสมุนไพรขมิ้นชันที่มีใช้กันมานานในแถบเอเชีย ซึ่งมีฤทธิ์ในการลดการอักเสบผ่านการ down regulation ของ NF-kB และ proinflammatory cytokines เช่น Tumor Necrotic Factor-α, Interleukin-1, Interleukin-8 และ Nitric Oxide Synthase มีการทดลองทางคลินิกมากมายที่สนับสนุนการรักษาแบบ combination therapy เพื่อเพิ่มประสิทธิภาพและความปลอดภัยของการใช้ยา

การทดลองเป็น Double blind prospective randomize control trial แบ่งผู้ป่วยข้อเข่าเสื่อมเป็นกลุ่ม 2 กลุ่ม การทดสอบเป็นการรักษาอาการข้อเข่าเสื่อม ระยะยาว ผู้ป่วยในกลุ่มแรกได้รับยา NSAIDs (diclofenac) 75 mg/d ร่วมกับ Placibo จำนวน 44 คน และในกลุ่มที่ 2 ได้รับยา NSAIDs (diclofenac) 75 mg/d ร่วมกับ Curcumin 1000 mg/d จำนวน 44 คน ติดตามการรักษา duration เป็นเวลา 3 เดือน โดยทำการประเมินด้วย Visual Analog Scale (VAS) for pain และ Knee injury and Osteoarthritis Outcome Score (KOOS) เมื่อติดตามผลต่างสูตรการรักษาผู้ป่วยจะรับการพิจารณาเป็นอิสระในกลุ่มแรกจำนวน 37 คน และในกลุ่มทดลอง 38 คน ผลการประเมินพบว่าค่าการประเมินความเจ็บปวดจาก VAS ระหว่างกลุ่มทดลองและกลุ่มเปรียบเทียบ พบว่าไม่มีความแตกต่างกันทางสถิติในทุกช่วงเวลา p-value = 0.923 (F = 0.009) ผลการเปรียบเทียบค่า KOOS ระหว่างกลุ่มทดลองและกลุ่มเปรียบเทียบ พบว่าไม่มีความแตกต่างกันทางสถิติในทุกช่วงเวลา p-value = 0.286 (F = 0.007)

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