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Research Article

The effect of additional therapy of *Curcuma longa* and *Boswellia serrata* on NSAIDs on functional activity in osteoarthritis patients

Rizaldy Taslim Pinzon[1]*, Jessica Herwanto[2]
[1] Department of Neurology, Duta Wacana Christian University School of Medicine, Special Region of Yogyakarta, Indonesia.
[2] Department of Pharmacy, Faculty of Pharmacy, University of Sanata Dharma, Special Region of Yogyakarta, Indonesia
* Corresponding Author's Email: drpinzon17@gmail.com

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ABSTRACT

Osteoarthritis (OA) is a chronic disease that causes joint pain, stiffness, and swelling. The knee is the most affected joint in osteoarthritis. A typical therapy that often used for osteoarthritis patients is NSAIDs, but a previous study showed that satisfactory pain control could not be achieved with NSAIDs alone, so that additional analgesic therapy is needed. Some previous studies showed the extracts of Curcuma longa and Boswellia serrata were promising in reducing pain and do not cause serious side effects in osteoarthritis patients. This research aims to measure the effect of additional therapy Curcuma longa and Boswellia serrata to NSAIDs on functional activities in knee osteoarthritis patients. The type of this research is cross-sectional, involving 71 patients. This study uses secondary data taken from previous RCT studies by completing questionnaires to determine the WOMAC score of osteoarthritis patients at Bethesda Hospital and Panti Rapih Hospital in Yogyakarta. Data were analyzed statistically using the licensed SPSS program with the Wilcoxon test and the Mann-Whitney test. The reduction of WOMAC scores was superior in the NSAIDs group with Curcuma longa and Boswellia serrata after being given therapy for four weeks but not significant (p = 0.372). The giving of additional therapy Curcuma Longa and Boswellia serrata to NSAIDs is not superior compared to NSAIDs in increasing functional activities in osteoarthritis patients.

1. INTRODUCTION

Osteoarthritis (OA) is a chronic disease that causes joints to feel painful, stiff, and swollen. The joints most commonly affected by osteoarthritis are the hands, knees, hips, and spine (The Royal Australian College of General Practitioners, 2018). Osteoarthritis can cause chronic pain and cause disability and can affect the patient's quality of life. Generally, this disease attacks older people (Sembiring, 2018).

Osteoarthritis is the most common joint disease, and its prevalence increases with age (Tamara, Leatemiab & Masjhoer, 2018). According to World Health Organization (2019), 9.6% of men and 18.0% of women aged over 60 years will experience symptomatic osteoarthritis, and 80% of the population suffering from osteoarthritis will have limitations in movement, and 25% will be unable to carry out normal life activities. The prevalence of the joint disease in Indonesia, according to Basic Health Research, is 7.3% (Kementrian Keseahatan Republik Indonesia, 2018).

The most commonly used therapies in OA patients are analgesics, such as acetaminophen and NSAIDs (Akuri, Barbalho, Val & Guiguer, 2017). NSAIDs are used for symptomatic treatment. NSAIDs are anti-inflammatory and analgesic drugs that are effective in inhibiting prostaglandin biosynthesis at the level of the enzymes cyclooxygenase (COX), namely COX-1 and COX-2 (Crofford, 2013). However, the use of NSAID drugs in the long term can cause gastrointestinal (GI) and cardiovascular (CV) side effects (Akuri et al., 2017). According to Osani et al. and Lanas et al. obtained higher GI and CV side effects in OA patients using NSAIDs (Lanas, Garcia-Tell, Armada & Oteo-Alvaro, 2011; Osani, Vaysbrot, Zhou, McAlindon & Bannuru, 2019). Research on the effectiveness of diclofenac vs. paracetamol in OA patients also found that the diclofenac group reported more frequent GI than paracetamol (Verkleij et al., 2015). Based on data on research, there were 60.9% of OA patients who still felt pain after receiving NSAID therapy (Conaghan et al., 2015). Therefore, additional analgesic therapy is needed if the pain due to OA does not improve after taking NSAIDs (Park et al., 2012).

Curcuma longa and *Boswellia serrata* extracts are one of the drugs that have been evaluated and can relieve pain due to OA (Abdel-Tawab, Werz & Schubert-Zsilavec, 2011; Akuri et al., 2017). Previous studies mentioned that *C. longa* extract has a safe profile and excellent efficacy in treating primary knee pain due to OA (Madhu, Chanda & Saji, 2013). Besides, the research conducted by Haroyan et al. (2008), suggested that combining *C. longa* and *B. serrata* extracts increased the efficacy of OA treatment when compared with placebo. The research suggested that *C. longa* extract suppressed inflammation, brought clinical improvement through decreasing the level of VAS/WOMAC score, and improving the quality of life of patients when compared to placebo (Srivastava, Saksena, Khattri, Kumar & Dagur, 2016). Research states that the formula containing *C. longa* and *B. serrata* has greater efficacy than NSAID drugs (celecoxib) in OA patients (Kizhakkedath, 2013). Research also mentioned that *C. longa* was effective in reducing pain in arthritis patients compared to placebo or NSAIDs, is safe to use without serious side effects, and is a better choice for arthritis patients who need long-term analgesics (Pinzon & Sanyasi, 2018).

The parameter used in this study is the WOMAC score. WOMAC is the instrument most widely used in patients with knee or hip osteoarthritis and has proven efficacy in physical health psychometrics (Barber-Westin & Noyes, 2017). This study aims to measure the effect of supplemental therapy with *C. longa* and *B. serrata* on NSAIDs compared to single NSAID therapy on functional activity in osteoarthritis patients.

2. MATERIALS AND METHODS

This type of research is cross-sectional. This research was conducted through secondary data collection from previous RCT studies. Data will be taken from two groups who will be randomly divided and given two different therapies. The therapies used were CB extract (350 mg *C. longa* and 150 mg *B. serrata*) and NSAIDs (400 mg ibuprofen or 50 mg diclofenac sodium). The first group, as the experimental group, will be given NSAID therapy with *C. longa* and *B. serrata*, while the second group as the control group will be given NSAID therapy. Each drug is taken 2 times a day 1 tablet for 4 weeks. This research lasted for 4 weeks and was visited three times. On visit 1, the test subject will fill out the WOMAC questionnaire before being given therapy, At visit 2 (week 2) a drug side effect check will be carried out, and at visit 3 (week 4) the test subject will fill out the WOMAC questionnaire sheet again and check the drug side effects. A total of 10 500 mg paracetamol tablets were given to each subject as rescue medication in visits 1 and 2.

Research subject

The research subjects used were OA patients who received NSAID therapy with *C. longa* and *B. serrata* or NSAID only with a level (Kellgen and Laurence) KL 2-3 at Bethesda Hospital and Rapih Panti Hospital Yogyakarta concerning inclusion and exclusion criteria. The inclusion criteria in this study were male and female OA patients, aged > 18 years and had grade 2 or 3 KL. While the exclusion criteria were patients who refused to participate in the study, patients who were hypersensitive with *C. longa*/*B. serrata* or NSAIDs, followed a clinical trial. Others in the last one month were pregnant/had a pregnancy program were unable to give consent and filled out a questionnaire, and received other pain medications. Simple randomization was performed with the help of an openepi calculator (https://www.openepi.com/Random/Random.htm).

The minimum sample size is calculated with the help of an openepi calculator (https://www.openepi.com/SampleSize/SSMean.htm). On research (Srivastava et al., 2016) with a 95% confidence interval and 80% power, the mean and SD results of *C. longa* extract were 4.51 and 0.21, while the mean and SD results of placebo +

diclofenac sodium were 4.70 and 0.23. These results are inputted into the sample size calculator, and the minimum sample requirement in this study is 22 subjects per group.

Data Analysis

Data collection was carried out using secondary data obtained from the Case Report Form, which included basic patient data (subject number, subject name, medical record number, date of birth, gender, marital status, educational background, occupation, type of insurance, level of TOS). The data also contained co-morbidities (hypertension, diabetes mellitus, cardiovascular disease, gastrointestinal disease), rescue medication, WOMAC questionnaire sheet, and side effect sheet. The data obtained were analyzed using the intention to treat principle. Descriptive analysis was carried out to see the characteristics of the subject. Data analysis of this study used IBM SPSS Statistics 22. Normality test used test Shapiro-Wilk. Then proceed with the paired t-test/Wilcoxon test to see the relationship between therapy and increased functional activity in osteoarthritis patients and unpaired t-test / Mann-Whitney test to find out whether there is a significant difference between the two groups.

Ethical Worthiness

This research has gone through an ethical suitability check and was approved by the Ethics Committee for Health Research at Bethesda Hospital Yogyakarta with No.84/KEPK-RSB/V/20.

3. RESULTS AND DISCUSSIONS

Basic Data and Subject Characteristics

This study was conducted on 71 osteoarthritis patients at Bethesda Hospital and Panti Rapih Hospital Yogyakarta. They had met the inclusion and exclusion criteria where the research data were obtained at visit 1 (before being given NSAID therapy with *C. longa* and *B. serrata* or NSAID) and visit 3 (after given NSAID therapy with *C. longa* and *B. serrata* or NSAIDs). At visits 2 and 3 5 subjects did not succeed in following the study to completion due to drug side effects or loss to follow up so that the number of subjects studied at visits 2 and 3 was reduced to 66 subjects.

Subject characteristic data were obtained from a total of 71 osteoarthritis patients who participated in this study. Knee osteoarthritis occurs in 10% of men and 13% of women aged ≥ 60 years (Zhang & Jordan, 2011). These results are the same as the results of the study obtained where patients with osteoarthritis were 65 years old, consisting of 12 male subjects (16.9%) and 59 (83.1%) female subjects. Age or aging is a significant risk factor for osteoarthritis (Zhang & Jordan, 2011). Increasing age causes changes in joint function and joint tissue, which results in loss of healthy bone structure, increased feeling of stiffness in ligaments and muscles, weakening of

Table 1. Subject characteristics

Characteristics	**Criteria**	**NSAIDs + *Curcuma longa* and *Boswellia serrata*** n (%)	**NSAID** n (%)	**Total** n (%)	**p**
Age		65 ± 7,8	64 ± 9.7	65 ± 8.7	0.711
Gender	Male	5 (13.2)	7 (21.2)	12 (16.9)	0.366
	Girl	33 (86.8)	26 (78.8)	59 (83.1)	
Status	Married	27 (71.1)	22 (66.7)	49 (69.0)	0.924
	Divorce	10 (26.3)	10 (30.3)	20 (28.2)	
	Single	1 (2.6)	1 (3.0)	2 (2.8)	
Profession	Government employees	2 (5,3)	0 (0)	2 (2.8)	0.387
	Businessman	4 (10.5)	3 (9,1)	7 (9.9)	
	Private employees	3 (7.9)	1 (3.0)	4 (5,6)	
	Pension	11 (28.9)	15 (45.5)	26 (36.6)	
	Unemployment	0 (0)	1 (3.0)	1 (1,4)	
	Others	18 (47.4)	13 (39.4)	31 (43.7)	
KL rate	Level II	22 (57.9)	20 (60,6)	42 (59.2)	0.817
	Level III	16 (42.1)	13 (39.4)	29 (40.8)	
Another comorbidity	Hypertension	19 (50.0)	18 (54.5)	37 (52.1)	0.702
	Diabetes mellitus	5 (13.2)	6 (18.2)	11 (15.5)	0.560
	Cardiovascular	4 (10.5)	6 (18.2)	10 (14.1)	0.355
	Gastrointestinal	8 (21.1)	5 (15.2)	13 (18.3)	0.521
	Others	4 (10.5)	6 (18.2)	10 (14.1)	0.355

joints, sarcopenia, and loss of proprioception and balance (Anderson & Loeser, 2011). Aging also causes changes in collagen or proteoglycans, resulting in collagen tissue tension or increased glycation, which triggers functional disorders of cartilage and joint function (Hügle, Geurts, Nüesch, Müller-Gerbl & Valderrabano, 2012). Osteoarthritis is more common in women than men after the age of 50 because estrogen levels fall in postmenopausal women (Hussain, Cicuttini, Alyousef & Wang, 2018). Decreased levels of estrogen lead to degradation of articular cartilage and reduce anti-inflammatory effects so that the incidence of OA increases in postmenopausal women (Karsdal, Bay-Jensen, Henriksen & Christiansen, 2012; Liu, Li, Xin & Xu, 2018).

Osteoarthritis patients often have one or more co-morbidities, such as hypertension, diabetes mellitus, cardiovascular disease, and gastrointestinal disease (Hochberg, 2010). The data obtained showed that there were 52.1% of osteoarthritis patients experiencing hypertension and 15.5% experiencing diabetes mellitus. These results were the same with research (Kim et al., 2016), which states that hypertension and type 2 diabetes mellitus are commonly observed in elderly patients who have knee OA with data that 55% of knee OA patients aged ≥ 65 years have hypertension and 13% have diabetes mellitus.

Hypertension can affect osteoarthritis through narrowing of blood vessels and subchondral ischemia, which will degrade cartilage (Piva et al., 2015). Besides, increased pain in osteoarthritis patients with hypertension can occur because the damage to endothelial cells causes excess secretion of prostaglandins, increasing inflammation in the arteries and increasing blood pressure (Li, George, Jaarsma & Mao, 2016).

Diabetes mellitus has a relationship with osteoarthritis, where hyperglycemia reduces the transport of dehydroascorbate into chondrocytes, thereby interfering with type II collagen synthesis. This pathophysiological change causes increasing the production of reactive oxygen species (ROS), which can degrade cartilage, causing accumulation of glycation (AGE) and oxidative stress that contributes to bone stiffness cartilage, abnormal subchondral bone, and chondrocyte dysfunction (Berenbaum, 2011).

The mechanisms by which osteoarthritis and cardiovascular risk relate is unclear. However, several factors can explain this relationship, including the two diseases have the same risk factors (aging, obesity, gender), NSAID drugs prescribed to osteoarthritis patients are associated with an increased risk of vascular events, and lack of physical activity in osteoarthritis patients. Due to joint pain being a major cardiovascular risk factor (Kim et al., 2016; Wang, Bai, He, Hu & Liu, 2016).

NSAIDs are a common therapy in OA patients who work by inhibiting prostaglandins (PG) through COX-1 and COX-2 (Akuri et al., 2017; Crofford, 2013). Curcumin has strong anti-inflammatory properties by inhibiting primary inflammatory mediators (IL-6, IL-8, PGE2 and NO) and enzymes (COX-2 and iNOS) in chondrocytes and cartilage explants (Haroyan et al., 2018). Boswellic acid contained in the *B. serrata* extract has an anti-inflammatory activity that works by inhibiting the activity of cytokines (TNFα, IL-1β) and pro-inflammatory enzymes that inhibit the synthesis of leukotrienes through 5-LOX (5-lipooxygenase) (Abdel-Tawab et al., 2011). *B. serrata* can also inhibit the decrease in glycosaminoglycan levels, which function to repair cartilage (Kizhakkedath, 2013). Before being given therapy, the mean and SD score of WOMAC visit 1 in the NSAID + *C. longa* and *B. serrata* groups was 43.1 ± 20.2, while in the NSAID group, it was 35.7 ± 20.4. After being given therapy, the mean and SD WOMAC visit scores for the NSAID + *C. longa* and *B. serrata* groups were 31.5 ± 22.9, while in the NSAID group it was 27.8 ± 22.0. The results obtained in this study showed a significant reduction in WOMAC scores in group 1 and group 2, which means that the combination of NSAID therapy with *C. longa* and *B. serrata* or NSAID alone can increase functional activity in osteoarthritis patients after 4 weeks of therapy. These results are similar to those of the study which showed a significant reduction in WOMAC scores in the *C. longa* extract group compared to the placebo group (Srivastava et al., 2016).

A Decrease in The Intergroup WOMAC Score

Average delta score (Δ) WOMAC obtained in the NSAID + *C. longa* and *B. serrata* group was 11.3 ± 36.6, and in the NSAID group, it was 10.4 ± 25.9 with a significance value of p = 0.372. Although the NSAID group with *C. longa* and *B. serrata* showed a superior decrease in WOMAC scores after 4 weeks of therapy, the significance values obtained indicated that there was no significant difference between the two groups. It can be concluded that NSAID combination therapy with *C. longa* and *B. serrata* is not superior to NSAIDs in increasing functional activity in osteoarthritis patients. The results obtained in this study are the same as the research conducted by Pinsornsak and Niempoog (2012), in which the combination group curcumin with diclofenac and the diclofenac

Table 2. WOMAC score

Group	WOMAC visit 1	WOMAC visit 3	p
NSAIDs + Curcuma longa and Boswellia serrata	43.1 ± 20.2	31.5 ± 22.9	0.001
NSAID	35.7 ± 20.4	27.8 ± 22.0	0.016

Table 3. Delta (Δ) WOMAC

Group	Average Δ WOMAC	p
NSAIDs + Curcuma longa and Boswellia serrata (n = 36)	11.3 ± 36.6	0.372
NSAID (n = 30)	10.4 ± 25.9	

Table 4. Rescue medication

Group	Time Rescue Medication (mean)	p
NSAIDs + Curcuma longa and Boswellia serrata (n = 36)	7 tablets	.328
NSAID (n = 30)	5 tablets	

Table 5. The occurrence of side effects

Visit	NSAIDs + Curcuma longa and Boswellia serrata (n = 36)	NSAID (n = 30)	p
Visit 2	1	5	0.053
Visit 3	4	2	0.532

group experienced pain improvement but not significant. Research regarding the evaluation of formulas containing *C. longa* and *B. serrata* extracts in the therapy of knee osteoarthritis, it was also revealed that there was no significant difference in the reduction in pain scores between groups (Kizhakkedath, 2013). Meanwhile, research conducted by Srivastava et al. obtained a significant reduction in WOMAC scores between the two groups (Srivastava et al., 2016).

Rescue medication is a drug that can be given to patients to treat uncontrolled knee pain after receiving therapy. An analgesic drug that is used as a rescue medication to deal with uncontrolled knee pain is paracetamol 500 mg (Kivitz, Conaghan, Cinar, Lufkin & Kelley, 2019). A total of 20 500 mg paracetamol tablets were given to each subject as a rescue medication, and the remaining paracetamol tablets were counted at the end of the study. From table IV, data is obtained that the NSAID group with *C. longa* and *B. serrata* used 13 tablets of rescue medication and 15 tablets of the NSAID group. Although the use of rescue medication in the NSAID group was more than the NSAID group with *C. longa* and *B. serrata*, the significance value obtained stated that the use of 500 mg paracetamol as a rescue medication did not show any significant difference between the two groups. It can be concluded that the administration of NSAID combination therapy with *C. longa* and *B. serrata* or NSAID alone has the same opportunity to use rescue medication. According to previous studies, *C. longa* to OA patients can decrease the use of rescue medication (Madhu et al., 2013; Onakpoya, Spencer, Perera & Heneghan, 2017). These findings were consistent with the results of the study where the use of rescue medication was less in the combination group of NSAIDs with *C. longa* and *B. serrata*.

The NSAID group reported more frequent adverse events than the NSAID group with *C. longa* and *B. serrata*. A total of two subjects from the NSAID group were unable to complete the study due to drug side effects. The side effect most often felt by test subjects taking NSAIDs was abdominal pain. This is because NSAIDs inhibit the cyclooxygenase enzymes (COX-1 and COX-2) so that prostaglandins do not form. The inhibition of prostaglandins in COX-1 causes the gastroprotective effect not to form and causes pain in the stomach, while the inhibition of prostaglandins in COX-2 provides an analgesic effect (Chisholm-Burns et al., 2013).

There was one case of side effects associated with NSAID administration with *C. longa* and *B. serrata*, namely dizziness and five cases related to NSAID administration, namely abdominal pain. There were no severe or life-threatening side effects with any of the treatments given, and no patient needed to be treated in hospital due to side effects. The results obtained showed that there was no significant difference regarding the incidence of side effects between the two groups. The results obtained are in accordance with the earlier research (Kuptniratsaikul et al., 2014), where abdominal pain was less joint in the *C. longa* group than in the NSAID group, and the number of subjects experiencing adverse events during the study did not differ significantly between the

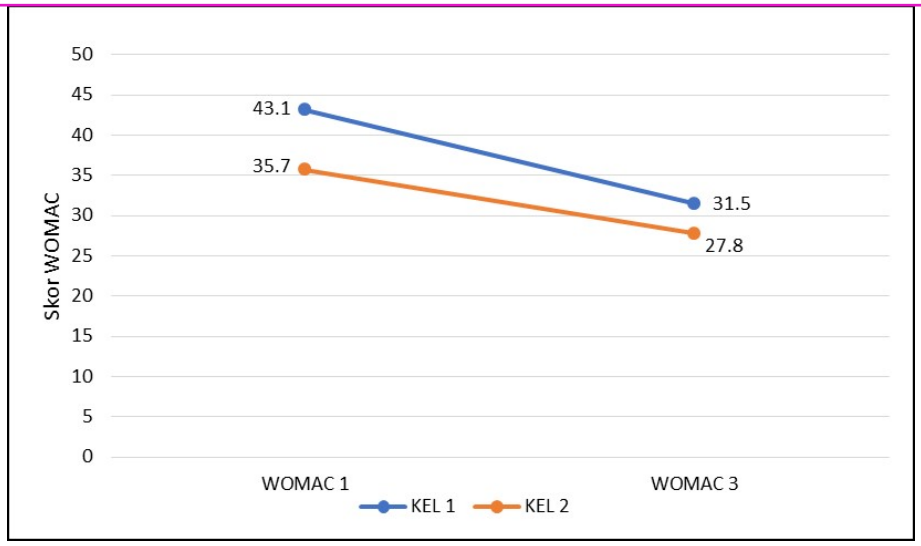

Figure 2. WOMAC delta (Δ) mean comparison graph

two groups. A previous study also mentioned that side effects were more common in the sodium diclofenac group than the combination of curcumin and sodium diclofenac (Chandran & Goel, 2012). Gastrointestinal side effects were less frequent and even did not occur in the curcumin group than in the NSAID group because curcumin has antiulcer and gastroprotective effects (effects that can protect the gastric mucosa). Curcumin has antiulcer activity by inhibiting 1L-6 and 5-LOX activity while as a gastroprotective agent by preventing the inactivation of gastric peroxidase by NSAIDs (Nakagawa et al., 2014; Shep, Khanwelkar, Gade & Karad, 2019; Yadav, Sah, Jha, Sah & Shah, 2013).

This study has the advantage of being randomized, and the data obtained is analyzed using the intention to treat principle. The limitation of this study is the relatively short period; no blinding was done, which can increase the risk of bias.

4. CONCLUSIONS

The provision of additional therapy *C. longa* and *B. serrata* in NSAIDs is not superior compared to NSAIDs in increasing functional activity in osteoarthritis patients.

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