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BOSWELLIA SERRATA FOR OSTEOARTHRITIS IN ELDERLY: FROM *IN VITRO* TO CLINICAL EVIDENCES

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ABSTRACT

Introduction: Pain is a main problem among osteoarthritis (OA) patients. Non-steroidal anti-inflammatory drug (NSAID) is a common treatment in OA patients. The use of NSAID was limited du to many side effects. Previous studies of Biocurpain extract (combination of *Boswellia serrata* and *Curcuma longa*) showed promising alternative pain medication in OA. **Objective**: Measure the effectiveness of Biocurpain extract for reducing pain in patients with osteoarthritis. **Method**: This was a randomized controlled trial study for 4 weeks. Subjects divided into 3 groups randomly; group I: combination of BC extract (150mg *Boswellia serrata* and 350mg of *Curcuma longa*) and NSAID (400 mg of ibuprofen or 50mg of diclofenac sodium), group II: BC extract alone, and group III: NSAID alone. The pain severity was measured using visual analogue scale (VAS). Any adverse event would be monitored. The analysis is intention to treat based. **Result**: Total of 105 subjects were enrolled the study. The mean aged 63 years. Seven subjects were lost to follow up and three subjects were excluded from the study due to medication side effect. There were 95 subjects remained for complete analysis. The greatest reduction of VAS score was seen in group I, whereas the least reduction was seen in group III. All VAS score reduction was statistically significant in all groups ($p < 0.001$).). The most frequent AE were reported from subjects in group III. **Conclusion**: Combination of 150mg *Boswellia serrata* and 350mg of *Curcuma longa* proved to be effective for pain treatment in OA patients and has a good safety profile.

KEYWORDS

Boswellia serrata, Curcuma longa, Osteoarthritis and Pain.

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease that is a leading cause of physical disability and impaired quality of life in industrialized nations. The evidence about etiology of OA is still not obvious yet. Age is related as one of the most strongest risk factor of the development of OA. However, obesity, trauma and physically demanding occupations also increase the risk of OA

of the hand, knee and hip. The data from NHANES III (the Third National Health and Nutrition Examination Survey) revealed that > 8% of adults in the USA have symptomatic OA[1].

Boswellia serrata is an ancient medication herbs that has been modified in this few past decades to be taken orally as a capsule, tablet or its raw decoction. There were no consensus or guideline that stated the recommended dosage for *Boswellia*. The daily administration is based on historical practice or available literatures. Furthermore, the optimal dose required to balance the efficacy and minimize adverse effect is still not fully understood. As a traditional herb, the production of *Boswellia* products may differs from one to another. The preparation and extraction methods used may varies between each factory, this makes it even more difficult for standardization to happen. It is important to note that most of the trials used various products made by various manufacturers, so clinical effects may not be comparable[2].

Osteoarthritis (OA) is a very common joint disorder in elderly, thus it is always challenging to learn of new developments in the treatment of this potentially disabling and painful disorder. Previous studies showed that NSAID as main pain treatment will increase some serious consequences in gastrointestinal, kidney, and cardiovascular system[1]. The aim of this study is measure the effectiveness of combination Biocrupain force extract (*Bonseweilla serrata* 150mg and Curcuma longa 350mg) compared with NSAID for patients with osteoarthritis.

METHODS

Design

This was a randomized controlled trial (RCT) at Bethesda Hospital Yogyakarta, Indonesia. Each subject in this study received treatment for 4 weeks. Subjects randomly divided into 3 groups by computerized block randomization. Group I was subject with oral administration of Biocurpain extract (combination of 150mg *Boswellia serrata* and 350mg of *Curcuma longa*) and NSAID. Group II was subject with oral administration of Biocurpain extract. Group III was subject with oral administration of NSAID.NSAIDs used in this study were 400mg ibuprofen or 50mg diclofenac sodium. Each medication was taken two times per day for 4 weeks.

Subjects

Male or female patients, age >18 years old with Kellgren-Lawrence grade II or III knee osteoarthritis. The exclusion criteria were subject with a known hypersensitivity to Biocurpain (combination of 150 mg *Boswellia serrata* and 350mg of *Curcuma longa*), ibuprofen, and diclofenac sodium, participation in other clinical trial in the last 1 month before this study, pregnant or has a pregnancy program, incompetent to give a consent and answer the questionnaire, and receiving other pain treatment in the last 24 hours before this study. After sample calculation, the minimum sample requirement was 25 subjects in each group. For achieving normal distribution, total of 100 subjects were enrolled. The sample size calculation based on the assumption of 95% confidence interval and 80% power of study.

Variables and Measurement

Demographic profile including sex, age, occupation, marital status, education background, comorbidity, and co-treatment. The degree of knee osteoarthritis was using Kellgren-Lawrence grading scale, determined based on the result of knee X-Ray. The pain severity measured by visual analogue scale (VAS). It is a subjective parameters assessed on 0-10 scale, which is 0 indicates pain free, where is 10 indicates severe pain. The VAS was measured 3 times, at the initial visit, second, and fourth week. Physician Global Assessment (PGA) was an instrument to measure the physicians' satisfaction to medication. PGA is a subjective parameters assessed on 0-10 scale. Adverse event (AE) monitored strictly. Any AE was recorded in case report form, reported to principal investigator, and followed-up by researcher. Each AE was assessed based on the type of AE, the degree of AE.

Analysis

The analysis of this study is intention to treat based. The participants demographic profile mentioned in

percentage. After normality test with Kolmogorov-Smirnov test, numeric variables analyzed using paired t-test or wilcoxon signed rank test. ANOVA used to identify the mean differences between three groups. The significant level was set at $p < 0.05$.

Ethical Clearance

This study was verified by Duta Wacana Christian University School of Medicine Ethical Research Committee, Yogyakarta, Indonesia. The number of ethical clearance is 867/C.16/FK/2018.

RESULTS AND DISCUSSION

There were 105 subjects enrolled at the study. Subjects were dominated by female (80%) with mean aged 63 years. Table No.1 showed the baseline characteristics of the subjects.

Two subjects were lost to follow up and one subject was excluded from the study due to medication side effect at the second week. At the last week, five subjects were lost to follow up and two subjects were excluded from the study due to medication side effect. Ninety five subjects remained in the last week of study.

The reduction of VAS score from the baseline to the second week and fourth defined as ΔVAS I-II and ΔVAS I-IV respectively. The greatest reduction was seen in group I, whereas the least reduction was seen in group III. All VAS score reduction was statistically significant in all groups. Based on the result of ANOVA, the mean differences between groups was not statistically significant (ΔVAS I-II: 0.096; ΔVAS I-IV: 0.236).

Figure No.2 showed the reduction of mean VAS score in each group at first, second, and fourth week. The reduction in VAS was shown in all groups. The greatest reduction of score mean was observed in group I.

Physician's satisfaction to medication measured using PGA. After a week of treatment, the highest score of satisfaction was in group II, whereas the lowest was in group III. The satisfaction level was increasing in all groups.

The most frequent AE were reported from subjects in group III. Gastric pain was the most common complain among them. Subjects in group II have the least reported AE. Each subject with AE was treated based on the symptoms and the degree of adverse event. Three subjects need to discontinue the medication due to the AE, two among them were subjects in group III and one among them was subject in group II. No fatal AE was seen during this study. No subject needed an inpatient treatment due to the AE. After further investigation, only one case (dizziness) of AE that related to the administration of BC extract and 4 cases (gastric pain) related to the administration of NSAID. There were no statistically different of the prevalence of AE between group at the second week (p: 0.374) and at the last week (p: 0.764).

***In vitro* studies**

In vitro studies and animal models show that boswellic acids were found to inhibit the synthesis of pro-inflammatory enzyme, 5-lipoxygenase (5-LO) including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB-4), which cause bronchoconstriction, chemo taxis, and increased vascular permeability[3]. Other anti-inflammatory plant constituents, such as quercetin, also block this enzyme, but they do so in a more general fashion, as an antioxidant, where asboswellic acids seem to be specific inhibitor of 5-LO.5-LO generates inflammatory leukotrienes, which cause inflammation by promoting free radical damage, calcium dislocation, cell-adhesion and migration of inflammation-producing cells to the inflamed body area[4].

In contrast to non-steroidal anti-inflammatory drugs (NSAIDS), which are well known to disrupt glycosaminoglycan synthesis, thus accelerating articular damage in arthritic conditions, boswellic acids have been shown to significantly reduce glycosaminoglycan degradation[5]. *In vivo* study examining the effect of *Boswellia* extract and ketoprofen on glycosaminoglycan metabolism showed that *Boswellia* considerably reduced the degradation of glycosaminoglycans compared to controls, whereas ketoprofen caused a reduction in total tissue glycosaminoglycan content[4].

***In vivo* studies**

Previous study reported that pure compound from

Boswellia serrata extract exhibits antiinammatory property in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages through inhibition of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), NO and mitogen activated protein (MAP) kinases[6]. Incensole acetate, a novel antiinammatory compound isolated from *Boswellia* resin inhibits nuclear factor-kappa B activation[7]. Boswellic acids are direct 5-LO inhibitors that efficiently suppress 5-LO product synthesis in common *in vitro* test models[8]. Acetyl-11-keto-β- boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2- mediated angiogenesis[9].

Clinical evidences

The randomized, double-blind, placebo-controlled, crossover study to assess the efficacy, safety and tolerability of Boswellia extract performed in 30 patients with osteoarthritis of the knee. Patients were divided into two groups of 15 patients each, with one group receiving active treatment and the other placebo for eight weeks[10]. All patients receiving Boswellia extract reported a significant decrease in knee pain, increased knee flexion and increased walking distance.. The dose used was 1,000 mg of extract per day containing 40 percent Boswellic acids. Boswellia was well-tolerated by the patients, with the exception of minor gastrointestinal adverse reactions.

Anoyher randomized study that compared Boswellia extract with valdecoxib, a selective COX-2 inhibitor[11]. Patients (n: 66) received either 1,000mg/day Boswellia extract (containing 40 percent Boswellic acids) or valdecoxib, 10mg/day, for six months. Boswellia was slower in onset than the drug, but by the end of the second month was providing comparable symptom relief[12]. The two treatments worked equivalently for the rest of the trial.

Boswellia patients were still experiencing highly significant relief of their symptoms ($p<0.001$).

The other trial, 75 patients with knee OA received either Boswellia extract (containing 100mg or 250mg of selected Boswellic acids/day) or placebo for 90 days. Boswellia conferred a clinically and statistically significant dose-response improvement in pain and physical function scores. Symptom alleviation was faster in the higher-dose Boswellia group (as early as seven days) and a significant reduction in synovial fluid levels of matrix metalloproteinase-3 (a cartilage-degrading enzyme) was also observed for the Boswellia groups.

The protective effects of curcumin against arthritis are mediated through inhibition of neutrophil activation, suppression of synoviocyte proliferation and inhibition of angiogenesis as suggested by curcumin's ability to inhibit collagenase and stromelysin in chondrocytes[13]. Further, the suppression of NF-kB by curcumin has been found to be associated with its inhibition of the expression of COX-2, NO, PGE_2, IL-1b, IL-6, IL-8, MMP-3 and MMP-9 in human chondrocytes[14].

The limitation of this study is the unmasked measurement of the outcome. The follow up period is only 4 weeks. Further trials with longer follow up are warranted. The measurement of any other important outcome (functional status, quality of life are warranted).

Table No.1: Baseline characteristics of the subjects

S.No	Characteristics	n	%
Age (mean)		63.24 ± 8.77 years	
Gender			
1	Male	21	20
2	Female	84	80
Marital status			
3	Married	78	74.3
4	Divorce	23	21.9
5	Not married	4	3.8
Educational background			
6	Elementary school	16	15.2
7	Junior high school	15	14.3
8	Senior high school	38	36.2
9	Bachelor degree	23	21.9
10	Others	13	12.4
Occupation			
11	Civil servant	4	3.8
12	Entrepreneur	11	10.5
13	Private employee	7	6.7
14	Retired	33	31.4
15	Unemployment	2	1.9
16	Others	48	45.7
KL Grade			
17	Grade II	60	57.1
18	Grade III	45	42.9
Comorbidity			
19	Hypertension	54	51.4
20	DM type 2	14	13.3
21	CVD	25	23.8
22	GIT Disease	23	21.9
23	Others	8	7.6

KL: Kellgren-Lawrence, DM: Diabetes Mellitus, CVD: Cardiovascular Disease, GIT: Gastrointestinal Tract

Table No.2: The Mean of VAS Score Reduction

S.No	Group	ΔVAS I-II	p	ΔVAS I-IV	p
1	Group I	1.602 ± 1.179	< 0.001	2.671 ± 1.844	< 0.001
2	Group II	1.018 ± 1.180	< 0.001	2.170 ± 2.025	< 0.001
3	Group III	0.856 ± 1.152	< 0.001	1.856 ± 2.113	< 0.001

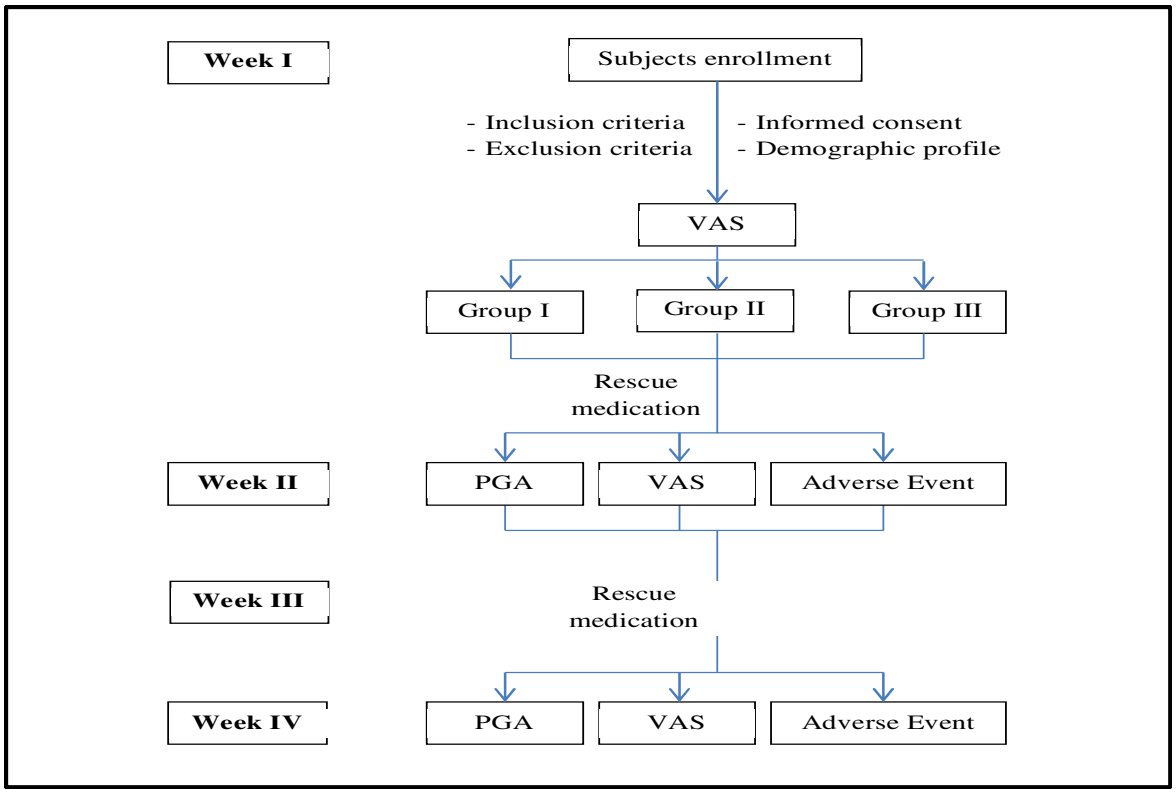

Figure No.1: Study diagram

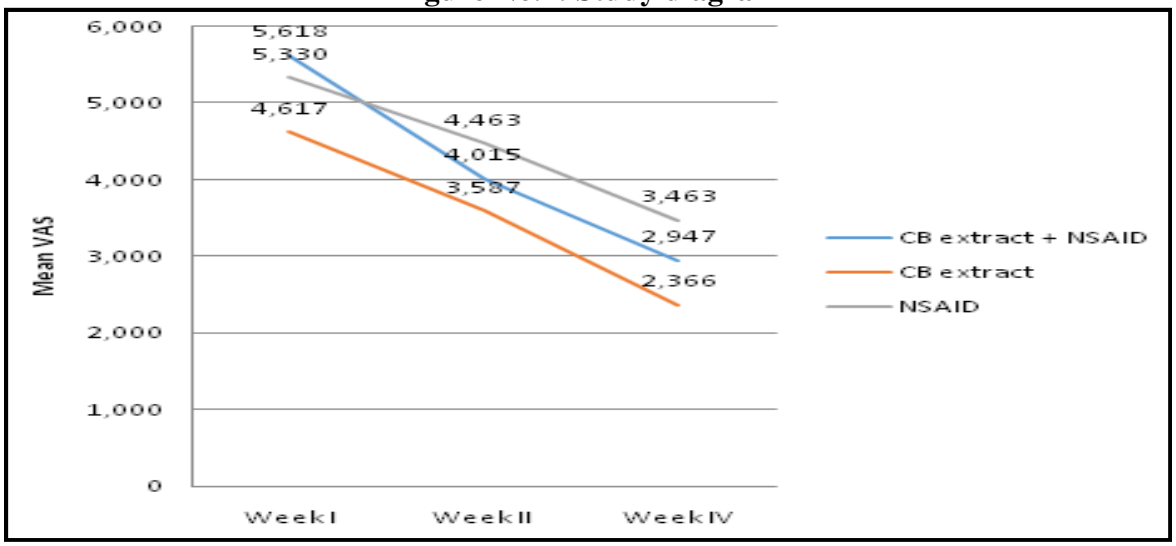

Figure No.2: The mean of VAS score

CONCLUSION

Combination of 150mg *Boswellia serrata* and 350mg of *Curcuma longa* proved to be effective for pain treatment in OA patients and has a good safety profile.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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