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The benefit of *Curcuma longa* and *Boswellia serrata* to improve quality of life in osteoarthritis patients: a randomized controlled trial

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ABSTRACT

Background: Quality of life (QoL) can be affected by chronic pain in osteoarthritis (OA). Previous studies showed that combination of *Curcuma longa* (CL) and *Boswellia serrata* (BS) extract (CB extract) are promising for alternative treatment for pain in OA. This study aimed to measure the benefit of CB extract to improve QoL in patients with OA.
Methods: This was a randomized controlled trial (RCT) in OA patients. Subjects were randomized to 3 different group (Group 1: CB extract (350 mg of CL and 150 mg BS) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium); group 2: CB extract; group 3: NSAID). Each medication was taken two times per day for 4 weeks. QoL measured using 5Q-5D-5L that include five dimensiones in 5Q-5D: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with 5 levels of severity.
Results: There were 105 subjects at baseline. After 4 weeks of study, remained 95 subjects. The most common problem in group 1, 2, and 3 was pain (n=23, n=8, n=15 respectively). The improvement of level of severity in group 1 after 4 weeks of treatment was significant in mobility problems (p=0.002), pain/discomfort (p<0.001), and anxiety/depression (p=0.008). A significant improvement was only seen in usual activity problems (p=0.013) in group 2. The decrease of level of severity in usual activity problems (p=0.034), pain/discomfort (p=0.005), and anxiety/depression (p=0.018) in group 3 were also statistically significant.
Conclusions: CB extract was beneficial to improve QoL in OA patients with a less side effect compared to NSAID.

Keywords: *Curcuma longa*, *Boswellia serrata*, Osteoarthritis, 5Q-5D-5L, Quality of life

INTRODUCTION

Quality of life (QoL) can be affected by chronic pain. Pain was reported to not only disrupt daily activities yet also interfere sleep, personal relationship, and mental health.[1] People who suffering a chronic pain feel less confident in their self-sufficient compared with the general public (61% vs 73%, respectively, p<0.05).[1] According to the study by Axford et al, over 40% patients with lower limb osteoarthritis (OA) suffered from clinically significant anxiety or depression.[2] A study by Hasche et al showed that clients with depression consistently had lower quality of life and life satisfaction than non-depressed clients.[3]

Pain and loss of joint function are the most problematic symptoms in patient with OA.[4] OA is the most common joint disease worldwide and it also a leading cause of

disability around the globe.[5,6] OA often characterized not only by degradation of the articular cartilage but also with chronic joint pain and disability.[4]

Based on those findings, a good treatment of chronic pain should be an important part of OA management. Unfortunately, no treatments that are known to modify disease progression of OA in the long term.[7] Non steroid anti inflamatory drug (NSAID) has been one of the most frequently used drugs for symptomatic OA. Long-term NSAIDs used has been associated with significant health risks.[8] The major problem of NSAIDs use is that adverse event are common, especially gastrointestinal problems.[9]

Turmeric *(Curcuma longa (syn. Curcuma domestica))* is a member of the ginger family (*Zingiberaceae*).[10] A study conducted by Kuptniratsaikul et al concluded that curcumin extracts use are as effective as ibuprofen, not only its effectiveness but also curcumin had adverse event (AE) profile that similar with ibuprofen group with fewer gastrointestinal AE reports in patients with knee osteoarthritis.[11] Many studies showed that combination of *Curcuma longa* (CL) and *Boswellia serrata* (BS) extract increases the efficacy of OA treatment. The research focusing on the combination of CL extract and BS extract (CB extract) in Indonesia is very limited. This study aimed to identify the benefit of CB extract to improve QoL in patients with OA.

METHODS

Study design and criteria of subjects

This was a randomized controlled trial (RCT). The site of this research was in Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia, conducted from 21 January 2019 to 14 March 2019. Subject enrollment included male or female patients, age >18 years old, and has knee osteoarthritis with Kellgren-Lawrence (KL) grade II or III. The sample size calculation based on the assumption of 95% confidence interval and 80% power of study. The minimum sample requirement was 25 subjects in each group. Total of 100 subjects were enrolled for achieving normal distribution. Subjects divided into 3 groups randomly. The randomization was using computerized block randomization with openepi software. The implementation of the random allocation sequence was assigned an equal number to each group. The random allocation sequence, subjects enrollment, and subjects assignment to interventions were done by researchers.

The treatment used in this trial were CB extract (350 mg of *Curcuma longa* and 150 mg *Boswellia serrata*) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium). Group 1 was subjects received the CB extract and NSAID, group 2 received CB extract, and group 3 received NSAID. Each medication was taken two times per day for 4 weeks. Paracetamol tablet 500 mg was given to each subject as a rescue medication. The remaining number of rescue medication at the third visit was calculated at the end of study. Subject with a known hypersensitivity to CB extract, ibuprofen, diclofenac sodium and/or paracetamol, 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, or receiving other pain treatment in the last 24 hours before this study was excluded in this study. Figure 1 shows the schematic of study process. Each subject signed an informed consent form. Subjects followed three times (visit I, visit II, and visit III) with interval of 2 weeks between each visit.

Demographic profile including sex (male or female), age (described in mean number), occupation (working or unemployement), marital status (maried or single), education background (elementary school, junior high school, senior high school, bachelor degree, or others), comorbidity (has a comorbity or without comorbidity), and the degree of OA (KL grade II or grade III). The degree of knee OA determined based on the result of knee X-Ray, and interpreted by radiologist.

EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group that include five levels of severity in each of the existing five EQ-5D dimensions. We use EQ-5D-5L in Indonesian version. Five dimensiones in 5Q-5D : mobility, self care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 levels of severity : no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5). Each subject asked to indicate his/her health state by ticking or placing a cross in the box against the most appropriate statement in each of the five dimensions. The health state is defined by combining 1 level from each of the 5 dimensions. The last component of EQ-5D-5L is a 20 cm vertical of visual analogue scale (VAS) to measure health status, with end-points labelled ‘the best health you can imagine’ and ‘the worst health you can imagine’.

Any adverse event (AE) would be monitored strictly. The assessment of AE is based on the type of AE, the degree of AE, the correlation to administration of CB extract or NSAID, and the action taken to treat the AE. The number of rescue medication taken by subjects was also analyzed in this study.

Ethical clearance

All data obtained from this study is classified. Each subject involved in this study must signed an informed consent form. 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.

Analysis

The analysis of this study is intention to treat based. Univariate analysis, for demographic profile of subjects,

mentioned in percentage. The 5D-5Q-5L and numeric variables were analyzed using t-test or wilcoxon signed rank test after tested for normality with Kolmogorov-Smirnov test. ANOVA or Kruskal Wallis test was used to identify the mean differences between three groups after tested for homogeinity. The significant level was set at $p<0.05$.

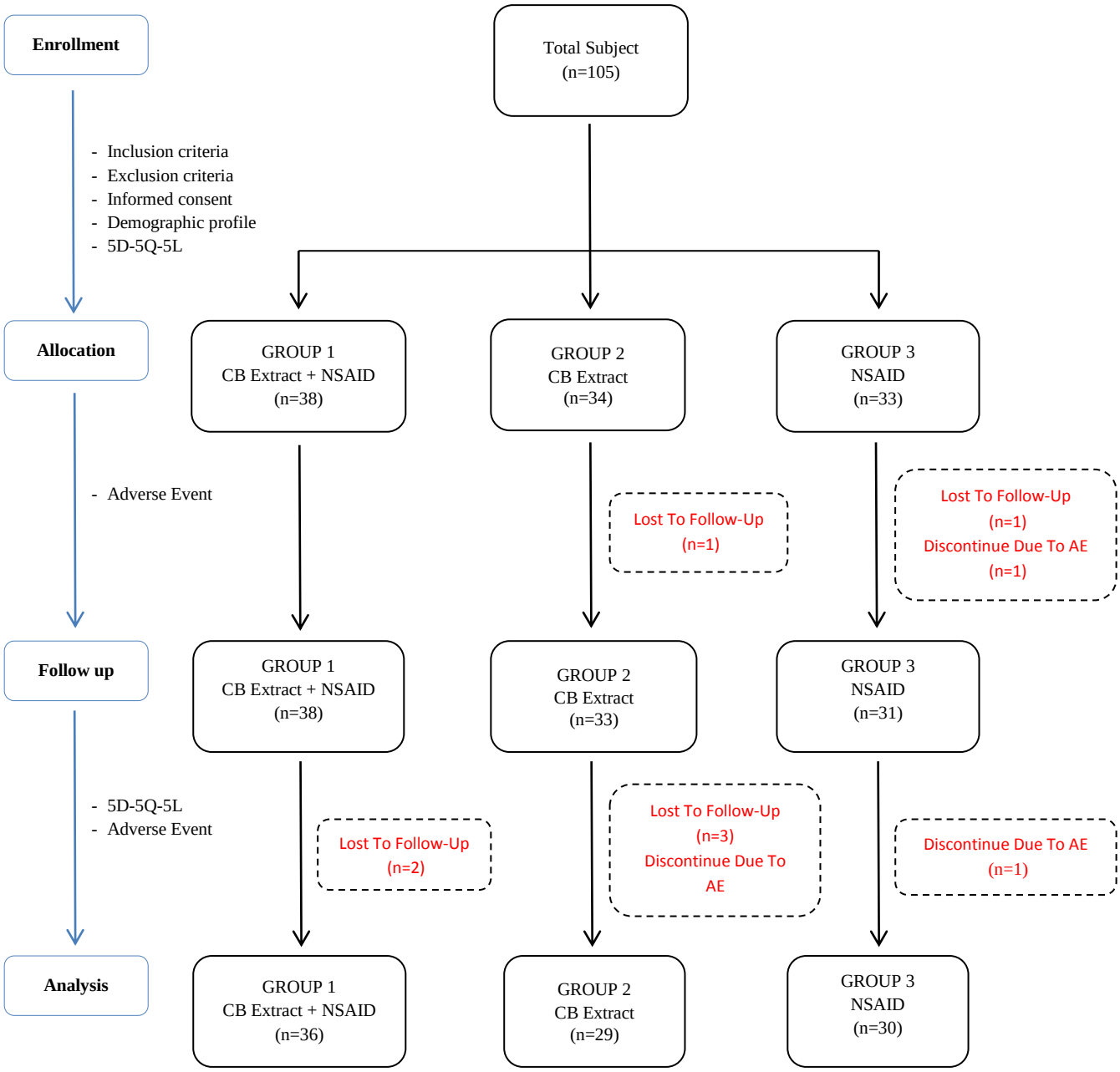

Figure 1: The flow diagram of the research.

RESULTS

There were 105 subjects at baseline, consist of 38 subjects in group 1, 34 subjects in group 2, and 33 subjects in group 3. After 4 weeks of study, remained 95 subjects for complete analysis consist of 36 subjects in group 1, 29 subjects in group 2, and 30 subjects in group 3 (Figure 1). Subjects were dominated by age 60s, female, married, has an occupation, has a KL grade 2, and has a comorbidity (Table 1).

This study measure the number of subject based on the level of severity, from level 3 (moderate) to level 5 (extreme), as it significantly interfere their daily living. At the baseline, most subjects in group 1 had a problem of pain (n=23), followed by mobility (n=15), anxiety / depression (n=10), usual activity (n=9), and self-care (n=6). After 4 weeks of treatment, the number was decreased into 7, 5, 5, 6, and 4 respectively (Figure 2).

Table 1: The characteristics of subjects at baseline.

Characteristics	Group 1	Group 2	Group 3
	N (%)	N (%)	N (%)
Age in years (mean±SD)	63.8±7.8	62.8±9.2	62.9±9.5
Gender			
Male	5 (13.2)	9 (26.5)	7 (21.2)
Female	33 (86.8)	25 (73.5)	26 (78.8)
Marital status			
Married	27 (71.1)	29 (85.3)	22 (66.7)
Single	11 (28.9)	5 (14.7)	11 (33.3)
Educational background			
Elementary school	9 (23.6)	3 (8.8)	4 (12.1)
Junior high school	9 (23.6)	4 (11.8)	2 (0.6)
Senior high school	7 (18.4)	15 (44.1)	16 (48.5)
Bachelor degree	9 (23.6)	7 (20.6)	7 (21.2)
Others	4 (10.5)	5 (14.7)	4 (12.1)
Occupation			
Working	27 (71.1)	26 (76.5)	17 (51.5)
Unemployment	11 (28.9)	8 (23.5)	16 (48.5)
KL grade			
Grade II	22 (57.8)	18 (52.9)	20 (60.6)
Grade III	16 (42.2)	16 (47.1)	13 (39.4)
Comorbidity			
Yes	25 (65.7)	27 (79.4)	27 (81.8)
No	13 (34.3)	7 (20.6)	6 (18.2)

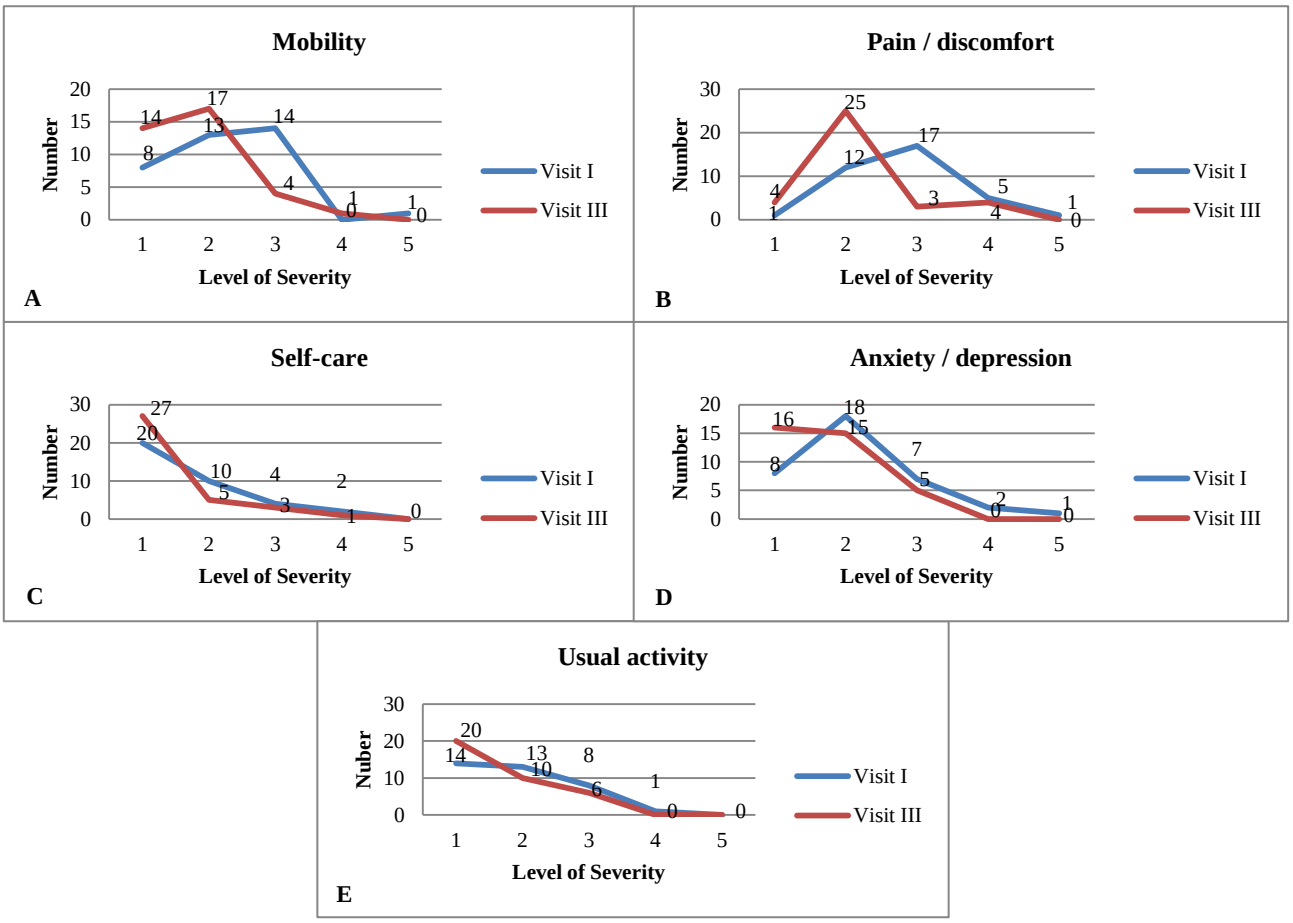

Figure 2 (A-E): The quality of life in group 1.

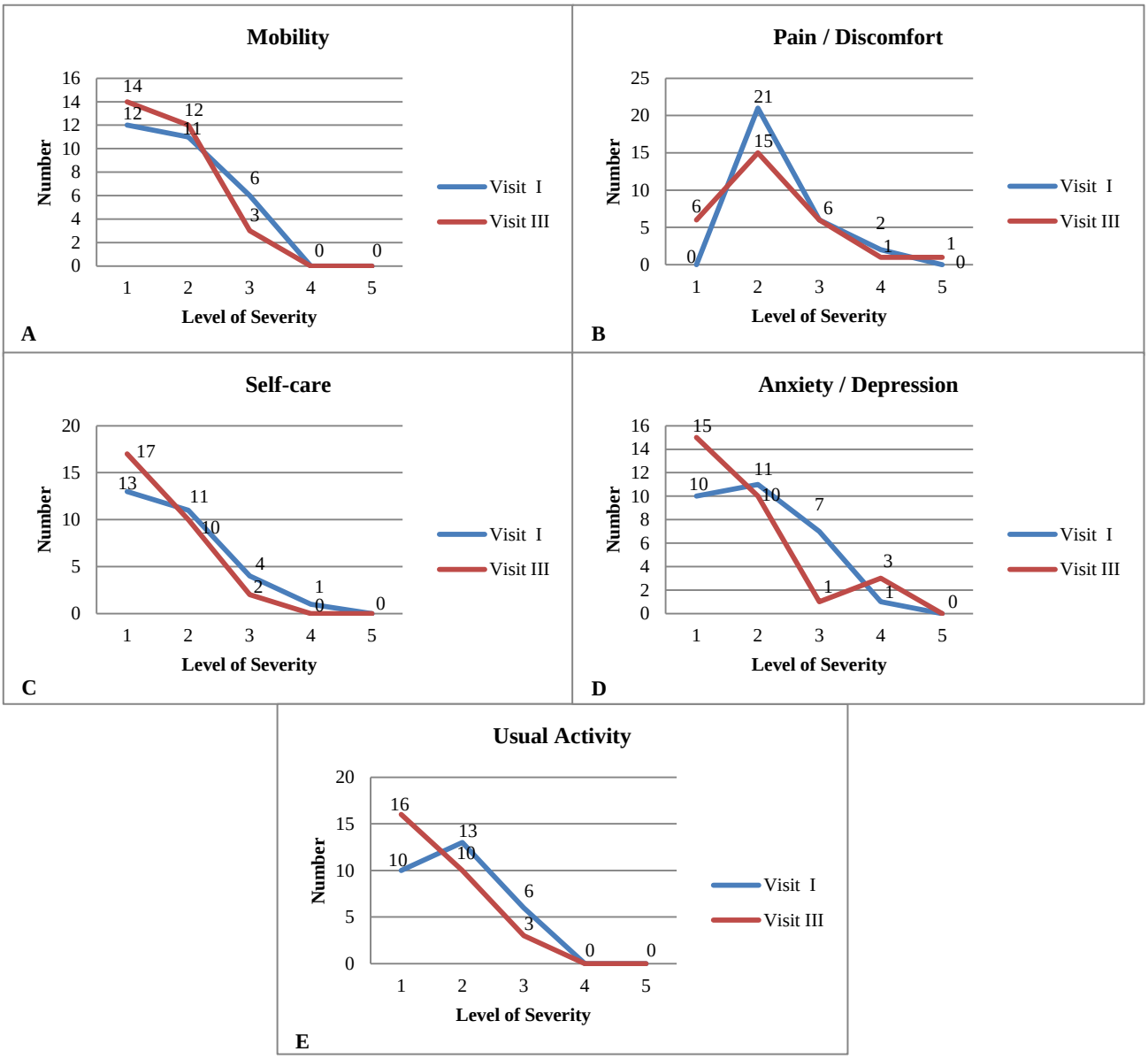

Figure 3 (A-E): The quality of life in group 2.

Group 2 had a high complain of pain / discomfort (n=8) and anxiety /depression (n=8), followed by mobility problems (n=6), usual activity problems (n=6), and self-care problems (n=5). After 4 weeks of treatment, the number of complain in pain / discomfort was same (n=8). The improvement showed in anxiety / depression problem (n=4), mobility problems (n=3), usual activity problems (n=3), and self care problems (n=2) (Figure 3).

Pain / discomfort was the most common complain in group 3 (n=15), followed by anxiety / depression (n=11), mobility problems (n=4), usual activity problems (n=4), and self-care problems (n=3). The improvement after 4 weeks of treatment with NSAID showed in all dimensions except in mobility and self-care problems (Figure 4).

The improvement of level of severity in each dimension in group 1 was significant in mobility problems, pain / discomfort, and anxiety / depression. A significant improvement was only seen in usual activity problems in group 2. The decrease of level of severity in usual activity problems, pain / discomfort, and anxiety / depression in group 3 were also statisticaly significant (Table 2).

Health scale in 5D-5Q-5L is a 20 cm vertical visual analogue scale. The higher score indicates the better health status. The lowest health scale mean score at the baseline was in group 2 and the highest was in group 1. Delta (Δ) Score defined as the subtraction between health scale score from viti III and visit I. The highest Δ score was seen in group 3 and it was statisticaly significant (Table 3).

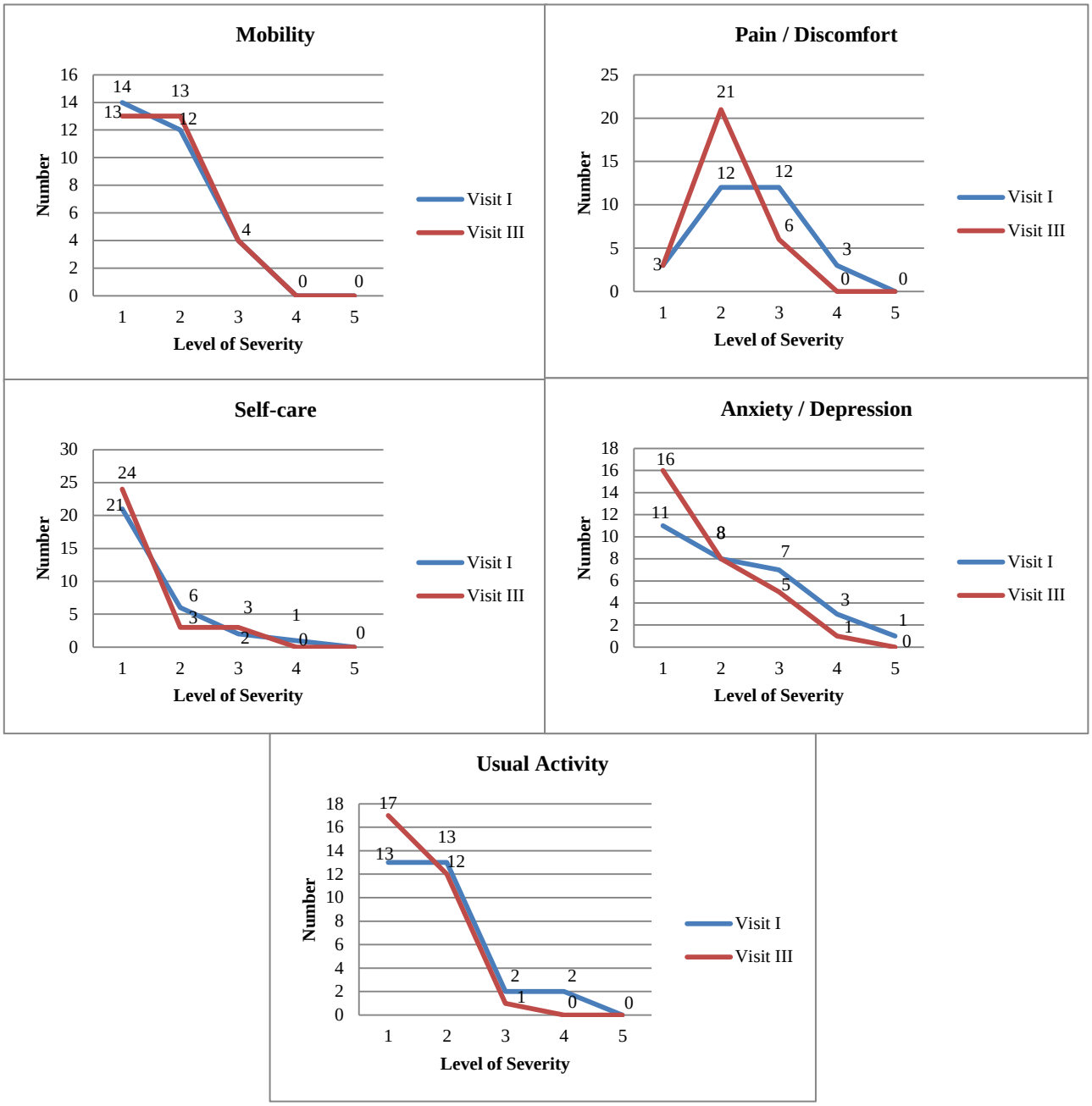

Figure 4: The quality of life in group 3.

Table 2: The significant level for each dimension.

5D-5Q-5L	Group 1	Group 2	Group 3
Mobility	0.002	0.132	0.808
Self-care	0.064	0.106	0.357
Usual activity	0.079	0.013	0.034
Pain / discomfort	< 0.001	0.198	0.005
Anxiety / depression	0.008	0.138	0.018

Paracetamol was the rescue medication in this research. The highest consumption of rescue medication was seen in group 3, whereas the least was in group 2 (Table 4). There was no statistical different of rescue medication consumption between groups (p=0.346).

Table 3: Mean score of health scale.

Health scale	Group 1			Group 2			Group 3		
	Visit I	Visit III	Δ Score	Visit I	Visit III	Δ Score	Visit I	Visit III	Δ Score
Mean	74.5±14.1	77.8±13.3	2.5±18.4	70.7±16.2	74.1±15.3	4.79±15.4	73.6±16.5	80.2±12.5	5.7±13.9
P value	0.260			0.109			0.038		

Table 4. The mean number of rescue medication.

Group	The remaining number of rescue medication (mean)
Group 1	7 tablets
Group 2	8 tablets
Group 3	5 tablets

Table 5. Adverse Events

Group	Type of adverse event			
	Visit II	Correlation to CB extract/NSAID	Visit III	Corelation to CB extract/NSAID
Group I (Total n=5)	Angioedema (n=1)	Not correlated	Flank pain (n=1) Constipation (n=1) Nausea and loss of appetite (n=1) Malaise and dizziness (n=1)	Not correlated
Group II (Total n=4)	Dizziness (n=1) Urticaria (n=1)	Correlated to CB extract Not correlated	Nausea and loss of appetite (n=1) Dizziness (n=1)	Not correlated
Group III (Total n=7)	Abdominal pain (n=5)	Correlated to NSAID (n=4)	Abdominal pain (n=1) Muscle pain/spasm (n=1)	Correlated to NSAID Not correlated

Table 5 showed the detail of AE in each group at vivit II and visit III. The highest AE was seen in group 3. Group 2 had the least AE. One AE was correlated to CB extract and 5 AE were correlated to NSAID. There were no statistically different of the prevalence of AE between groups at the visit II (p=0.119) and at the visit III (p=0.767).

DISCUSSION

Knee osteoarthritis (OA) has a significant negative impact on QoL.[12] There are many instruments to measure QoL. Cross-sectional study with 93 knee OA patients using SF-36 questionnaire showed individuals with OA have a low perception of their quality of life in functional capacity, functional limitation, and pain.[13] Other instrument to measure QoL in OA patients is EQ-5D-5L. Result of study by Bilbao, et al., 2018 support the reliability, validity, and responsiveness of the EQ-5D-5L and could be very useful as an outcome measure, at least in patients with hip or knee OA.[14]

The main objective in this research was to identify the benefit of CB extract to improve QoL in OA patients. QoL in subjects measured using EQ-5D-5L. We hypothezied that subjects with OA has a poor QoL at the baseline, indicates by ≥50% from in each group has a high level of severity (level 3 to level 5) in ≥1 dimension.

This study showed that pain / discomfort was the most common complain among subjects at the baseline (group 1=23 from 36 subjects, group 3=15 from 30 subjects), whereas in group 2 pain / discomfort and anxiety / depression were the most common complain (group 2=8 from 29 subjects in each dimension). Usual activity and self-care were rarely complained by subjects in all groups.

Knee OA is among the top 10 causes of disability worldwide.[15,16] The relationship between OA and low QoL is indirect. It is through pain and joint damage in OA patophysiology. Chronic pain is the most common complaint among OA patients.[17] There is an important relationship between psychosocial factors and pain reporting in OA, particularly anxiety, depression, and social isolation.[18] Stiffness and gelling in OA have a contributions to functional limitations in OA patients, with well-documented associations of pain severity with degree of functional limitation.[19] In a longitudinal panel survey conducted by the US Census bureau, arthritis was the most commonly reported cause of disability and difficulties related to lower extremity functioning or activities were the most commonly reported limitations among all respondents. Based upon NHANES III data, about 80% patients with OA have some degree of movement limitation, 25% cannot perform major

activities of daily living, 11% require help with personal care, and 14% need help with routine needs.[19]

The second hypothesis in this study was the administration of CB extract improves QoL by reducing the level of severity (level 3 to level 5) by ≥50% in ≥3 dimensions. After 4 weeks of treatment, improvement was seen in all groups. Group 1, which receive a combination of CB extract and NSAID, showed an improvement in all dimensions (from 23 to 7 subjects in pain / discomfort, 15 to 5 subjects in mobility, 10 to 5 subjects in anxiety / depression, 9 to 6 subjects in usual activity, and 6 to 4 subjects in self-care). The number of subjects in level of severity 3 to 5 reduce by 50% in 3 from 5 dimensions. However, it was only significant in pain / discomfort ($p<0.001$), mobility ($p=0.002$), and anxiety / depression ($p=0.008$).

Group 2 (CB extract group) showed an improvement only in 4 dimensions : from 8 subjects remained 8 subjects in pain / discomfort, 8 to 4 subjects in anxiety / depression, 6 to 3 subjects in mobility, 6 to 3 subjects in usual activity, and 5 to 2 subjects in self-care. A further analysis was performed. The number of subjects in level of severity 3 to 5 reduce by 50% in 4 from 5 dimensions. It showed that usual activity was the only dimension significantly improves in group 2 ($p=0.013$).

Group 3 (NSAID group) showed an improvement only in 3 dimensions : from 15 to 6 subjects in pain / discomfort, 11 to 6 subjects in anxiety / depression, from 4 remained 4 subjects in mobility, 4 to 1 subjects in usual activity, and 3 to 3 subjects in self-care. The number of subjects in level of severity 3 to 5 reduce by 50% in 3 from 5 dimensions. Pain / discomfort ($p=0.005$), anxiety / depression (0.018), and usual activity ($p=0.034$) were significantly improve in group 3.

In patophysiology of OA, the synovial fluid has been found to contain multiple inflammatory. C-reactive protein, proposed as a marker for development and progression of OA, prostaglandins (PGE2), leukotrienes (LKB-4), cytokines (Tumor Necrotic Factor (TNF), interleukine (IL) -1β, IL-6, IL-15, IL-17, IL-18, IL-21), growth factors (TGF-β, FGFs, VEGF, NGF), nitric oxide, and complement components have an important role in the development of OA.[20,21]

The effect of CL centered upon a substance called "curcumin".[22] Curcumin has many positive effects including an antioxidant and anti-inflammatory.[22-24] An earlier in vitro study revealed the anti-inflammatory property of CL.[25] CL extract is down regulate activation of NF-kappaB and proinflammatory cytokines such as TNF-α, IL-1, IL-8, and Nitric Oxide Syntase.[26] Due to this property, CL and its extract are useful in various illnesses range including OA. BS also has an anti-inflammatory effect and beneficial to treat a chronic inflammatory disease.[27] An oral administration of the extract of BS resulted in reduced level of IL-1β, IL-6, TNF-α, IFN-γ, and PGE2.[28]

This study proves that CB extract is effective to reduces anxiety / depression, improves mobility, usual activity, and self-care by 50%. Consumption of CB extract also proves to reduce the need of rescue medication (Table 4) and has the least AE (Table 5) compared with combination of CB extract and NSAID and NSAID alone. This result was in concordance with previous studies.

As many as 44 patients were randomized to take diclofenac 75 mg/day with placebo and the other 44 took diclofenac 75 mg/day with curcumin 1,000 mg/day for 3 months. The curcumin with diclofenac group had tendency to be better in pain and function in daily living. However there were no statistic different in all group ($p=0.412$ ($F=0.683$), $p=0.814$ ($F=0.056$), $p=0.446$ ($F=0.589$), $p=0.224$ ($F=1.511$ and $p=0.938$ ($F=0.006$)).[26] Panahi, et al. showed that treatment with curcuminoids (1500 mg per day in three divided doses) of OA patients resulted in a reduction in pain and physical function scores.[29] Turmeric extract has also shown to be safe and effective in reducing the pain and improving the function of OA patients. In a study conducted with 367 patients, administration of Curcuma domestica extracts (1500 mg per day for 4 weeks) resulted in improved OA index, and its efficacy was found to be quite comparable with that of ibuprofen.[11]

A long-term medication using NSAID correlated to many side effects and adverse events, especially in gastrointestinal tract and cardiovascular system.[30] Study by Appelboom et al and Haroyan et al were also reported an excellent tolerance in patients using CL extract or CB extract.[31,32] Even though there was no statistical different between groups in this study, administration of CB extract provide an equal pain relieve with minimum AE compared to NSAID alone.

CONCLUSION

CB extract proven to be effective to improve QoL with minimal side effect on OA patients.

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Ethical approval: The study was approved by the institutional ethics committee

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