PREEMPTIVE ANALGESIA IN TOTAL KNEE ARTHROPLASTY:

COMPARING THE EFFECTS OF SINGLE DOSE COMBINED CELECOXIB WITH PREGABALINE AND REPETITION DOSE COMBINED CELECOXIB WITH PREGABALINE (DOUBLE BLIND CONTROLLED CLINICAL TRIAL)

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ABSTRACT

Introduction. Acute Pain is the most common early complication after total knee arthroplasty that caused delayed mobilization, demands of morphine, and higher operative cost. There were many researches that had been done in analgesia method to find the most effective analgesia, lowest side effect, and easy to apply. Preemptive analgesia of combined celecoxib and pregabalin were reported to give a promising outcome.

Method. In a randomized, double blind controlled clinical trial, 30 subjects underwent surgery for total knee arthroplasty using 15-20mg bupivacaine 5% epidural anesthesia. All subjects were divided into three groups. First group was given celecoxib 400mg and pregabaline 150mg 1 hour before operation, second group was given celecoxib 200mg and pregabaline 75mg twice daily started from 3 days before operation, and the last group was given placebo. The outcome was measured with VAS, knee ROM, and post-operative mobilization.

Results. There was a significant difference in post-operative morphine usage between the groups taken preemptive analgesia and the placebo group, but there was no any significant difference found between first and second group that consumed preemptive analgesia with different dosage. ROM and post-operative mobilization were not significantly different among three groups.

Discussion and Conclusion. Preemptive analgesia had been proven to reduce post-operative usage of morphine regardless of the dosage. We recommend the usage of combined celecoxib and pregabaline as the preemptive analgesia in total knee arthroplasty procedure. Nausea side effect was found in 2 subjects of the first group, 1 subject in the second group, and 1 subject in the third group.

Keywords: preemptive analgesia, celecoxib, pregabaline, morphine, VAS

INTRODUCTION

Total knee arthroplasty is one of the most satisfactory operation procedure in orthopaedic field.[1] There were many researches that had been done to prove that TKA procedure increase the Quality of Life of the patients.[2,3] Crowder, Duffy, and Trousdale,[4] reported that after 10 years of follow up, 99% of the patients that underwent TKA procedure showed good functional outcome. TKA procedure was indicated for patients had chronic pain caused by severe damage of the joint. Although this procedure was frequently giving a good outcome, it is still followed by few complications.[5]

Acute pain following TKA has been reported as one of the most common complication of the procedure.[6,7] There are many factors that contribute to emerging pain sensation, such as infection, inflammatory reaction caused by the procedure, and racial factor. Post-operative pain management is a crucial factor that must be considered. The demands of opioid usage that increased regarding this phenomenon cause the increasing of drug side effect, impeding the rehabilitation process and causing longer hospital stay period that associated with increasing treatment cost and lowering satisfaction of the patients.[8,9]

The usage of multimodality of analgesia intra-operative and post-operatively has been reported recently.[10,11] Epidural, peripheral nerve block, and local articular injection has been reported to give a good result but associated with many side effects such as headache, hypotension, neurologic bladder, and contra lateral numbness.[12,13] Patient Control Analgesia (PCA) using morphine also reported to reduce post-operative acute pain but also associated with nausea and vomitting.[14,15] The usage of multimodality analgesia is rational considering that there is no any single analgesia that can cover all type of pain.[16]

Preemptive analgesia is a pharmacological therapy to cope pain sensation before operative procedure. The aim of this therapy is to prevent central pain sensitization through the inhibition of pain stimuli and afferent signaling from operation site.[17,18,19] A literature review by Katz[20] showed the benefit of preemptive analgesia in many surgical procedure. There was a 60% cases of decreasing pain sensation and lower post-operative analgesia usage. Many preemptive analgesia could be taken post-operatively, such as NSAID, NMDA, local anesthesia, and systemic antiepileptic drugs.[16]

The usage of oral analgesia as preemptive analgesia has been reported to give promising result.[21] Celecoxib and Pregabaline could be used as preemptive analgesia. Their synergic effect could inhibit pain stimuli in different ways. Celecoxib has a better analgesia effect with lower rate of side effect compared to ibuprofen, and pregabaline has similar analgesia effect with lower rate of side effect compared to gabapentine.[22,23] A study by Niruthisard et al. showed the combination of celecoxib and pregabaline taken 1 hour before TKA procedure capable in decreasing pain during motion and post-operative anxiety.[24] In spite of these promising effect, the research about repetitive dose of preemptive analgesia in TKA procedure has not been done until recently. The aim of this research is to compare the therapeutic effect of single dose and repetitive dose of combined celecoxib and pregabaline.

MATERIALS AND METHODS

All procedures undertaken in this study have been approved by The Ethical Committee of Faculty of Medicine Universitas Indonesia No.851/UN2.F1/ETIK/2015. Verbal and written informed consents were obtained before the study. The study was carried out in accordance of the approved guidelines.

The study design that was used in this study was double blind control clinical trial design. This study was executed from July 2015 to December 2016. Total 30 subjects of the study were collected by consecutive sampling from adults who underwent TKA procedure and fulfilled the inclusion criteria. The inclusion criteria are 55-80 years old patients who come to orthopaedic polyclinic, underwent TKA procedure, have osteoarthritis, and consumed pain killer and anti-inflammatory drugs routinely. The exclusion criteria are patients with psychiatric disorder, have history of renal disease, history of chronic neuropathic, have genu arthritis that caused by rheumatoid arthritis and infection., diabetic and obesity, coagulopathy, and patients with severe pain that needed immediate analgesia regimen.

All surgeries were done by one experienced orthopaedic surgeon. The tested subjects were allocated randomly into three groups, which are group 1 (taking single dose of celecoxib 400mg and pregabaline 150mg), group 2 (taking repetitive dose of celecoxib 200mg and pregabaline 75mg twice daily, since 3 days pre-operatively), and group 3 (taking placebo). All groups of subjects underwent same procedure of epidural anesthesia with 15-20mg bupivacaine 5% before TKA procedure. Two hours after the procedure, post-operative analgesia that consist of paracetamol 1000mg + PCA morphine 2mg/kg BW administration with maximal dose of 6mg/hr and 5 minutes interval were given.

The efficacy of preemptive analgesia among the groups were measured in post-operative follow up that consist of 4 parameters, which are total morphine consumption 3 days post-operative, VAS 0-24 hours, 25-48hours, 49-72 hours post operative, range of motion, and mobilization exercise. All the side effect of post-operative therapy were monitored and treated.

Outcome Parameters

Total Morphine Consumption. This is the main outcome parameter to measure the efficacy of the preemptive analgesia of combined celecoxib and pregabaline. In this study, morphine is given by patient control analgesia (PCA).

Post-operative Pain. The acute pain is measured and evaluated by Visual Analogue Scale every morning before the patients begin their rehabilitation program. This parameter is measured from the first day until the third post-operative day.

Knee functional outcome. Measured by knee range of motion. The measurement is done in the morning from the first day until the third post-operative day. The patient is asked to move the knee joint actively, and the knee angle is measured by goniometer.

Mobilization. The patient is expected to be able to do sitting motion on the first day, standing on the second day, and walking on the third day.

Statistical Analysis

The outcome of this research was counted as numerical variable that included total of morphine consumption, VAS, range of motion, and mobilization exercise. The differences among the three groups were measured within the first day until the third post-operative day.

Statistical analysis was performed with SPSS software version 20. The normality of distribution for numeric variables was assessed by Saphiro-Wilk test. According to normally distributed or not, the variables are presented as means with SD or medians with inter-quartile range (95%CI). The data will be tested using One-way ANOVA if the data were normally distributed, and tested with Kruskal-Wallis if it were not normally distributed. If there are Any significant difference found by one-way ANOVA, it then will be analyzed by Bonferroni post hoc test to assess the significance of each group.

RESULTS

Thirty subjects that mostly consist of more than 65 years old female were divided into three groups. Each group consist of ten randomized subjects. The characteristics of the patients can be seen in table 1.

No	Variable	Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)
1	Gender	Man (3) Woman (7)	Man (3) Woman (7)	Man (1) Woman (9)
2	Age (years)	66.1 ± 7.79	65.9 ± 5.82	68.2 ± 6.35

Total Morphine Consumption

On the third day post-operatively, the morphine consumption of all subjects from each group were being measured by PCA. There was a significant difference of total morphine consumption among the groups (p<0.001). The results of morphine consumption measurement can be seen on table 2.

Total Morphine Consumption (PCA) among the groups after underwent TKA procedure

	Group 1 (1 hr preemptive analgesia)	Group 2 (72 hrs preemptive analgesia)	Group 3 (Placebo)	p-value*
	N=10	N=10	N=10	
Morphine (PCA)	10.60(2.675)	9.90(1.524)	30.20(5.308)	<0.001

The data were normally distributed

The p-value was measured using ANOVA parametric test

The post-hoc Bonferroni test concluded a significant difference of total morphine consumption between the first and third group (p<0.001), between the second and the third group (p<0.001), but there was no significant difference between the first and the second group.

Post-Operative Pain

Post-operative pain was measured with VAS. The measurement was done on the first day until the third day. The VAS within each group was generally decreased from day-one until day- three. From this research, it was found that there were a significant differences of VAS comparison among the groups (p<0.001) on the first day, second day, and the third day. The third group showed higher score of VAS than the first and the second group.

VAS measurement among the groups after underwent TKA procedure that evaluated from the first day until the third day

	VAS D-1	VAS D-2	VAS D-3	p-value*
	N=10	N=10	N=10	
Group 1 (1 hr preemptive analgesia)	2 (2-3)	1 (1-2)	1 (1-2)	<0,001
Group 2 (72 hrs preemptive analgesia)	2.5 (2-3)	2 (1-2)	1.2 (1-2)	0,001
Group 3 (Placebo)	4(2-5)	3 (2-4)	3 (2-3)	0,001

The data were not normally distributed
The p-value was measured using Kruskal-wallis non-parametric test

The post-hoc Bonferroni test concluded a significant difference of total morphine consumption between the first and third group (p<0.001), between the second and the third group (p<0.001), but there were no significant differences between the first and the second group.

Knee Functional Outcome

The outcome was defined by the measurement of knee range of motion. In general, the range of motion in all groups was getting better from day-one until day-three. The results of this parameter were a little different from the previous parameters. It was found that there was no significant difference of ROM among all groups) on the first day (p=0.886), on the second day (p=0.131), and on the third day (p=0.011). Nevertheless, the clinical outcome showed a different result. The ROM were getting better significantly each day.

	ROM D-1	ROM D-2	ROM D-3
	N=10	N=10	N=10
Group 1 (1 hr preemptive analgesia)	15 (10-30)	60 (15-60)	90 (60-90)
Group 2 (72 hrs preemptive analgesia)	15 (15-20)	30 (30-60)	60 (45-90)
Group 3 (Placebo)	15(15-20)	30 (30-60)	60 (60-90)
p-value	0.886	0.131	0.011

The data were not normally distributed
The p-value was measured using Kruskal-wallis non-parametric test

Mobilization

The outcome was defined by the capability of doing motion on the first, second, and third day. Almost all of the subjects from each group can do sitting motion on the first day, standing motion on the second day, and walking motion on the third day. There was no significant difference among the groups (p=1.00)

Mobilization measurement among the groups after underwent TKA procedure that evaluated from the first day until the third day

	Motion D-1 (sitting) N=10	Motion D-2 (standing) N=10	Motion D-3 (walking) N=10	p-value*
Group 1 (1 hr preemptive analgesia)	9(90%)	8 (80 %)	10 (100%)	<0,001
Group 2 (72 hrs preemptive analgesia)	8 (80%)	7 (70 %)	7 (70%)	0,001
Group 3 (Placebo)	9 (90%)	7 (70%)	8 (80%)	0,001

The data were not normally distributed
The p-value was measured using Kruskal-wallis non-parametric test

DISCUSSION

Osteoarthritis are often involved in geriatric patients. The incidence are increasing by age and more often affected women than men.[25] These demographic characteristic are similar about the findings in this study. Because more than half subjects of TKA procedure come from late adult or geriatric patients that would rather have more complication rate, intensive evaluation are often needed in the usage of analgesia.[26,27] In this study, The usage of morphine has been found significantly lower in the groups that received preemptive analgesia regardless of the duration compared to the placebo group. These results are supported by the study that has been done by Lee et al.[28] and Huang Yu et al.[29] said that the usage of celecoxib (400mg) combined with pregabaline (150mg) given 1 hour prior to the TKA procedure were proven lowering the usage of morphine and post-operative pain. However, in this study we found that there was no significant difference whether the preemptive analgesia combination was given 1 hour or 72 hours prior to the procedure.

This study also use VAS to measure the efficacy of preemptive analgesia. We found that VAS in the groups that were taken preemptive analgesia was lower than the placebo group. This result was similar with the study that has been done by Buvanendran et al.[19] and Carmichael et al.[30] that said the using of repetitive dosage of celecoxib and pregabaline succeed in lowering

acute and chronic post-operative pain. Even in this study we did not measure the outcome of chronic pain among the groups, it was found that in general, there was a decreasing VAS score from day-one to day-three that significantly different from the group that used either single dose or repetitive dose of preemptive analgesia compared to placebo group. Another confounding such as racial, gender, and the method of VAS measurement should be considered in later study.

Rehabilitation program hold a significant portion in post-operative outcome of the patients. It has been reported that the early mobilization after TKA procedure gives a better outcome with lower morbidity and hospital stay period of the patients. Range of Motion is important to ensure early mobilization of patients. The fact that ROM is directly affected with pain conclude that lowering the post-operative pain with preemptive analgesia should increase ROM and early mobilization rate of the patients. In this study, ROM is proven to be increasing from day to day but we found that there was no significant difference of ROM between subjects that were given preemptive analgesia compared to placebo group. According to the study that has been done by Miner et al.[31] and Jacobsen et al.[32] the using of ROM as the parameter of TKA procedure outcome is still controversial. Their study reported that many factors like knee soft tissue, knee alignment, knee muscle strength, psychological condition, pre-operative ROM, and operative procedure determined the post-operative ROM. The result of our study supports the fact that ROM is not only affected by pain but also by multifactorial aspects that were not been studied in our research.

Preemptive analgesia also expected to permit the early mobilization of post-operative patients. With early mobilization, a complication like DVT could be avoided, besides with early mobilization the healing process and functional outcome of the patients are expected to be better.[33,34] In this study, it was found that there was no significant differences of mobilization period among the groups. Bade reported that pre-operative mobilization directly affected post-operative mobilization outcome. There are many factors that affect the post-operative mobilization such as age, comorbidity, muscle strength, and psychological factors. The result of our study supported the fact that patient's mobilization is not only affected by post-operative pain, and the possibility that preemptive analgesia only lowering static post-operative pain, not lowering the pain sensation during mobilization.

In our study, we also monitored the side effect of preemptive analgesia. And we found that the side effect were dose dependent and often emerge in prolonged using of celecoxib combination with pregabaline. Buvanendran[19] reported that the using of 300mg pregabaline 1 hour post-operatively has been followed by sedative, confusing, and dry mouth side effect. Lee et al.[28] in their study compare the using of 400mg celecoxib and 150mg pregabaline combination with 400mg celecoxib alone and found that the side effect were emerge in the combination group. In our study, we found that 2 subjects in first group, 1 subject in second group, and 1 subject in third group were having nausea.

CONCLUSION

Preemptive analgesia with the combination of celecoxib and pregabaline are effective in decreasing acute pain sensation after TKA procedure regardless of the dose and repetition. This combination preemptive analgesia also proven ineffective in decreasing pain sensation during motion. In this study, the using of combination preemptive analgesia didn't show any significant side effects.

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