Tramadol versus naproxen for pain relief in knee osteoarthritis: a pragmatic randomized controlled trial

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ABSTRACT

OBJECTIVE

To compare the efficacy in term of pain relief between tramadol and naproxen in patients with knee osteoarthritis.

METHODS

We randomly assigned patients with knee osteoarthritis at Khon Kaen Hospital, Thailand to either tramadol or naproxen. The primary endpoint was the pain dimension of Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC) at the end of two weeks, the higher scores indicating more severe symptoms. Our secondary endpoints included stiffness, and physical-function dimension of WOMAC scores as well as its total score, serum liver enzymes, creatinine, estimated glomerular filtration rate (eGFR), and their adverse events at the end of two weeks.

RESULTS

A total of 40 patients with knee osteoarthritis; 20 in the tramadol group and 20 in the naproxen group, were qualified for the intention-to-treat analysis. There were no statistically significant differences between the two groups regarding median change of pain of WOMAC score from baseline (-0.8; P=0.90). There was also no statistically significant difference in term of stiffness-WOMAC (0.4; P=0.95), physical function-WOMAC (-0.5; P=0.67), and the total score of WOMAC (2.0; P=0.97). There were no significant differences between the two treatment groups with respect to all secondary endpoints. The frequency of adverse events did not differ significantly between the two groups.

CONCLUSION

We found that the effect of pain relief of tramadol was similar to that of naproxen in knee osteoarthritis. (Thai Clinical Trials Registry (TCTR), 20180216003)

INTRODUCTION

Osteoarthritis (OA), a degenerative joint disease, is one of the most common forms of arthritis which affects around 10% of men and nearly 20% of women in elderly worldwide.[1] It leads to a major cause of disability in elderly.[2,3] As elderly population increases, its prevalence also increases.[4-6] In Thailand, 34.5-45.6% of the elderly suffer from osteoarthritis and knee is the main affected joint.[7-11] Many non-surgical modalities are used to control pain, including pharmacological treatment.[12,13] Oral non-steroidal and inflammatory drugs (NSAIDs) show benefit for pain controlling in osteoarthritis.[14-17] However, gastrointestinal adverse effects from NSAIDs use are also common especially in the elderly[18-19] as well as hepatic and renal toxicity.[20,21] Moreover, there is also the robust evidence of myocardial infarction for long-term use of the NSAIDs.[22-24] Naproxen is claimed to be the most safety NSAID.[25-27] Oral weak-opioid such as tramadol hydrochloride has an efficacy to relief pain in osteoarthritis with less of these side effects.[28,29] However, there is no trial directly comparing efficacy and safety of tramadol and naproxen in those with knee osteoarthritis. The aims of this study was to compare the efficacy in term of pain relief between tramadol and naproxen in patients with knee osteoarthritis.

METHODS

STUDY DESIGN AND OVERSIGHT

This pragmatic, double-blinded superiority randomized controlled trial was conducted as a single center study in Nong Waeng primary care unit, Khon Kaen Hospital, Thailand from October to November 2017.

The protocol was approved by Khon Kaen Hospital Institute Review Board (approval number: KE60043). The study complied with Declaration of Helsinki, October 2013. The protocol of the current study was registered with the Thai Clinical Trials Registry (TCTR), issued number was 20180216003.

RANDOMIZATION

In order to create proper randomization, this study used the permuted-block stratified randomized technique. Two stratified factors were age (<60 years or ≥60 years) and body mass index (BMI) (<23 or ≥23 kg/m^2), patients were randomly assigned into two groups, tramadol or naproxen, in a 1:1 ratio by computer generated using random allocation software, crossover of patient between group were not allowed.

ALLOCATION CONCEALMENT

To keep concealing, the randomized sequence was kept in a sealed opaque envelope. The envelopes were kept in the tray that was locked all the time at the study site. The envelopes were opened at the end of the study.

BLINDING

To keep blinding, tramadol and naproxen were revised into identical empty capsules (500 mg); tramadol was removed from their original capsule and repack in the new capsule and naproxen was ground and fill in the new capsule then contained in bottles. From this process, the patients, the doctors, and the pharmacists were unable to identify the treatment.

PATIENTS

Eligible patients were 20 years of age or older with a diagnosis of unilateral primary or secondary osteoarthritis of the knee defined by the American

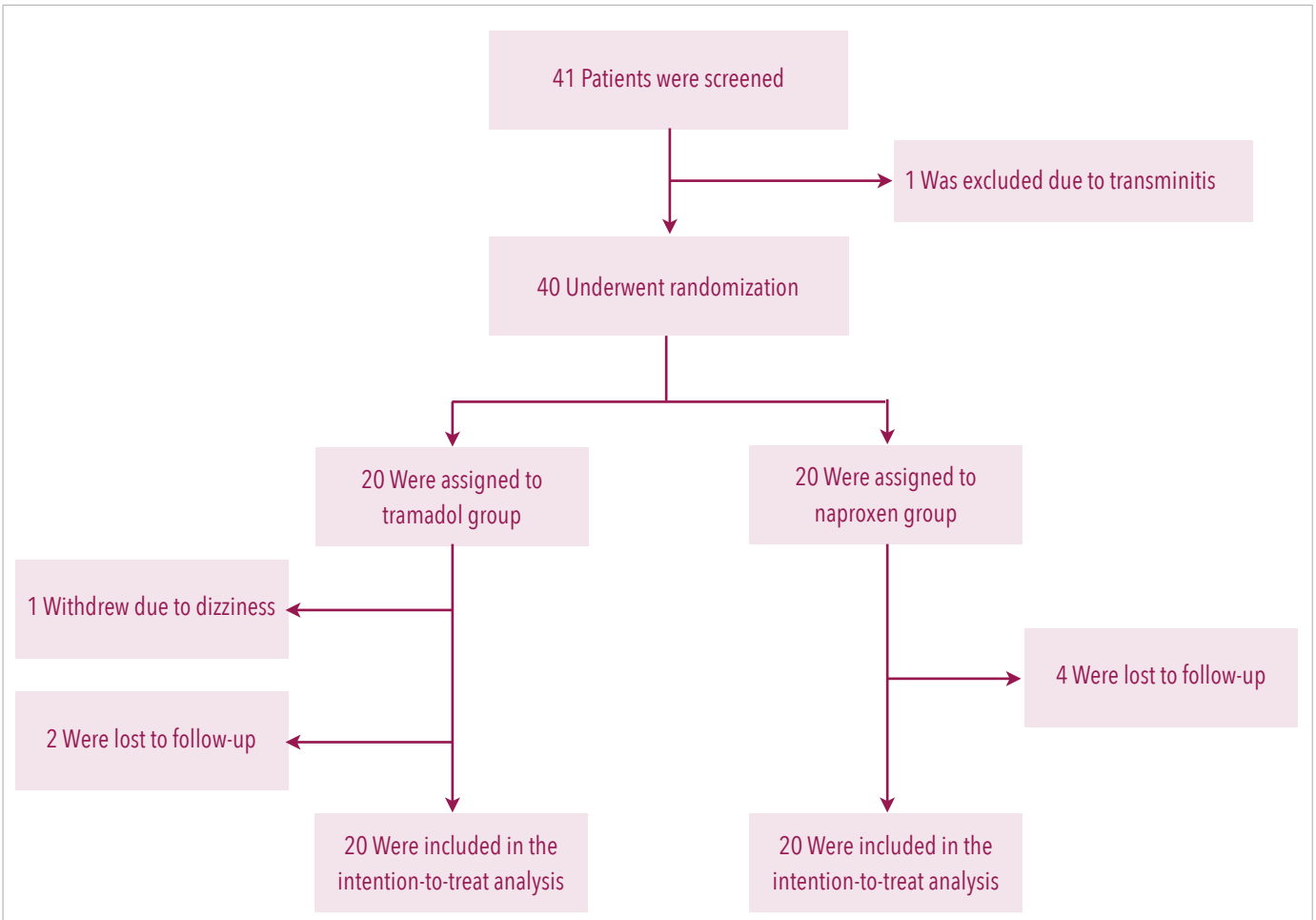

Figure 1. Flow of the study

College of Rheumatology criteria.[30] Patients were excluded if they had used of analgesic e.g., acetaminophen, topical NSAIDs, and topical methyl salicylate or anti-inflammatory drugs including NSAIDs and corticosteroids within one week before recruitment, diagnosed with rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, active gout, pseudogout, or other inflammatory disorder, inflammatory or post-infectious arthritis, previous major knee trauma (knee fracture, knee subluxation/dislocation, neurovascular injury), previous arthroscopic treatment or total knee replacement, previous drug allergy or intolerance for opioid or NSAIDs, history of atherosclerotic cardiovascular disease (ASCVD; stroke, coronary heart disease) or high risk for ASCVD, history of drug or alcohol abuse, history of peptic ulcer disease, from patient or recorded in the patient card, hepatic or renal impairment (AST or ALT above normal range, GFR below 30 ml/min/1.73 m^2),

diagnosis of severe persistent asthma or COPD (uncontrolled symptom with exacerbate everyday), platelet <100,000 mm^3, pregnancy or breast feeding by last menstrual period.

INTERVENTIONS

The patients were assigned into two groups; the intervention group received one tablet of oral tramadol (50 mg) for maximum two times per day, every 12 hours as needed for pain, no rescue medication was allowed and the control group received one tablet of oral naproxen (250 mg) with the same protocol. If they were unable to tolerate the adverse reaction or experienced drug allergy, they were advised to stop taking the given intervention immediately and notify researchers via given contact detail in the patient information sheet.

OUTCOME MEASURES

The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were used for measure three components of the outcomes: pain, stiffness, physical function of the patients, assessed using a visual analog scale (VAS) ranging from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively. Total score for pain dimension ranged from 0 to 50, stiffness dimension ranged from 0 to 20, physical-function dimension ranged from 0 to 150, summarized to overall score ranged from 0 to 220.31 In the present study, pain-WOMAC at two weeks after randomization was used as the primary outcome. The secondary outcomes were stiffness-WOMAC, physical function-WOMAC and total-WOMAC. Serum liver enzyme; aspartate transaminase (AST) and alanine transaminase (ALT), serum creatinine and estimated glomerular filtration rate (eGFR) at two weeks after randomization were also collected as the secondary outcomes. The safety outcomes were the frequencies of adverse reactions of the individual in the two-week period starting from the randomization. This included rash, nausea or vomiting, abdominal pain, diarrhea, constipation, somnolence, hematemesis, jaundice, and gross hematuria. Suspected of drug allergy were verified by the clinician and pharmacist at the study site. All adverse events were recorded and reviewed by the researcher before the final diagnosis.

DATA COLLECTION

Data regarding baseline characteristic of the patients e.g., sex, age, and body mass index (BMI) were collected at the screening session before randomization. For the outcome, every patient was given the log book containing tables of self-rating VAS, time to take medications, and their adverse reactions. Patients were asked to record baseline pain at the screening session and at two weeks after randomization. Patients were self-recording the time and their adverse event in the log book each time they took the medication. After the end of the study, their logbooks were collected by the researcher for outcome assessment. Blood samples were collected at the screening session and at two weeks after randomization.

STATISTICAL ANALYSIS

The sample size was calculated based on 5% and 20% of alpha and beta errors, respectively with mean difference of pain reduction between the two groups of 1.6 and pooled standard deviation (SD) of 8.1, the total sample size was 40, with the

Table 1. Baseline Characteristics of the Patients.

Characteristic	Tramadol (N=20)	Naproxen (N=20)
Age - yr		
Median	63.0	63.5
Interquartile range	58.3-72.0	54.8-71.0
Male sex - no. (%)	3 (15.0)	3 (15.0)
Body-mass index†	27.1±3.7	26.5±4.1
Primary osteoarthritis - no. (%)	18 (90.0)	15 (75.0)
Duration of osteoarthritis - yr		
Median	1.0	1.0
Interquartile range	0.4-2.8	0.5-2.0
WOMAC*		
Pain		
Median	29.2	28.1
Interquartile range	28.6-39.3	24.0-30.1
Stiffness		
Median	12.2	12.3
Interquartile range	10.0-15.6	11.0-14.3
Physical function		
Median	87.5	88.9
Interquartile range	72.5-108.2	85.6-103.5
Total score		
Median	128.4	102.0
Interquartile range	120.5-154.8	127.4-145.9
Liver function (U/L)		
AST		
Median	23.0	23.5
Interquartile range	21.3-24.0	21.3-25.0
ALT		
Median	20.5	21.0
Interquartile range	16.8-21.0	20.0-23.0
Creatinine (μmol/L)		
Median	0.74	0.74
Interquartile range	0.63-0.80	0.70-0.80

Table 1. (Continued)		
GFR (ml/min/1.73m^2)		
Median	85.8	85.8
Interquartile range	82.9-93.6	81.3-91.8

Plus minus values are means±SD

*Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were assessed with the use of a visual-analogue scale that ranged from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively.

additional allowance for up to 20% of the loss to follow-up. All data were cleaned before the analyses. The patients' baseline characteristics were presented with number and percentage for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. The primary and secondary outcomes were expressed in term of between-group median difference from baseline using Mann-Whitney U test, adverse events were described using frequency. A two-sided $P<0.05$ indicated statistical significance. All outcomes were analyzed based on an intention-to-treat basis.

RESULTS

PATIENTS

The patients were recruited during the period from October through November 2017 (Figure 1). All of them were screened at Nong Waeng Primary Care Unit. Of these, one was excluded due to transaminitis, 40 (98%) underwent randomization, 20 to the intervention and 20 to the control group. A total of 33 patients; 17 in the intervention group and 16 in the control group were complete at two weeks. Of these 40, more than three quarters were female, nearly all of them were older than 60 years old with high BMI and diagnosed with primary osteoarthritis for median one year. At baseline, they generally had moderate pain-WOMAC, and their baseline characteristics did not differ significantly (Table 1).

PRIMARY OUTCOME

At the end of the study at two weeks, we found that WOMAC scores were improved in both groups excepted the score on physical function-WOMAC in the intervention group (Figure 2). However, for the primary outcomes, median change of pain-WOMAC from baseline was not statistically different between the two groups (-0.8; P=0.90) (Table 2). We were also analyzed on per protocol basis, these analyses showed consistent non-significant differences between the two groups (-1.4; P=0.78).

SECONDARY OUTCOMES

The same pattern was also observed for the median change of stiffness-WOMAC from baseline between the two groups (0.4; P=0.95), median change of physical function-WOMAC from baseline between the two groups (-0.5; P=0.67), median change of total score-WOMAC from baseline between the two groups (2.0; P=0.97). No significant differences between the intervention group and the control

Table 2. Outcomes

Outcome	Group	Median		Between-Group Median Change from baseline*	P Value	Median		Between-Group Median Change from baseline†	P Value
		Baseline	2 Wk			Baseline	2 Wk		
WOMAC‡									
Pain	Tramadol	29.2	19.3	-0.8	0.90	31.9	25.0	-1.4	0.78
	Naproxen	28.1	19.0			21.9	16.4		
Stiffness	Tramadol	12.2	9.2	0.4	0.95	13.0	9.8	0.3	0.92
	Naproxen	12.3	8.9			11.3	7.8		
Physical function	Tramadol	87.5	72.5	-0.5	0.67	88.1	77.9	7.1	0.63
	Naproxen	88.9	74.4			86.8	69.5		
Total score	Tramadol	128.4	102.0	2.0	0.97	133.1	109.6	6.0	0.75
	Naproxen	128.7	100.3			123.2	93.7		
Liver function (U/L)									
AST	Tramadol	23.0	21.5	0	0.67	23.7	21.8	-1.4	0.71
	Naproxen	23.5	22.0			22.8	22.3		
ALT	Tramadol	20.5	17.5	0	0.69	19.6	16.6	-1.5	0.69
	Naproxen	21.0	18.0			22.5	21.0		
Creatinine (μmol/L)	Tramadol	0.74	0.75	0	0.57	0.72	0.72	-0.02	0.67
	Naproxen	0.74	0.75			0.76	0.78		
GFR (ml/min/1.73 m^2)	Tramadol	85.8	84.7	1.1	0.87	86.9	86.9	2.2	0.59
	Naproxen	85.8	83.6			84.5	82.3		

*From intention-to-treat analysis
† From per protocol analysis

group were found for the change from baseline in secondary outcomes at two weeks (Table 2), the median change in the AST was -1.5 in the intervention group and -1.5 in the control group, a difference of 0 (P=0.67); the median change in the ALT was -3.0 in the intervention group and -3.0 in the control group, a difference of 0 (P=0.69); the median change in the creatinine was 0.01 in the intervention group and 0.01 in the control group, a difference of 0 (P=0.57); the median change in the GFR was -1.1 in the intervention group and -2.2 in the control group, a difference of 1.1 (P=0.87).

ADVERSE EVENTS

The number of adverse events did not differ significantly between the two groups (five events in the intervention group and three events in the control group, P=0.451) (Table 3), no serious adverse events were found. The main adverse event was nausea and vomiting involving two patients each group and constipation which reported by three patients in the intervention group and one patient in the control group. One patient in the intervention group withdrew from our study due to dizziness symptom after taking the medication.

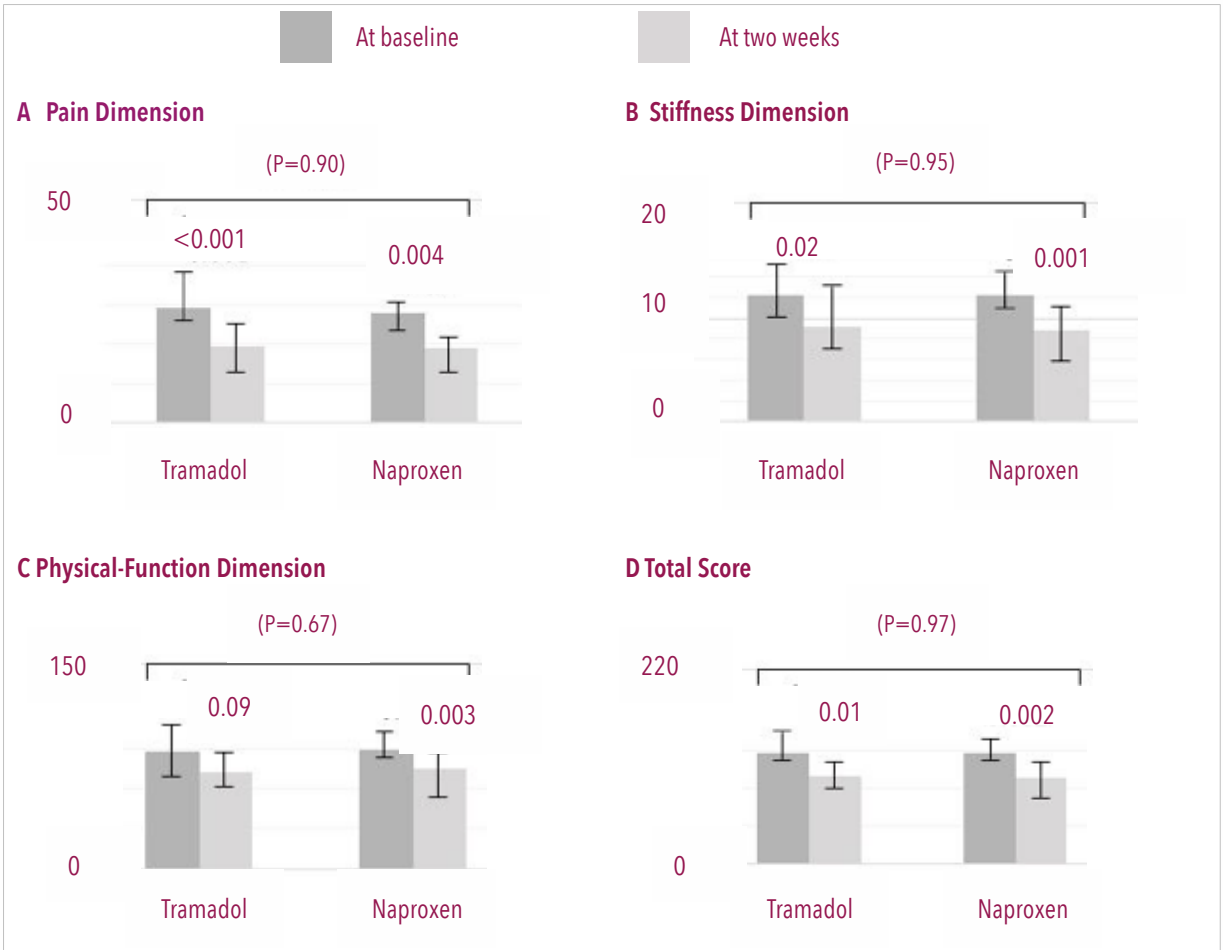

Figure 2. Median changes on WOMAC Score at baseline and after two weeks

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were assessed with the use of a visual-analogue scale that ranged from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively. Panel A is pain dimension, Panel B is stiffness dimension, Panel C is physical function dimension and Panel D is total score. I bars represent interquartile range. P values without brackets are for the change from baseline in each group. P values with brackets are for between-group differences at week 2.

DISCUSSION

MAJOR FINDINGS

In the present study, In the present study, tramadol was representative for weak-opioid and naproxen was for NSAID. Both drugs were analgesics used for mild to moderate pain in the analgesic ladder of world health organization (WHO).[32] We found that the effect of pain relief of tramadol, administered at a dose of 50 mg twice daily as needed for pain, was similar to that of naproxen at a dose of 250 mg. The results were similar regarding the secondary outcomes on stiffness, physical function, and total WOMAC score. Our findings also demonstrated no

Table 3. Adverse events

Event	Tramadol (N=17)	Naproxen (N=16)
	no. (%)	
Overall	5 (26.3)	3 (15.0)
Nausea or vomiting	2 (10.5)	2 (10.0)
Constipation	3 (15.8)	1 (5.0)
Rash	0	0
Abdominal pain	0	0
Diarrhea	0	0
Somnolence	0	0
Hematemesis	0	0
Jaundice	0	0
Gross hematuria	0	0

differences in serum liver enzymes, creatinine, eGFR, and adverse events. This can result in the same effect for pain relief in knee osteoarthritis.

For physical function-WOMAC, similar effects of the two interventions might be due to a short study period. Changes may require longer follow-up as the resolution of inflammation needs more times. For liver and renal outcomes, the AST, ALT, creatinine, and eGFR reflected pharmacodynamics of both drugs. No elevated liver and renal functions were observed explaining by their normal therapeutic range and short study time. Moreover, the patients only took the medication if pain occurred. In safety aspect, the main adverse event was constipation, mostly in the tramadol group, according to the normal gastrointestinal side effect of opioid, followed by nausea which was equally found in both groups.

COMPARISON WITH OTHER STUDIES

In our study, the interventions were able to demonstrate the positive effect on pain, stiffness, physical function of WOMAC even in the short period of time. This was similar to the findings of two previous systematic reviews.[28,29] However, we were the first to directly compare tramadol and naproxen. For magnitude of pain relieving, The effects of our intervention at a dose of tramadol of 100 mg per day were able to show the efficacy and these findings were found at two weeks, compared to other studies in the systematic review which titrate the intervention dosage from 50 to 400 mg per day and most of them measure the outcome on at least four weeks.[28] For the control group, the effect for pain relief at a dose of naproxen of 500 mg per day was also found, compared to previous studies in the systematic review which titrate the

dose equal to exceeding 1000 mg per day on at least 2-13 weeks.[15] In relation to the adverse events of the two interventions, we found no significant increase of serum liver enzymes and creatinine levels. However, no prior study examined these effects of the two interventions on the liver and renal functions. Nonetheless, the findings regarding nausea, vomiting, and constipation, the effects were found more commonly in the tramadol group, supported the findings found from the previous study.[34] The rate of side effect of constipation was closely from our study (15.8%) and a previous study (21%).[34] But for nausea or vomiting, our finding was half from the previous study (10.5% and 24.2% respectively).[34] Withdrew were from minor adverse events and from the loss to follow up similar to the previous studies.[33,34]

STRENGTH AND LIMITATIONS

To our knowledge, this is the first study with the direct comparison of tramadol and naproxen in those with knee osteoarthritis. However, our study held several limitations. Firstly, we did not vary dosages of tramadol and naproxen. Thus, the conclusion was solely based on the mentioned dosage in our study. Secondly, 2-weeks study period was far too short to investigate the outcomes such as physical functions. This required longer follow-up study to envisage the long-term effects of the interventions. Thirdly, we did not perform subgroup analysis due to the small number of the patients. A larger trial should be purposed. Finally, most outcomes were subjective, as the WOMAC score using VAS can be varied due to the patients' perception. Pain threshold was also subjected to be varied.

CONCLUSION AND IMPLICATION

We found that the effect of pain relief of tramadol was similar to that of naproxen in knee osteoarthritis as well as the adverse events. This implied the interchangeability of the two drugs. However, for a robust conclusion of the effects of tramadol and naproxen in knee osteoarthritis, a larger randomized controlled trial with various dosages of both drugs and a longer follow-up time should be conducted.

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COMPETING INTERESTS: This study has no competing on interest.

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