

Comparative evaluation of analgesic efficacy of tramadol and diclofenac-sodium in post-operative orthopedic patients

Rama Paudel^{1*}, Anjali Deka², Hemant Kumar Gupta³, Hari Prasad Nepal⁴

¹Department of Pharmacology, Universal College of Medical Sciences-Teaching Hospital, Bhairahawa, Nepal

²Department of Pharmacology, College of Medical Sciences-Teaching Hospital, Bharatpur, Nepal

³Department of Orthopedics, College of Medical Sciences-Teaching Hospital, Bharatpur, Nepal

⁴Department of Microbiology, Trinity School of Medicine, St. Vincent and the Grenadines

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***Correspondence to:**

Dr. Rama Paudel,
Email: paudelrama2015@gmail.com

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ABSTRACT

Background: Post-operative pain management is an important consideration in the orthopedic department. The purpose of this study was to compare the analgesic efficacy of tramadol with diclofenac sodium in patients with postoperative orthopedic pain.

Methods: A hospital based, prospective, observational study was undertaken in Department of Orthopedics for a period of one year. A group of 60 patients having post-operative pain intensity assessed as 6cm or more on a 10cm visual analogue scale (VAS) were assigned to receive either tramadol thrice a day (n=30) or diclofenac sodium thrice a day (n=30). Both drugs were administered parenterally for initial 24hr, then orally for next 96 hr. The primary efficacy outcome measures were pain intensity difference assessed at 2hr, 4hr, 8hr, 16hr, 24hr, 32hr, 40hr, 48hr, 56hr, 64hr, 72hr, 80hr, 96hr, 104hr, 112hr and 120hr using a VAS and sum of pain intensity differences assessed at 8hr, 24hr, 48hr, 72hr, 96hr and 120hr whereas secondary efficacy measures included maximum fall in pain intensity, number of patients who required rescue medication and their quality of sleep in the night.

Results: Mean pain intensity differences assessed on 10cm VAS were significantly better for tramadol group compared to diclofenac group at all the time points except 88 hr. Sum of pain intensity differences over 8hr, 24hr, 48hr, 72hr, 96hr and 120 hr for the tramadol group was significantly superior than diclofenac group. Maximum fall in pain intensity score was also significantly superior in the tramadol group as compared to the diclofenac group. However, no patients required rescue medication in either of the groups. Patient's quality of sleep improved with both drugs but tramadol produced significantly better quality of sleep every night than did diclofenac. Both the study medications produced effective analgesia and were well tolerated with no incidence of serious adverse effects throughout the study.

Conclusions: Tramadol has a more pronounced analgesic effect than diclofenac. Thus, tramadol can be considered as an effective alternative to traditional NSAIDs in the treatment of post-operative pain.

Keywords: Analgesic efficacy, Diclofenac, Post-operative orthopedic pain, Tramadol, VAS

INTRODUCTION

Pain is the most common clinical complaint and causes considerable human suffering.¹ Pain control is such an important factor that it has permitted surgery to progress enormously; however, postoperative pain still tends to be underestimated, is generally treated inadequately, and

therefore, is not assessed with regard to how it harms the patient and impedes successful recovery.² The clinicians do everything possible to eliminate postoperative pain without causing additional problems, such as respiratory or vascular depression, gastrointestinal and visceral motility disorders, coagulation anomalies, and drug tolerance and dependence.²

Despite the availability of a wide variety of analgesic drugs, routine management of postoperative pain remains a continuing challenge.³ Approaches to pain relief may differ depending on the type of surgery, the patient, and the drugs administered.² The best postoperative pain regimen is one that offers broad analgesic coverage, is easy to administer, and is safe.²

In the past, narcotics were used as strong analgesics as they were used in relieving severe acute or chronic pain.⁴ However, high dose of narcotics leads to side effects such as respiratory depression, apnoea, nausea, vomiting, itching and physical and mental dependence.⁴ Moreover, the use of high dose of bolus or continuous infusion of some narcotics, such as alfentanil, increase pain because of the fast absorption and tolerance.⁴

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for post-operative pain treatment.⁵ Among NSAIDs, diclofenac-sodium is widely used as a most efficacious agent.⁶ It has an analgesic, antipyretic and anti-inflammatory effects.⁷ Therefore, it could have an influence on fracture healing. The action of this drug is based on the inhibition of cyclo-oxygenase (COX) which converts the arachidonic acid that is set free from the cell wall into prostaglandin, prostacycline and thromboxane.⁷ However, NSAIDs have been reported to be associated with various complications such as upper gastrointestinal complication, platelet function inhibition, increase in peri-operative bleeding and nephrotoxicity in patients with and without pre-existing renal insufficiency.^{5,8}

The search for appropriate drugs to treat patients with moderate-to-severe pain has led to the development of tramadol hydrochloride.² It is a synthetic drug that offers interesting characteristics.⁹ The drug is a centrally acting aminocyclohexanol analgesic with complementary mechanisms including activation of μ - opioid receptors and inhibition of norepinephrine and serotonin reuptake.¹⁰ There is less evidence of drug dependence, respiratory depression and gastrointestinal disorders.¹¹

Though numerous studies have compared tramadol and diclofenac in post-operative pain treatment in various types of surgical procedures, comparative studies on their efficacy in post-operative orthopedic patients are very limited.¹²⁻¹⁵ Therefore, we aimed to conduct this study in post-operative orthopedic patients at College of Medical Sciences-Teaching Hospital (CMS-TH), Chitwan, Nepal.

METHODS

The study was a hospital based, prospective, observational study conducted during the period of one year (July 2012-June 2013) in the Department of Orthopedics at College of Medical Sciences-Teaching Hospital (CMS-TH), a tertiary care center located at Bharatpur, Chitwan, Nepal. Sixty patients who had undergone orthopedic surgery and fulfilled the inclusion criteria were included in the study (Table 1).

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients willing to participate in the study	Patients allergic to NSAIDs or opioids
Patients of both genders above 18 years	Pregnant women
Patients who have undergone orthopedic surgery	Patients with known alcohol or drug addiction or abuse
Patients weighing 50 to 80 kg	Patients receiving any other NSAIDs (except for the study medication)
Patients with pain intensity at rest of at least 6 cm on a horizontal 10 cm visual analogue scale (VAS)	Patients receiving CNS depressants or warfarin
	Patients with increased intra cranial pressure or head injury
	Patients weighing less than 50 kg or more than 80 kg
	Patients with history or suspicion of gastro duodenal ulcer and gastro intestinal (GI) bleeding
	Patients with cardiac, hepatic or renal insufficiency

A total of 30 eligible patients were selected in each of two groups. Each of the patients received either diclofenac-sodium or tramadol as an analgesic therapy. Both the drugs were administered parenterally for initial 24hr then, orally for next 4 days (Table 2).

Table 2: Dose and duration of study medication.

Drug	Dose and duration
Diclofenac-sodium	75mg IM thrice a day for 24hr followed by 50mg oral thrice a day for next 4 days
Tramadol	100mg IM thrice a day for 24hr followed by 50mg oral thrice a day for next 4 days

Pain assessment

Pain was assessed at different time points (2hr, 4hr, 8hr, 16hr, 24hr, 32hr, 40hr, 48hr, 56hr, 64hr, 72hr, 80hr, 96hr, 104hr, 112hr and 120hr) using a VAS, a 10cm line with the maximum pain indicated at the right hand side, and no pain at the left hand side (0-no pain, 2-mild pain, 4-tolerable pain, 6-distressfull pain, 8-severe pain, 10-totally disabling pain) (Figure 1).^{16,17}

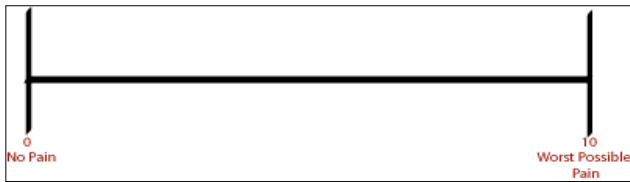


Figure 1: 10cm Visual Analogue Scale (VAS)

The pain level was also assessed from the quality of sleep every night using 5 point scale (0-no sleep, 1-frequent waking, 2-shallow sleep every night, 3-good sleep, 4-deep sleep) as was done by Pagliara et al.⁹

Efficacy criteria

The primary efficacy outcome measures were pain intensity difference (PID) assessed at different time intervals (0-2hr, 0-4hr, 0-8hr, 0-16hr, 0-24hr, 0-32hr, 0-40hr, 0-48hr, 0-56hr, 0-64hr, 0-72hr, 0-80hr, 0-88hr, 0-96hr, 0-104hr, 0-112hr and 0-120hr) and sum of pain intensity differences (SPID) for the first 8hr, 24hr, 48hr, 72hr, 96hr and 120hr) whereas secondary efficacy measures included maximum fall in pain intensity in each group, number of patients who required rescue medication and their quality of sleep in the night.^{3,9,18}

Rescue analgesia

If the patient complained of severe pain (>8cm on VAS), acetamenophen upto 650mg thrice a day was considered to administer to the patients needing rescue analgesia as was used by Beaulieu et al.^{3,19}

Adverse events

Any adverse effects of the drugs were noted.

Statistical analysis

Data were recorded on predesigned proforma, entered in a Microsoft Office Excel Worksheet. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 16.0. Data were expressed in mean, standard deviation (SD) and percentage. Student’s t test and chi-square test were performed to determine the significance. P value <0.05 was considered to be statistically significant.

All the patients were informed before surgery about the study and written informed consent was taken from them prior to the study commencement.

RESULTS

Demographic features of the study population

Among a total of 60 post-operative orthopedic patients in our study, the following demographic features were observed:

Gender wise distribution

In the present study, 33 patients (55%) were males and 27 (45%) were females. The gender wise distribution of patients in Tramadol and Diclofenac groups was uniform (P >0.05) (Figure 2).

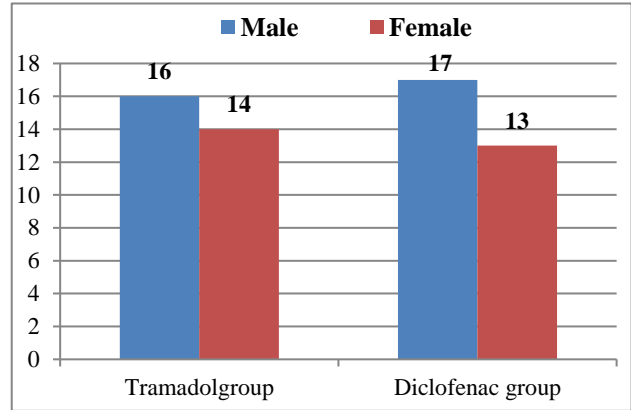


Figure 2: Gender wise distribution of patients.

Mean age of the patients in two groups

The patients in this study ranged from 19 to 65 years. Mean age of the patients in both the treatment groups is shown in Table 3.

Table 3: Mean age of the patients.

Variable	Tramadol Group (n=30)	Diclofenac Group (n=30)	P value
Age (year)	34.70±13.38	32.83±11.70	0.568*
*Not significant			

Mean weight of the patients in two groups

Weight of the patients ranged from 51-76kg. The mean age for each group is presented in Table 4.

Table 4: Mean weight of the patients.

Variable	Tramadol Group (n=30)	Diclofenac Group (n=30)	P value
Weight (kg)	61.33±7.71	61.16±7.53	0.933*
*Not significant			

Clinical diagnosis of the patients

The clinical diagnosis of the patients in each of two treatment groups is depicted in Table 5.

Majority of the patients had femur fracture (18.3%) followed by humerus fracture (15%).

Table 5: Clinical diagnosis of the patients.

Diagnosis	Tramadol Group (n=30)	Diclofenac Group (n=30)	Total (n=60)
Acetabulum fracture	1	0	1 (1.7%)
Bilateral nasal bone fracture	0	1	1 (1.7%)
Calcaneus fracture	1	2	3 (5.0%)
Femur and ulna fracture	0	1	1 (1.7%)
Femur fracture	8	3	11 (18.3%)
Humerus fracture	7	2	9 (15%)
Malleolus fracture	2	2	4 (6.6%)
Metatarsal fracture	0	1	1 (1.7%)
Navicular bone fracture	0	1	1 (1.7%)
Patella fracture	2	2	4 (6.6%)
Phalanges fracture	1	1	2 (3.3%)
Pubic fracture	0	2	2 (3.3%)
Radius and ulna fracture	0	2	2 (3.3%)
Radius and patella fracture	1	0	1 (1.7%)
Radius fracture	2	5	7 (11.7%)
Talus fracture	1	0	1 (1.7%)
Tibia and fibula fracture	1	3	4 (6.6%)
Tibia fracture	3	2	5 (8.4%)

Table 6: Comparison of mean VAS score between tramadol and diclofenac groups at different time points.

No.	Time (hour)	Mean VAS score (cm)		Mean difference	P value	95% Confidence interval	
		Tramadol group (n=30)	Diclofenac group (n=30)			LL	UL
1.	0 (Baseline)	6.90±0.49	6.70±0.53	0.20	0.131*	-0.06	0.46
2.	2	5.09±0.68	5.59±0.73	-0.49	0.009**	-0.86	-1.2
3.	4	4.43±0.52	5.00±0.68	-0.57	0.001**	-0.88	-0.25
4.	8	4.09±0.42	4.36±0.51	-0.26	0.035**	-0.50	-0.01
5.	16	4.21±0.55	4.54±0.48	-0.33	0.016**	-0.60	-0.06
6.	24	3.85±0.47	4.17±0.47	-0.32	0.011**	-0.56	-0.07
7.	32	3.77±0.44	3.99±0.38	-0.22	0.045**	-0.43	-0.01
8.	40	3.38±0.56	3.71±0.63	-0.33	0.037**	-0.63	-0.02
9.	48	3.30±0.52	3.58±0.49	-0.27	0.041**	-0.54	-0.01
10.	56	3.40±0.51	3.57±0.52	-0.17	0.196*	-0.44	0.09
11.	64	3.54±0.58	3.76±0.42	-0.22	0.090*	-0.48	0.03
12.	72	2.95±0.64	3.29±0.61	-0.34	0.039**	-0.66	-0.01
13.	80	2.93±0.59	3.23±0.56	-0.30	0.048**	-0.60	-0.01
14.	88	3.17±0.70	3.28±0.47	-0.11	0.482*	-0.42	0.20
15.	96	2.88±0.57	3.22±0.36	-0.34	0.009**	-0.59	-0.08
16.	104	2.77±0.75	3.13±0.55	-0.35	0.042**	-0.69	-0.01
17.	112	2.79±0.47	3.12±0.33	-0.33	0.002**	-0.54	-0.12
18.	120	2.48±0.59	2.88±0.59	-0.40	0.012**	-0.70	-0.09

*Not significant; **Significant (P<0.05); LL-Lower limit; UL-Upper limit

Pain assessment by visual analogue scale (VAS)

Mean pain intensity difference (PID)

At baseline, mean pain intensity score in the tramadol group was 6.90±0.49cm while in diclofenac group, it was

6.70±0.53cm. After drug administration, the VAS scores in each of the group is presented in Table 6.

The mean pain intensity difference assessed on 10cm VAS was significantly greater (P<0.05) for tramadol group compared to the diclofenac group at all the time points except 88 hr (Figure 3).

Sum of pain intensity difference (SPID)

In the tramadol group, the sum of pain intensity difference over first 8 hours after the study drug administration was significantly greater than in the diclofenac group. Similarly, sum of pain intensity difference over 24, 48, 72, 96 and 120 hours in the tramadol group was also significantly greater ($P<0.05$) in the diclofenac group (Figure 4).

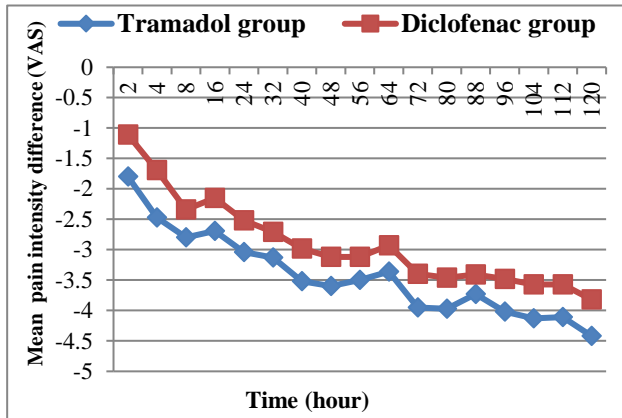


Figure 3: Mean pain intensity difference at each time points for 120 hours.

Maximum fall in pain intensity in each group

Over the 120 hr period (5 days), both the group reported maximum fall in pain intensity scores. Tramadol group

reported a maximum fall of 4.42 ± 0.70 cm in pain intensity score against a fall of 3.82 ± 0.68 cm in the diclofenac group, the difference being statistically significant ($P<0.05$).

Pain assessment by quality of sleep

The quality of sleep was assessed daily. For statistical analysis of the results in all patients, we compared the baseline (day 1) with days 2, 3, 4 and 5. Both the groups showed improvement in the quality of sleep. However, it was more significant in tramadol group compared to diclofenac group (Table 7).

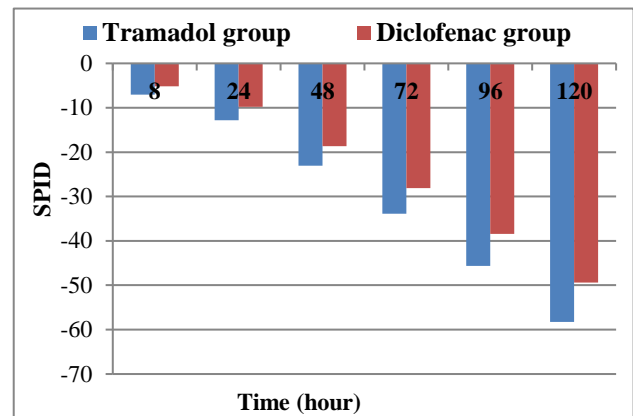


Figure 4: Sum of pain intensity difference (SPID) over different time points.

Table 7: Comparison of mean sleep score in tramadol and diclofenac groups.

SN	Day	Mean sleep score		Mean difference	P value	95% Confidence interval	
		Tramadol group (n=30)	Diclofenac group (n=30)			LL	UL
1.	1 (Baseline)	0.80±0.66	0.73±0.63	0.06	0.694*	-0.27	0.40
2.	2	1.53±0.50	1.26±0.44	0.26	0.035**	0.01	0.51
3.	3	2.16±0.37	1.80±0.61	0.36	0.007**	0.10	0.62
4.	4	2.46±0.62	2.16±0.46	0.30	0.039**	0.01	0.58
5.	5	3.00±0.52	2.46±0.57	0.53	<0.001**	0.24	0.81

*Not significant; **Significant ($P<0.05$); LL-Lower limit; UL-Upper limit

Rescue analgesia

Rescue analgesia was not needed for any patients under our study.

Adverse drug effects (ADE)

Two patients in tramadol group and three patients in diclofenac group reported minor adverse effects but serious adverse effects were not noted in this study (Table 8).

Table 8: Adverse effects noted in tramadol and diclofenac groups.

ADE	Number of patients presenting ADE		Total
	Tramadol group (n=30)	Diclofenac group (n=30)	
Nausea	1	1	2
Headache	1	0	1
Gastritis	0	2	2

DISCUSSION

In this study, patients were equally distributed ($P > 0.05$) between the two treatment groups with respect to demographic features and baseline characteristics.

All the admitted patients under our study were traumatic patients who had suffered from fracture of their bones. The most common presentation was limb fracture (femur fracture in tramadol group and radius fracture in diclofenac group), similar to the observation of Pagliara et al, who noticed that fracture of upper and lower limbs was the most common finding while studying the safety and efficacy of tramadol compared with diclofenac in traumatic musculoskeletal pain.⁹

Analgesic efficacy

Though the need for a placebo in trials of analgesic efficacy has been emphasized, in this study a placebo was not used because both medications are well established analgesics, and thus it was considered unethical to administer a placebo to patients known to require effective analgesia.^{20,21}

Many patients cannot tolerate oral medication or may experience compromised gastrointestinal absorptive function after surgery; hence there is a need for the parenteral formulations of study medication.³ Therefore, injectable forms of the tramadol and diclofenac were used in this study for the initial 24 hours followed by oral form of the drugs.

Numerous studies have compared tramadol with diclofenac in post-operative pain treatment in various types of surgical procedures.¹²⁻¹⁵ However, regarding their analgesic efficacy, there is no uniform agreement and their efficacy varies from study to study.

Courtney et al, conducted a single-blind (surgeon and research team member), prospective, randomized, controlled clinical trial in 64 patients, 11 years and older undergoing bipolar electro-cautery tonsillectomy.¹⁵ The patients received either oral tramadol or the oral diclofenac in the post-operative period. Pain scores for the 14 days were not significantly different between the oral tramadol and oral diclofenac groups.

Alwan et al, compared the effectiveness of paracetamol, diclofenac-sodium, and tramadol in controlling post tonsillectomy pain in 60 patients in their immediate post-operative period.¹² Tramadol and diclofenac sodium were found quite effective in controlling post tonsillectomy pain but there was no significant difference in analgesic efficacy between tramadol and diclofenac groups.

Joshi et al, compared analgesic efficacy of tramadol and diclofenac-sodium used as a rectal suppository in a prospective, randomized, single blind and hospital based study in 60 patients of ASA grade 2 posted for cesarean

section.¹⁴ Rectal suppository of diclofenac was found better alternative for postoperative analgesia in cesarean section as compared to tramadol.

In a double blind, randomized trial, the efficacy of tramadol hydrochloride with diclofenac sodium was compared in sixty patients who had undergone third molar surgery.¹³ The analgesic efficacy of the two drugs was equal except on day one when tramadol did better than diclofenac.

In a study of Cander et al, the effectiveness of diclofenac sodium, tramadol and metamizole sodium was compared in 100 patients who presented to the emergency room with traumatic injuries or fractures of the extremities.²² Tramadol was found to be the most effective analgesic among others.

A trial also showed an excellent results in the use of intramuscular tramadol for pain due to orthopedic and traumatologic surgery.² Similar to the trial, the pain-relieving action of tramadol in our study was quicker, as seen after the first dose and confirmed by patient assessments of pain after the operation. It has been reported that intramuscular tramadol 100mg, given postoperatively, has an analgesic effect equivalent to 30mg of pentazocine and is less potent than 10 mg of morphine.^{23,24}

In the present study, the differences in pain intensity from both treatment groups began to emerge from 2 hours after the first dose administration. Mean pain intensity difference assessed on 10 cm VAS was significantly greater in the tramadol group compared to diclofenac group at all the time points except 88 hr till the study period (i.e, upto 120 hr).

Sum of pain intensity difference (SPID) is an outcome measure that summarizes treatment response over a clinically relevant period.²⁵ In the present study, SPID was compared over 8, 24, 48, 72, 96 and over 120 hours. In the tramadol group, SPID observed at these time points was significantly greater than that was in the diclofenac group.

Moreover, in this study, tramadol also demonstrated superiority over diclofenac in terms of secondary efficacy variables like maximum fall in pain intensity score. Tramadol group reported a maximum fall of 4.42 ± 0.70 cm in pain intensity score against a fall of 3.82 ± 0.68 cm in the diclofenac group. Thus, though both of the drugs produced good analgesic effect in the patients, the analgesic efficacy of tramadol was found significantly superior to that of diclofenac. Our findings were in accordance with the observation of pagliara et al.⁹

Quality of sleep

Since lack of sleep can exacerbate pain, improvement of sleep is an important goal of pain management.²⁶ In the current study, both of the drugs showed an improvement

in quality of sleep in the study period, similar to the report of Pagliara et al, who assessed the quality of sleep in 120 patients randomized to receive either tramadol or diclofenac for relief of traumatic musculoskeletal pain and found that both the drugs showed improvements in quality of sleep.⁹ However, in contrast to their report where there was no statistical significance between the groups, we noticed that tramadol has shown significantly better quality of sleep every night than diclofenac.

Adverse effects

No serious adverse effects were observed in either of the treatment groups in this study. Only few minor side effects noted in our study may be due to an assessment of adverse effects over short period of our study time.

The major limitations of our study were the following:

- The study was an open label study. Double blind comparisons would give more valid result.
- The study had small number of research cases. Involvement of large number of cases would strengthen the statistical validity.

CONCLUSION

The results of this study indicate that tramadol thrice a day provides an effective and well tolerated relief from postoperative pain with better quality of sleep than diclofenac-sodium thrice a day. Hence tramadol can be considered as an effective alternative to traditional NSAIDs in the treatment of postoperative pain in orthopedic patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Review Committee of CMS-TH

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