Original Article

Comparison of Continuous Infusions of Ketorolac, Paracetamol and Parecoxib for postoperative pain management in orthopedic lower limb surgery undergoing spinal anesthesia

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Abstract

Background: the effect of three drugs; Ketorolac, Paracetamol and Parecoxib, on patients undergoing lower extremities orthopedic surgeries were compared regarding their analgesic effects.

Materials and methods: 140 patients undergoing lower extremities orthopedic surgery were assigned in four groups: 35 patients in each. In Parecoxib group, 20 mg of the drug was infused in 20 minutes and then 60 mg of Parecoxib was added to the pump and the rest of the pump was filled with normal saline up to100 ml. In Ketorolac group, 15 mg Ketorolac was infused in 20 minutes and then, 45 mg of Ketorolac was added into the pump and the rest of the pump was filled with normal saline up to 100 ml. In Paracetamol group 500 mg Paracetamol was infused in 20 minutes and then 1500 mg of Paracetamol was added into the pump and the rest of the pump was filled with normal saline up to 100 ml. In the placebo group, infusion pump was filled with 100 ml of normal saline.

Results: Pain score was not significantly different between Paracetamol and placebo groups. Six hours after operation, only the difference in the mean pain scores between Parecoxib and placebo groups was significant. However, 12 and 18 hours after operation, the mean pain score in Parecoxib group was significantly lower than Paracetamol and placebo groups ($p<0.05$). Nevertheless, 24 hours after operation, the mean pain score in Parecoxib and Ketorolac groups were significantly lower than placebo group ($p<0.05$).

Conclusion: The results showed that Parecoxib could be used for postoperative pain management in orthopedic lower limb surgeries. Ketorolac and Paracetamol could reduce morphine requirements in similar patterns.

Keywords: Ketorolac, Paracetamol, Parecoxib

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Introduction

Postoperative pain particularly for orthopedic surgery is one of the physicians concerns since it causes patient dissatisfaction, bed dependency, and makes delay in ambulating. This may cause late hospital discharge, followed by additional costs for patients and the hospital (1).

Postoperative pain causes physiologic and sometimes pathologic changes that include; high blood sugar levels in diabetics, electrolytes and fluid retention, tachycardia, hypertension, cardiac dysrhythmia, ischemia in susceptible patients, reduction of vital capacity, hypoventilation especially in abdominal and thorax surgery, 25-50% reduction in functional residual capacity (FRC), tachypnea, hypocapnia which leads to hypercapnia failure due to the patience's fatigue, ileus that can lead to nausea and vomiting, food intolerance and delay in oral intake and inhibition of cellular and humoral immunity which can increase the risk of infection (2).

Various methods are used to control pain, which include; use of various drugs (non-steroidal anti-inflammatory drugs (NSAIDS) such as intramuscular Ketorolac, suppository Indomethacin, opioids), patient-controlled analgesia (PCA) with intramuscular, or intravenous analgesics injection, and different blocks such as lumbar or thoracic epidural block (3). Opioid is regarded as the initial postoperative pain therapy (4), and in recent years, their combination with other drugs such as nonsteroidal anti-inflammatory drugs are concerned (5). So that, patients receiving non-opioid drugs for postoperative pain control have experienced approximately 18% fewer side effects (6).

In the hospital wards with minimal staff, tendency to use non-opioid analgesics has increased. Although some studies have been performed with NSAIDS intramuscular or bolus injections (7-9), but the comparison of drug infusion, especially in the aforementioned drugs, has not been reported. New non-opioid injectable drugs and lack of comparison of these three drugs together is the purpose of the study. Hence, comparing and evaluating them, effective drugs with fewer side effects can be recommended. This study aimed to compare the analgesic effect of intravenous infusion of Ketorolac, Paracetamol and Parecoxib for postoperative pain in orthopedic lower limb surgery under spinal anesthesia.

Methods

This study was a randomized double-blind clinical trial, comparing the control and treatment groups. The study was performed in Ayatollah Kashani (trauma center) and Al-Zahra Hospitals (Isfahan, Iran) on 140 patients undergoing elective orthopedic surgery of lower extremities who had inclusion criteria. The sample size was determined 35 patients in each group. The sample size was calculated using the sample size for compare the means, taking into account confidence level of 95% and test power of 80%, and the standard deviation of postoperative pain intensity according to the amount of postoperative pain intensity was estimated as 1.17. The minimum significant difference between the groups was considered as 0.8.

Inclusion criteria was patients age of 18 to 60 years' old who underwent elective lower limb orthopedic surgery, using spinal anesthesia with general conditions in class I, II ASA, the patient consented to participate in the study. The exclusion criteria were steroid consumption, drug intake having interfere to prescribed drugs in the study in the last 24 hours, under antidepressants, sleeping pills, or other interfering drugs, psychologically problems, drug abuse, renal disease, respiratory problems (asthma), liver disease, acute gastritis, high blood pressure, and uncontrolled coronary disease. On the conditions of developing severe dyspnea, gastrointestinal bleeding, respiratory symptoms requiring medical intervention, cardiac chest pain, change in the algorithm of prescribing analgesics for pain control and changing the anesthesia procedure, the patients were excluded.

After sufficient justification of the purpose of study, from all patients oral and written consent was obtained. Patients were randomly placed into four groups of Placebo, Paracetamol, Parecoxib and Ketorolac.

In the used random sampling method, the four first patients were assigned randomly to one of the groups, and subsequent patients were placed consecutively in the mentioned four groups according to the entrance order so that the sample size in each group reached 35 patients. In all four groups, infusion pump was connected with the speed of 4 ml per hour; all patients underwent spinal anesthesia with 3 ml of 0.5% Marcaine for surgery. After surgery and after

regression of sensory block at two sensory dermatomes, the infusion pump was connected by the first personas following: In Parecoxib group, 20 mg was infused in 20 min and then 60 mg of Parecoxib was entered into the pump and the rest of the pump was filled with normal saline up to100 ml. In Ketorolac group, 15 mg Ketorolac was infused in 20 min and then 45 mg of Ketorolac was entered into the pump and the rest of the pump was filled with normal saline up to 100 ml. In Paracetamol group 500 mg Paracetamol was infused in 20 min and then 1500 mg of Paracetamol was entered into the pump and the rest of the pump was filled with normal saline up to 100 ml. In the placebo group, infusion pump was filled with 100 ml of normal saline. Then, the related questionnaire was filled by patients with the guidance of the second person (except first person who was aware of the content of the drug inside the pump). If the patient had visual analogue scale (VAS) more than 3, morphine 0.05 mg/kg IV was used. As necessary, this dose could have repeated after 20 minutes. If the VAS was more than five initial doses was 0.1 mg/kg. Morphine dosage used, VAS, VRS, and the side effects were recorded in the questionnaire. The sedation levels were noted in Ramsay sedation scale basis. For vomiting, 10 mg intravenous metoclopramide was used. In resistance cases intravenous ondansetron 4 mg was used and if vomiting was continued, for more evaluation and treatments patient excluded from study. After data collection, SPSS 12 analyzed the data. Statistical tests used for data analysis included Chi-Square test, one-way ANOVA, and ANOVA analysis with repeated observations.

Ramsay Sedation Scale:

- anxious and agitated or restless, or both (anxious)
- co-operative, oriented, and tranquil (conscious); responds to commands only (respond to order)
- exhibits rapid response to light glabellar tap or loud auditory stimulus (rapid response)
- exhibits a sluggish response to light glabellar tap or loud auditory stimulus (delay Response)
- exhibits no response (no response)

Results

Among 201 studied patients, 53 ones were not eligible; eight patients refused informed consent and

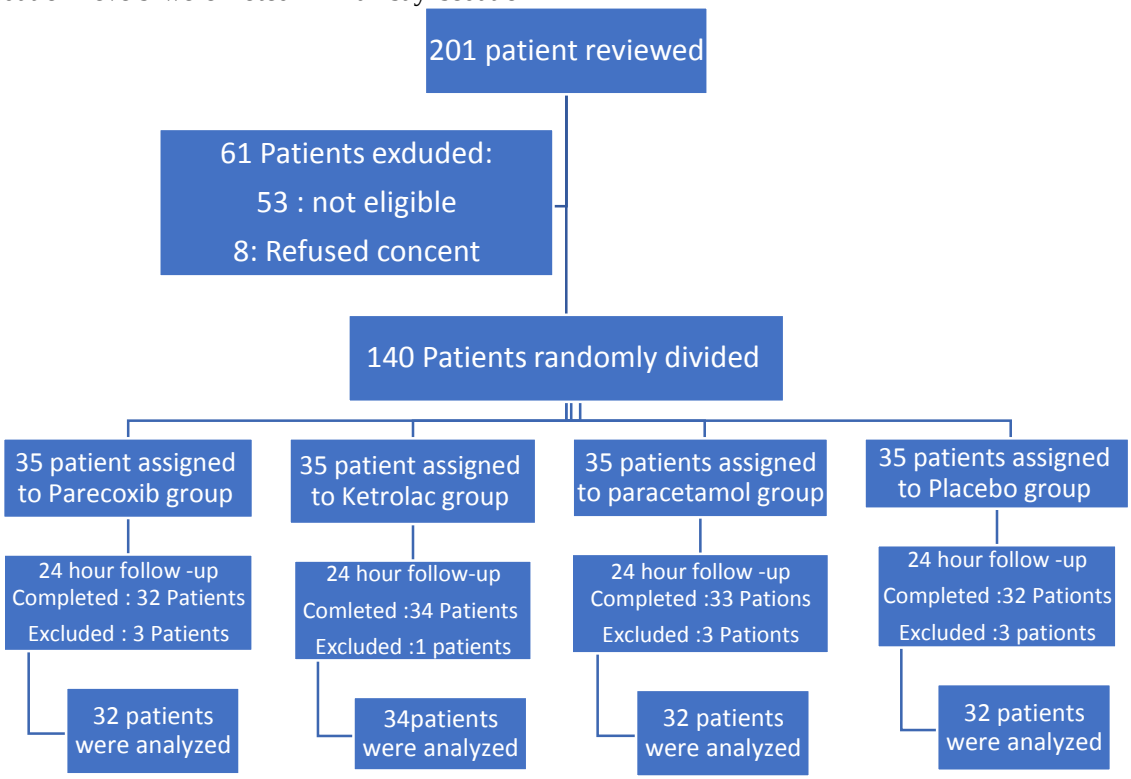

Figure 1. Patients who entered to the study, divided into the study groups and analyzed.

Table 1: Patients demographic and operative data

	Study groups				P-value
	Parecoxib (32)	**Ketorolac (34)**	**Paracetamol (32)**	**Placebo (32)**	
Age (year)	35.3 ± 12.1	36.2 ± 11.3	35.9 ± 12.2	35.4 ± 11.1	*0.99
Body weight (kg)	70.4 ± 13.5	70.3 ± 13.2	71.1 ± 13.3	71.2 ± 13.3	*0.98
Sex (male/female)	20.12	22.12	16.18	19.13	0.46#
Duration of surgery (min)	79 ± 9.3	81.5 ± 8	80.6 ± 10	80.2 ± 9.1	*0.71
Postoperative nausea	5(15.6)	7(20.6)	13(38.2)	11(34.4)	0.12#
Postoperative vomiting	2(6.2)	2(5.9)	6(17.6)	6(18.8)	0.22#
Gastric pain	1(3.3)	5(14.7)	2(5.9)	٠	0.08#

Data expressed as mean ± SD or number (percent)
P-values calculated by * one-way ANOVA and # Chi-square

did not enter to the study. Finally, 140 eligible patients were randomly assigned into intervention groups; then they were followed for 24 hours. During follow-up period, eight patients were excluded; eight patients due to side effects or other causes, and two patients did not desire to continue. One patient due to chest pain (ketorolac group) , four patient due to severe vomiting (a patient from Parecoxib group, a patient from Paracetamol group, 2 patients from placebo group) one patient from paracetamol group had hidden addiction , and two patient discharge earlier than 24 hour (a patient Parecoxib and a patient placebo). Finally, 32 patients in Parecoxib group, 34 patients in Ketorolac group, 32 patients in Paracetamol group and 32 patients in placebo group completed the study; in such a way that their data were analyzed (Table 1).

The mean age of the studied patients was 35.7±11.6 years. Seventy-seven (58.3%) were male and 55 (41.7%) were female. Table 1 shows patient's demographic and operative data. No significant differences were noted between intervention groups for mean of age, sex combination, weight, duration of surgery, and gastric pain ($p\geq0.5$). The frequency of postoperative nausea and vomiting in Paracetamol and placebo groups was more than Parecoxib and Ketorolac groups but was not significantly different ($P\geq0.5$).

Pain score measured by VAS among groups was compared at time points and results are shown in table 2. At baseline, the mean of pain score was not significantly different among groups ($p>0.05$). Between Paracetamol and placebo groups pain score was not significantly different at any time point. In Ketorolac group, pain score in hours 6, 12 and 18 was similar to placebo. At hour 6, only the difference in the mean of pain between Parecoxib and placebo groups was statistically significant. At hours 12 and 18, the mean of pain score in Parecoxib group was significantly lower than Paracetamol and placebo groups. At hours 24, the mean of pain score in Parecoxib and Ketorolac groups was significantly lower than placebo group (Figure 1).

Figure 2 shows the frequency of pain intensity measured by VRS among groups at time points. Accordingly, there was no significant difference among groups at baseline. At hours 6, 18.8% of patients in placebo group reported "severe pain" whereas in other groups "severe pain" was not reported ($p=0.003$). In addition, the frequency of pain intensity at hours 12 and 18 was significantly different among groups; "painless" was more frequent in Parecoxib group compare to other groups. At hours 24, painless was more frequent in Parecoxib group compare to other groups but the difference in frequency of pain levels among groups was not statistically significant.

Based on the results, the frequency of conscious

(grade two Ramsay sedation scale) at hours 6, 12 and 24, was more than other levels and in hour 18, the frequency of "rapid response" (grade four Ramsay sedation scale) was more than other levels. The hour 18 in most cases was at mid night and later. Totally, the frequency of sedation levels among groups at time points was similar and no significant differences were noted among groups ($p>0.05$). Figure 3 shows the results in comparison of the frequency of sedation levels among groups at time points.

The overall Morphine request mean in placebo group was significantly more than other groups. The mean of Morphine consumption in placebo group was 26.3 mg whereas in Parecoxib, Ketorolac and Paracetamol groups were 8.9, 11.9 and 14.7 mg, respectively. In addition, the difference between Parecoxib and Paracetamol groups was statistically significant. However, the differences between Ketorolac group with Parecoxib group or Paracetamol group was not statistically significant (Figure 4).

Discussion

One of the most important factors for early hospital discharge and mobilization of patient is adequacy of postoperative analgesia (10). Using of non-opioid analgesics in patients after surgery is important in reducing postoperative pain and opioid requirements. In this study, we investigated the influence of Parecoxib, Ketorolac and Paracetamol on postoperative pain and opioid consumption in patients underwent orthopedic surgery under spinal anesthesia. Our findings indicate that in compare to placebo, the intravenous infusion of Parecoxib significantly reduces pain in the first 24 hours after the surgery but decrease of pain intensity after administration of Ketorolac or Paracetamol was not significantly more than placebo.

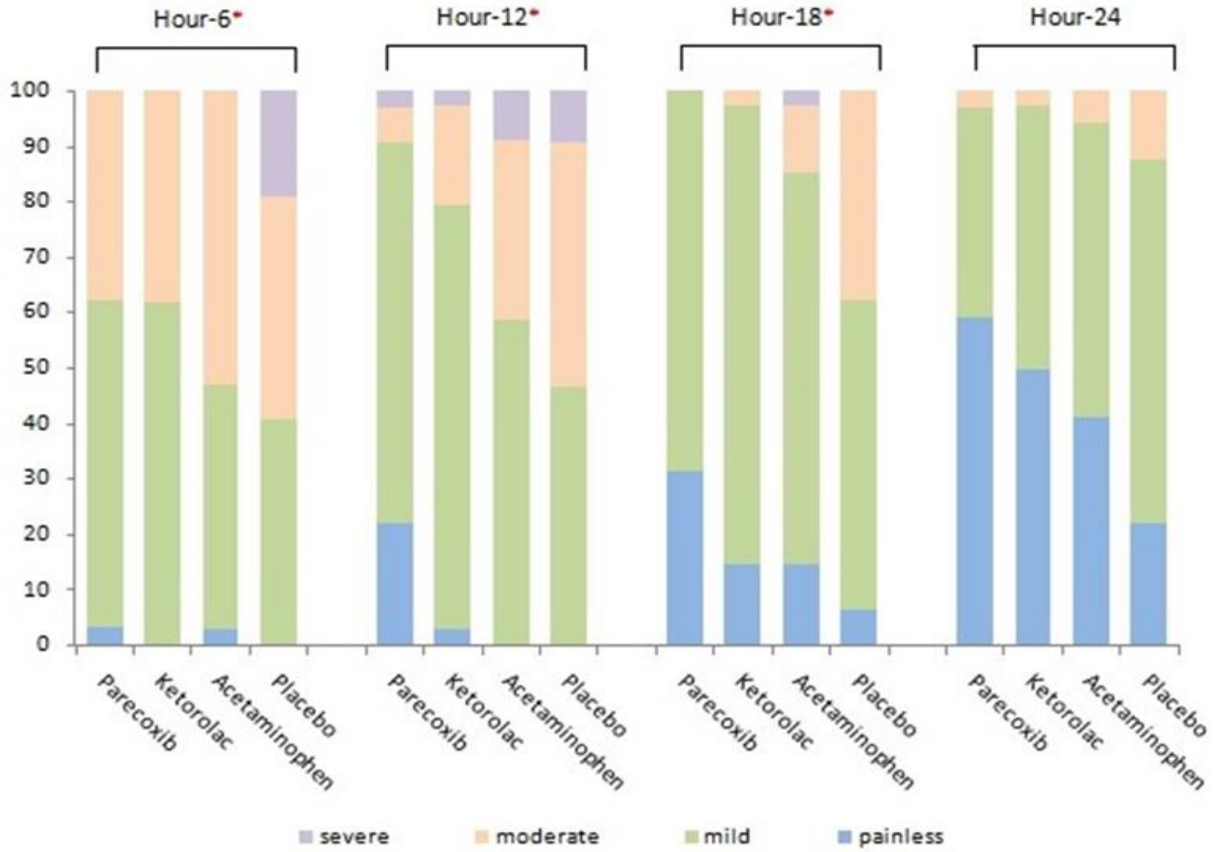

Figure 2. Comparison of pain level by verbal rating scale of among study groups at time point. The difference in pain was statistically significant among groups at hour 6, 12 and 18 ($P<0.05$).

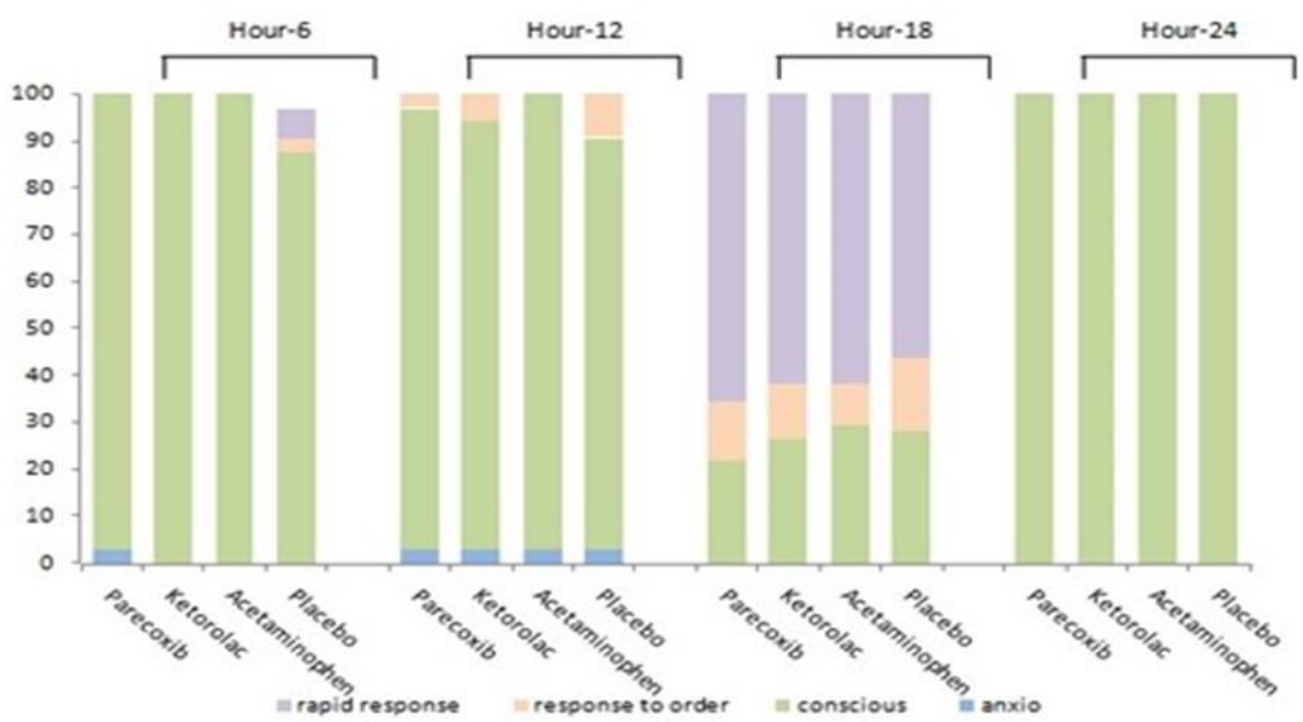

Figure 3. Comparison of the frequency of sedation level among study groups at time points. The difference in sedation levels was not statistically significant among groups at time points (P > 0.05). Equivalency to Ramsay sedation scale: anxious = 1, conscious= 2, respond to order =3, rapid response=4).

The comparison between Parecoxib and Ketorolac in some had different findings. Two studies compared the efficacy of intravenous 30 mg of ketorolac and intravenous 40 mg of Parecoxib at induction. First study by Ng et al, showed that in the first hour after laparoscopic sterilization Parecoxib at induction of anesthesia was less effective than Ketorolac (11). Other study by Siribumrungwong et al, reported that postoperative pain reduction in both the Ketorolac and Parecoxib was significantly better than

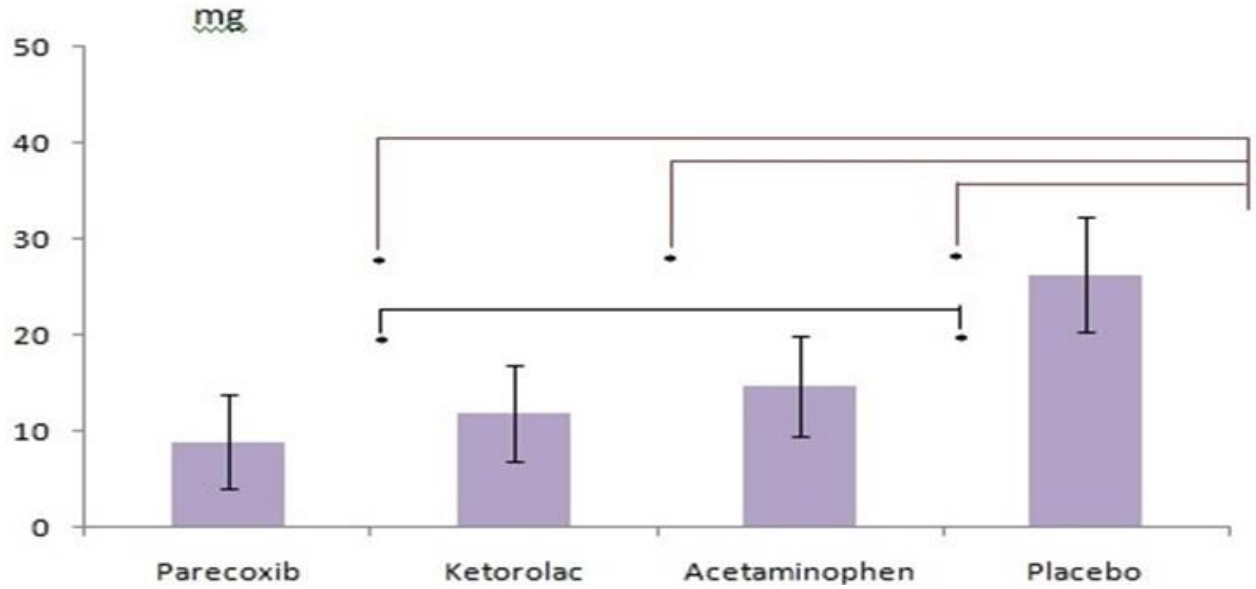

Figure 4. Morphine consumption (mg per 24 h) after Parecoxib, Ketorolac, Paracetamol, or placebo for postoperative analgesia. *P-values <0.05.

the placebo group but the pain scores of between Ketorolac and Parecoxib at any time points were not different (3). Our study showed that Ketorolac and Parecoxib was better than placebo and in contrast to these two studies in our study Parecoxib was more effective than Ketorolac in the first 24 hours after surgery for pain management. The differences between these findings might be explained by the difference in surgeries and the pharmacokinetics of Parecoxib and Ketorolac. Duration of surgeries in Ng A, et al, study (11) was shorter than our study, in our study was shorter than Siribumrungwong et al, study were (3).

In some randomized trial, Paracetamol was evaluated in compare to Parecoxib. In Gehling et al, study 8 and 24 h after surgery Parecoxib provides superior analgesia compared with placebo or Paracetamol (12). Gupta et al, in a randomized trial have evaluated the efficacy of postoperative intravenous Paracetamol and Parecoxib undergoing elective surgery and reported that pain score was significantly less in Parecoxib group at rest compared to Paracetamol group (13). Although, surgeries procedures were different but similar to other studies, our findings show the better effect of Parecoxib compare to Paracetamol in postoperative pain alleviation.

In a meta-analysis of randomized trials (14), the effect of perioperative single dose of Ketorolac to prevent postoperative pain was assessed and their findings showed that, overall, 24 hours' pain score did not significantly reduce compared with placebo like the present study. However, they reported that some trials showed that neither 30 nor 60 mg of Ketorolac is associated with a statistically significant reduction of 24 hours' pain, which was dissimilar to our study. The differences between our findings and other study can explain by different techniques whereas we used postoperative intravenous infusion of 60 mg ketorolac but other noted studies used pre-operative or intra-operative single dose of Ketorolac.

The other results of the present study proved that Parecoxib, Ketorolac or Paracetamol significantly reduce total morphine requirements during 24 hours after surgery. Parecoxib was reduce total Morphine requirements compare to Ketorolac or Paracetamol but was significantly more effective than Paracetamol. Similar to our results, several randomized controlled trials after Parecoxib use for patients after thyroid surgery, total hip or knee arthroplasty, hysterectomy and laparoscopic cholecystectomy reported a significant reduction in postoperative opioid consumption (12, 14, 15). In addition, similarly, Oliveira et al. in their meta-analysis showed that, overall, ketorolac significantly reduced postoperative opioid consumption compared with placebo (14). In contrast to our results, Siribumrungwong et al., did not found significant difference between Parecoxib, Ketorolac and placebo for total morphine requirements during 24 hours after surgery. Dissimilarity between our findings and Siribumrungwong et al. (3) findings in total morphine requirements can be explain by the different in time of injection and duration of surgery, whereas in Siribumrungwong et al. study drugs were injected around 30 minutes prior to incision and duration of surgery in this study was longer than our study.

Conclusion

We compared the clinical efficacy among Parecoxib, Ketorolac and Paracetamol for postoperative pain management. We found that the pain score and the total dose of morphine requirement in the Parecoxib treatment group were lower than that in Ketorolac, Paracetamol and placebo groups. Therefore, our study revealed that Parecoxib in conjunction with opioids can be used for postoperative pain management and Morphine requirement can be reduced same as Ketorolac as and more than Paracetamol.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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