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Effects of preemptive analgesia in laparoscopic cholecystectomy: a double-blind randomized controlled trial

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Abstract
Background This study aimed to investigate the effect of preemptive etoricoxib compared with placebo in laparoscopic cholecystectomy.
Methods This randomized, double-blind, placebo-controlled study enrolled 120 patients requiring elective laparoscopic cholecystectomy. The patients were randomized to receive either etoricoxib 120 mg plus diazepam or placebo plus diazepam. Postoperatively, the visual analog score (VAS) for pain, the rescue morphine requirement, and the side effects were recorded.
Results Between February 2006 and September 2007, 120 patients were enrolled in the study. The demographic data between two groups were similar except for mean age. The mean age of the placebo group was younger ($p = 0.007$). There were no significant differences in bleeding tendency rating scores, duration times between fentanyl and rescue morphine, number of rescue morphine doses, or length of postoperative hospital stay. But the number of oral analgesic drug usages was significantly less in the etoricoxib group ($p = 0.006$). The postoperative VAS was lower in the etoricoxib group at hours 10 ($p = 0.023$), 14 ($p = 0.045$), and 26 ($p = 0.011$), and the average VAS also was significantly less in the etoricoxib group ($p = 0.013$). The two groups did not differ significantly in terms of postoperative shoulder pain ($p = 0.065$). According to the verbal rating scale, the incidence of postoperative nausea and vomiting did not differ significantly between the two groups ($p = 0.797$), nor did the drug side effects or treatment complications.
Conclusion The authors recommend using etoricoxib as a preemptive analgesia to reduce postoperative pain after laparoscopic cholecystectomy.

Keywords Laparoscopic cholecystectomy · Preemptive analgesia · Etoricoxib

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Since the first laparoscopic cholecystectomy was reported in 1987 [1], this technique has been accepted worldwide due to its association with less pain than caused by standard open cholecystectomy. Some centers have adopted this operation as outpatient surgery. Nevertheless, pain is both the most frequent complaint and the most common cause of delayed discharge after surgery [2, 3]. From our experience, moderate to severe pain develops in some cases, especially 6 to 12 h postoperatively.

Apfelbaum et al. [4] surveyed 250 U.S. adults who had undergone a recent surgical procedure and showed that approximately 80% of patients experienced pain after surgery. Of these patients, 86% had moderate, severe, or extreme pain. Additional efforts are required to improve patients' postoperative experiences.

There has been considerable intervention using preemptive analgesia since Wall [5] raised the possibility that pain after surgery might be reduced by preventing intraoperative nociceptive impulses from reaching the spinal cord. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclooxygenase enzymes and decrease peripheral

and central prostaglandin production. These properties would seem to make NSAIDs ideal for use preemptively, in which analgesia is administered before unpleasant stimuli such as surgery, with the expectation that reduction in peripheral and central sensitization will lead to a decrease in pain [6].

We studied the effects of preemptive etoricoxib compared with placebo in laparoscopic cholecystectomy.

Materials and methods

This randomized, double-blind, placebo-controlled study obtained the approval of the local ethics committee. Informed consent was obtained from the patients at least 24 h before their operation. Healthy American Society of Anesthesiology (ASA) 1 and 2 patients ages 18 to 75 years who required elective laparoscopic cholecystectomy were eligible for enrollment in the study. The exclusion criteria ruled out patients with acute preoperative pain other than biliary colic; chronic pain treatment; advanced renal disease, heart failure, or fluid retention; use of preoperative NSAIDs or opioids within 24 h of the scheduled operation; a known hypersensitivity to NSAIDs; or pregnancy. Procedures converted to laparotomies and patients who underwent any surgical procedure in addition to laparoscopic cholecystectomy also were excluded.

On the day of surgery, eligible patients were randomized to receive etoricoxib 120 mg plus diazepam 0.2 mg/kg or placebo plus diazepam 0.2 mg/kg about 1 h before surgery based on a block of four randomization scheme from hospital pharmacists not involved with patient care or data collection,. Balanced anesthesia was introduced using intravenous thiopental (5 mg/kg), intubation with succinylcholine (1–2 mg/kg). Anesthesia was maintained with nitrous oxide (4 l/min) in oxygen (2 l/min), halothane (0.5–1%), fentanyl (1 μg/kg), and pavulon (0.8 mg/kg).

The operations were performed by the same group of surgeons using the same number, sizes, and sites of trocars. Pneumoperitoneum was maintained with carbon dioxide at 14 mmHg. Complications during surgery such as gallbladder perforation, visceral damage, bowel injury, and bleeding were noted. The surgeons also noted bleeding tendency rating scores of 0 (none), 1 (mild), and 2 (significant). The gallbladder was extracted via the umbilical entry port. No further opioid analgesia or local anesthetic infiltration was administered before the end of surgery. All patients received ondansetron 4 mg intravenously at the end of surgery.

After surgery, the neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg, and the patients were extubated when adequate spontaneous ventilations were established. The research nurse recorded the pain score at rest by visual analog score (VAS) every hour for the initial 6 h and then every 4 h for the next 18 h. Morphine 0.05 mg/kg was administered intravenously by a staff nurse as a rescue analgesic at the patient's demand or at a VAS of 3 or more. The total rescue morphine requirement over 24 h by each patient was recorded.

The side effects included nausea, vomiting, respiratory depression (respiratory rate ≤ 8 breaths/min or oxygen saturation $< 90\%$ without oxygen supplementation), vertigo ataxia, somnolent visual disturbance, lightheadedness, and headache. If indicated, side effects were treated as required. For example, in case of nausea/vomiting, metoclopramide was given.

The data included abdominal and trocar-site pain rated by VAS (0–100 mm); shoulder pain indicated by a numeric rating score of 0 (no pain), 1 (mild to moderate pain), or 2 (severe pain); nausea and vomiting assessed by a verbal rating scale of 0 (none), 1 (nausea), 2 (nausea with vomiting), or 3 (repeated vomiting ≥ 2 times/h); and evidence of epigastric pain, gastrointestinal bleeding, and wound bleeding during the first 24 h. After 360 min postoperatively, if the pain score was 3 to 6, pain control was administered by oral paracetamol, with two tablets of codeine (15 mg) given as needed every 4 to 6 h.

Data analysis

The sample size for this study was calculated aiming at 80% power to show a 30% reduction in morphine consumption with a 5% significance level. Demographic data were analyzed using chi-square and Fisher's exact test for categorical data. Student's t test and the Mann–Whitney U test were used for continuous data. A p value less than 0.05 was considered statistically significant.

Results

Between February 2006 and September 2007, 120 patients were enrolled in the study. We excluded one case because of conversion to open cholecystectomy, leaving 119 cases for the analysis. Of these patients; 60 received etoricoxib, and 59 received placebo. The demographic data were similar between the two groups except for the mean age, which was younger in the placebo group ($p = 0.007$) (Table 1).

We found no significant differences in bleeding tendency rating scores, duration times between fentanyl and rescue morphine, number of rescues by morphine, or length of postoperative hospital stay. However, the number of oral analgesic drug usages was significantly less in the etoricoxib group ($p = 0.006$) (Table 2).

Table 1 Baseline characteristics

Characteristics	Etoricoxib ($n = 60$)	Placebo ($n = 59$)	p value
Mean age (years)	53.6 ± 11.7	47.5 ± 12.6	0.007
Gender (M:F) (%)	31.7:68.3	37.3:62.7	0.519
Mean operative time (min)	52.9 ± 20.4	58.4 ± 21.8	0.161
Gallbladder perforation: *n* (%)	16 (26.7)	10 (16.9)	0.200
Visceral damage: *n* (%)	0	0	–
Bowel injury: *n* (%)	0	0	–

Table 2 Intra- and postoperative drug usage

Drug usage	Etoricoxib	Placebo	p value
Duration between fentanyl and rescue MO (min)	142.9 ± 46.6	146.5 ± 36.6	0.647
No. of rescue MO (dose)	0.9 ± 0.7	1.2 ± 0.9	0.117
Tablets of paracetamol consumed in hospital (dose)	0.2 ± 0.5	0.5 ± 0.8	0.006
LOS (days)	1.0 ± 0.1	1.1 ± 0.3	0.147

MO morphine, *LOS* hospital length of stay

Values are mean ± standard deviation

The postoperative VAS scores were lower in the etoricoxib group at hours 10 ($p = 0.023$), 14 ($p = 0.045$), and 26 ($p = 0.011$), and the average VAS score also was significantly lower in the etoricoxib group ($p = 0.013$) (Table 3). For postoperative shoulder pain, we found no significant difference between the two groups ($p = 0.065$) (Table 4).

The incidences of nausea and vomiting by the verbal rating scale showed no significant difference between the two groups ($p = 0.840$) (Table 5). Drug side effects (Table 6) and complications of treatment (Table 7) also did not differ significantly between the two groups.

Table 3 Postoperative visual analog scale (VAS) assessment

VAS	Etoricoxib	Placebo	p value
At hour 1	4.9 ± 2.8	5.3 ± 3.3	0.593
At hour 2	3.3 ± 1.9	3.7 ± 2.7	0.395
At hour 3	3.0 ± 1.8	3.3 ± 2.2	0.374
At hour 4	2.7 ± 2.2	3.1 ± 2.1	0.234
At hour 5	2.3 ± 1.8	2.7 ± 2.1	0.352
At hour 6	2.3 ± 2.1	2.5 ± 1.5	0.097
At hour 10	1.7 ± 1.6	2.4 ± 1.8	0.023
At hour 14	0.8 ± 1.3	1.4 ± 1.7	0.045
At hour 18	1.4 ± 1.7	1.7 ± 1.8	0.331
At hour 22	2.0 ± 1.8	2.6 ± 2.2	0.271
At hour 26	1.2 ± 1.2	2.4 ± 1.7	0.011
Average	2.4 ± 1.1	2.9 ± 1.2	0.013

Values are mean ± standard deviation

Table 4 Postoperative shoulder pain assessment

Shoulder pain	Etoricoxib *n* (%)	Placebo *n* (%)	p value
No	37 (61.7)	26 (44.1)	0.065
Yes			
Mild to moderate	19 (31.7)	31 (52.5)	
Severe	4 (6.6)	2 (3.4)	

Table 5 Incidence of postoperative nausea and vomiting

Nausea and vomiting	Etoricoxib *n* (%)	Placebo *n* (%)	p value
No	40 (67.8)	42 (73.7)	0.840
Yes			
Nausea	11 (18.6)	10 (17.5)	
Nausea with vomit	7 (11.9)	4 (7.0)	
Repeated vomit ≥2 times/h	1 (1.7)	1 (1.8)	

Table 6 Side effects of drug

Side effects	Etoricoxib *n* (%)	Placebo *n* (%)	p value
Respiratory depression	0	0	–
Vertigo	0	0	–
Somnolence	0	0	–
Visual disturbance	0	0	–
Lightheadedness	2 (3.3)	1 (1.7)	0.506
Headache	1 (1.7)	0	0.504

Discussion

Many trials of preemptive NSAIDs use have yielded equivocal results. Some trials of lower abdominal surgery [7], total knee replacement [8], and caesarian section [9] have shown the benefit of NSAIDs as a preemptive analgesia. However, other studies [10, 11] have concluded that using NSAIDs as a preemptive analgesia are no more effective than standard methods. These discrepancies may be due in part to controversy associated with the definition of preemptive analgesia and how to conduct the corresponding clinical trials.

For laparoscopic cholecystectomy, few clinical trials were found, and they reached conflicting results. Some [12, 13] showed that preoperative NSAIDs were a valuable

Table 7 Complications of treatment

Complications	Etoricoxib *n* (%)	Placebo *n* (%)	*p* value
Epigastric pain	0	2 (3.4)	0.244
GI bleeding	0	0	–
Wound bleeding	1 (1.7)	1 (1.7)	0.748
Bleeding tendency rating score			
None	59 (98.3)	59 (100.0)	0.319
Mild	1 (1.7)	0	
Significant	0	0	

GI gastrointestinal

opioid-sparing adjunct to the standard treatment of pain after laparoscopic cholecystectomy, improving postoperative pain scores. Another study [14] showed no statistically significant difference in the pain scores and morphine consumption between the two treatment groups.

O'Hanlon et al. [15] compared 20 mg of tenoxicam administered intravenously 30 min before ambulatory breast biopsy with administration of the same dose at the introduction of anesthesia. The results showed a striking advantage for patients who received the tenoxicam 30 min before surgery. This study [15] showed that NSAIDs had preemptive analgesic effects when administered at the proper time.

The current study was performed to evaluate the efficacy of oral etoricoxib administered about 1 h before laparoscopic surgery compared with placebo. The hypothesis was that patients receiving etoricoxib would experience less pain and request less supplemental opioid analgesic than patients receiving placebo. Etoricoxib is a cyclooxygenase (COX)-2-selective NSAID with a higher COX-1-to-COX-2 selectivity ratio than the other COX-2-selective NSAIDs such as rofecoxib, valdecoxib, or celecoxib [16]. With etoricoxib, once-daily dosing is appropriate based on its long half-life of 22 h. Rapid symptomatic responses are observed related to the short time to peak plasma concentration of about 1 h [17]. Etoricoxib has been shown to have fewer adverse gastrointestinal effects and a reduced tendency to bleed from platelet dysfunction, which is advantageous in the perioperative period [18, 19].

Our study showed that the demographic data between the two groups were similar except for the younger age of the placebo group. This may have been a limitation of randomization (block of four). There were no significant differences in bleeding tendency rating scores, postoperative nausea and vomiting, or side effects between the two groups, which suggests that it is safe to use etoricoxib as a preemptive analgesia. Etoricoxib showed that it can significantly reduce VAS pain scores postoperatively as well as the number of rescue oral analgesic drugs, but it did not affect the use of morphine and postoperative pain. This means that we must use multimodal preemptive analgesia rather than NSAIDs alone to reduce overall pain.

We recommend using etoricoxib as a preemptive analgesic to reduce postoperative pain after laparoscopic cholecystectomy.

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