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Review Article

The efficacy of pre-emptive etoricoxib for laparoscopic cholecystectomy: a systematic review and meta-analysis

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Abstract: Background: Pre-emptive etoricoxib may be beneficial for pain control in laparoscopic cholecystectomy patients. However, the results remain controversial. We conducted a systematic review and meta-analysis to explore the efficacy of etoricoxib after laparoscopic cholecystectomy. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of etoricoxib on pain intensity after laparoscopic cholecystectomy were included. Two investigators independently searched articles, extracted data, and assessed the quality of the included studies. This meta-analysis is performed using the random-effect model. Results: Four RCTs are included in the meta-analysis. Overall, compared with control intervention following laparoscopic cholecystectomy, etoricoxib intervention significantly reduce pain scores (Std. MD=-0.69; 95% CI=-1.02 to -0.37; P<0.0001) and the incidence of shoulder/flank pain (RR=0.65; 95% CI=0.50 to 0.85; P=0.002), but showed no notable impact on operation time (Std. MD=-0.18; 95% CI=-0.41 to 0.05; P=0.13), nausea and vomiting (RR=0.68; 95% CI=0.42 to 1.10; P=0.11), dizziness (RR=0.67; 95% CI=0.42 to 1.06; P=0.09), or headache (RR=0.96; 95% CI=0.44 to 2.09; P=0.92). Conclusions: Compared to control intervention after laparoscopic cholecystectomy, pre-emptive etoricoxib is found to significantly reduce the pain scores and the incidence of shoulder/flank pain, but has no substantial influence on nausea and vomiting, dizziness, and headache.

Keywords: Etoricoxib, laparoscopic cholecystectomy, pain control, randomized controlled trials, meta-analysis

Introduction

Laparoscopic cholecystectomy has been widely accepted as the gold standard for the surgical treatment of symptomatic gall stones [1-3]. Compared with classical open cholecystectomy, laparoscopic cholecystectomy is a minimally invasive procedure requiring significantly shorter hospital stay and permitting faster convalescence [4, 5]. However, post-operative pain is the most frequent complaint and the most common cause of delayed discharge after the surgery [6-8]. Some patients suffer from moderate to severe pain especially during the first 6-12 h postoperatively, and up to 65% of patients experience moderate, severe, or extreme pain after surgery [6, 9].

Etoricoxib, known as a cyclooxygenase (COX)-2-selective NSAID, has a higher COX-1-to-COX-2 selectivity ratio than other COX-2-selective NSAIDs (e.g. rofecoxib, valdecoxib, and celecoxib) [10]. The proper dose of once daily etoricoxib is based on its long half-life of 22 h [11]. Pre-emptive etoricoxib 120 mg has been reported to significantly reduce the postoperative pain scores and the number of oral analgesic drugs, but has no significant influence on the requirement of morphine and the incidence of postoperative shoulder pain [7, 12]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of etoricoxib intervention for laparoscopic cholecystectomy.

Materials and methods

This systematic review and meta-analysis are conducted according to the guidance of the Preferred Reporting Items for Systematic Re-

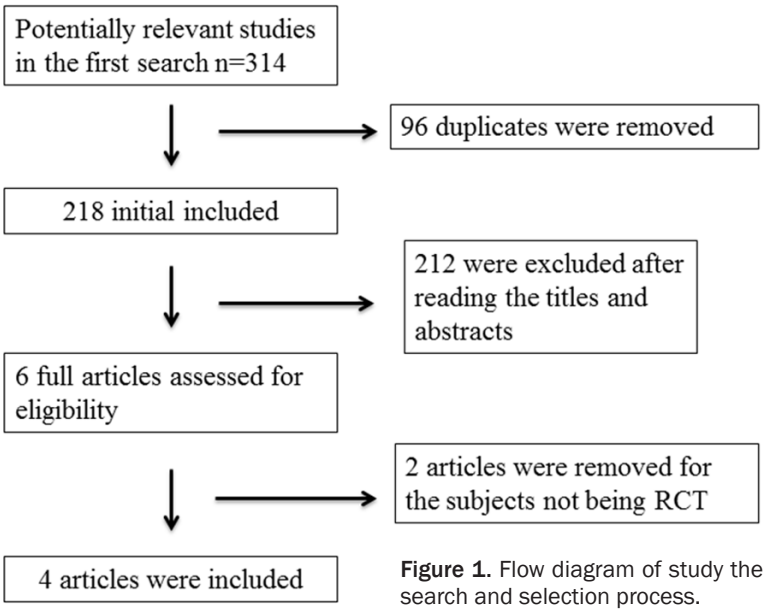

Figure 1. Flow diagram of study the search and selection process.

views and Meta-analysis statement [13] and the *Cochrane Handbook for Systematic Reviews of Interventions* [14]. All analyses are based on previous published studies, and thus no ethical approval and patient consent are required.

Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to November 2017, with the following keywords: etoricoxib, and laparoscopic cholecystectomy. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above is performed repeatedly until no further article was identified.

The inclusion criteria are as follows: (1) Study population are patients undergoing laparoscopic cholecystectomy; (2) Intervention treatments are etoricoxib versus placebo; (3) Study design is RCT.

Data extraction and outcome measures

The following information were extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, etoricoxib, control, and study design. Authors were contacted to acquire the data when necessary. The primary outcome was pain scores. Secondary outcomes included the incidence of shoulder/flank pain, operative time, nausea and vomiting, dizziness, and headache.

Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [15]. This scale consists of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding have been appropriately described. If the methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals were not recorded, then one point was deducted. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [16].

Statistical analysis

Standard mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (pain scores, operative time), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (the number of shoulder/flank pain, nausea and vomiting, dizziness, headache) were used to estimate the pooled effects. An I^2 value greater than 50% indicates significant heterogeneity. The random-effect model was applied for all the analysis. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. $P<0.05$ in two-tailed tests was considered statistically significant. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Table 1. Characteristics of included studies

NO.	Author	Etoricoxib group					Control group					Jada scores
		Number	Age (years)	Male (n)	BMI (kg/m^2) or Weight (kg)	Methods	Number	Age (years)	Male (n)	BMI (kg/m^2) or Weight (kg)	Methods	
1	Ko-lam 2016	60	51.0 ± 13.3	11	24.6 ± 4.1 kg/m^2	Pre-emptive etoricoxib 120 mg and intra-abdominal pressure of 7 mmHg	60	52.8 ± 12.1	18	24.3 ± 3.4 kg/m^2	Placebo and intra-abdominal pressure of 14 mmHg	3
2	Gautam 2014	27	41.7 ± 8.4	20	56.2 ± 9.9 kg	Etoricoxib 120 mg orally 1 h before the surgery	28	44.5 ± 8.8	17	55.7 ± 9.1 kg	Placebo 1 h before the surgery	5
3	Sandhu 2011	60	53.6 ± 11.7	19	-	Etoricoxib 120 mg plus diazepam 0.2 mg/kg 1 h before the surgery	59	47.5 ± 12.6	22	-	Placebo plus diazepam 0.2 mg/kg 1 h before the surgery	4
4	Puura 2006	24	46 ± 12.2	5	79 ± 14 kg	120 mg of etoricoxib 1 h before the surgery	23	45.3 ± 8.8	7	78 ± 15 kg	Placebo 1 h before the surgery	3

BMI: body mass index.

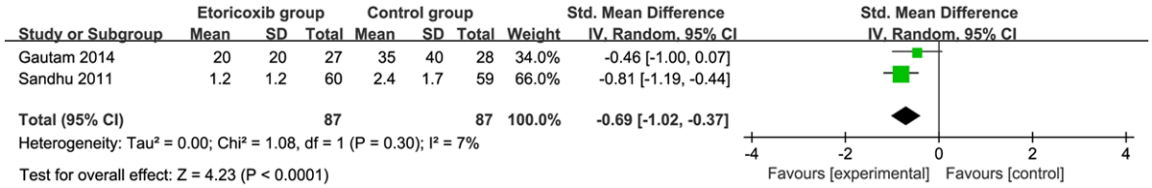

Figure 2. Forest plot for the meta-analysis of pain scores.

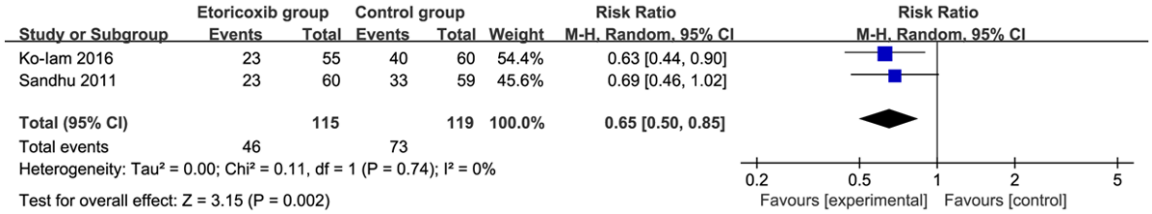

Figure 3. Forest plot for the meta-analysis of the incidence of shoulder/flank pain.

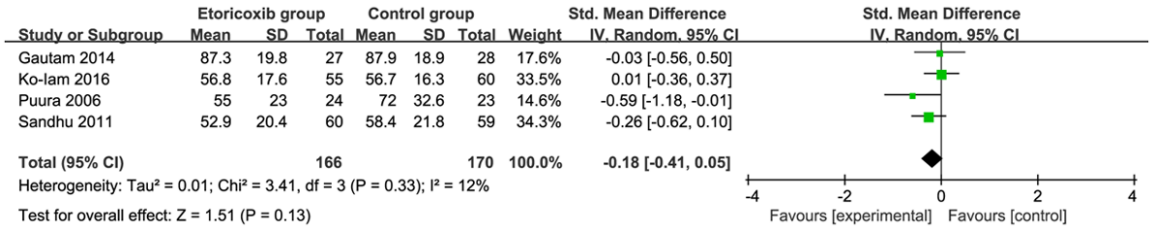

Figure 4. Forest plot for the meta-analysis of operative time (min).

Results

Literature search, study characteristics, and quality assessment

The flow chart for the selection process and detailed identification is presented in **Figure 1**. There were 314 publications identified through the initial search of databases. Ultimately, four RCTs are included in the meta-analysis [7, 17-19].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in **Table 1**. The four studies were published between 2006 and 2016, and sample sizes range from 47 to 120 with a total of 341. Patients in the etoricoxib group and the control group had similar baseline characteristics. Three included RCTs involved etoricoxib 120 mg orally before the surgery versus placebo [17-19], and the remaining RCT involved etoricoxib 120 mg plus diazepam 0.2 mg/kg 1 h before the surgery versus placebo plus diazepam 0.2 mg/kg 1 h before the surgery [7]. One included RCT reported a low intra-abdominal pressure of 7 mmHg [17].

Among the four RCTs, two studies reported the pain scores [7, 18], two studies reported the number of shoulder/flank pain [7, 17], four studies reported the operation time [7, 17-19], four studies reported nausea and vomiting [7, 17-19], and two studies report dizziness [7, 17] as well as headache [7, 17]. Jadad scores of the four included studies vary from 3 to 5, and all four studies are considered to be high-quality ones according to quality assessment.

Primary outcome: pain scores

The outcome data was analyzed with the random-effect model, and the pooled estimate of the two included RCTs suggesting that compared to the control group after laparoscopic cholecystectomy, etoricoxib intervention is associated with the significantly decreased pain scores (Std. MD=-0.69; 95% CI=-1.02 to -0.37; P<0.0001), and had low heterogeneity

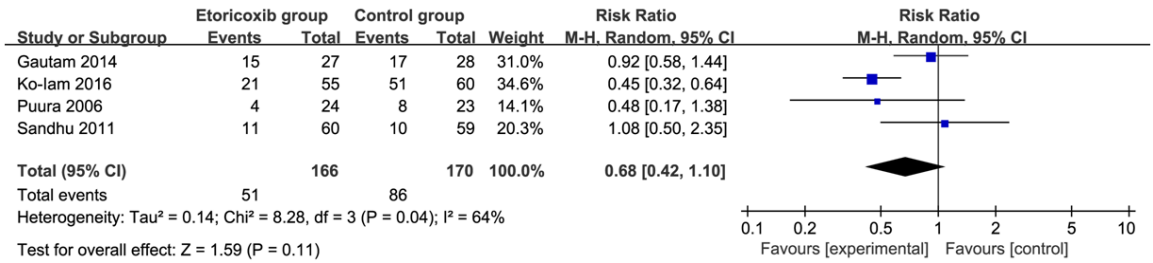

Figure 5. Forest plot for the meta-analysis of nausea and vomiting.

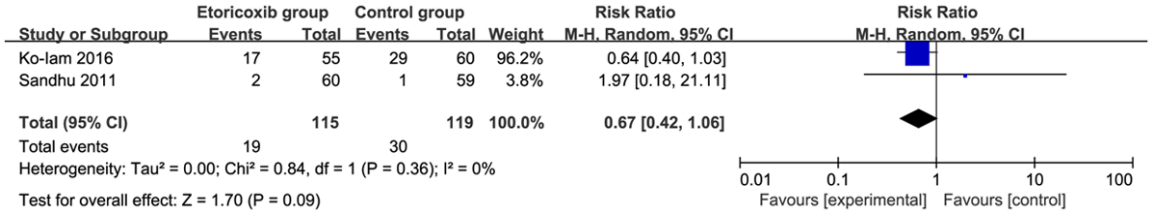

Figure 6. Forest plot for the meta-analysis of dizziness.

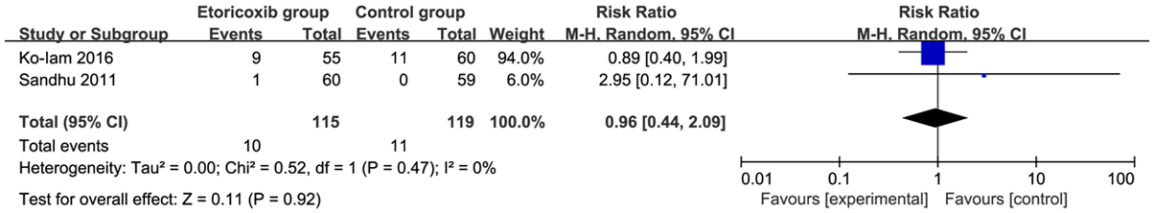

Figure 7. Forest plot for the meta-analysis of headache.

among the studies (I^2=7%, heterogeneity P= 0.30) (**Figure 2**).

Sensitivity analysis

Low heterogeneity was observed among the included studies for the pain scores. Thus, we did not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

Secondary outcomes

Compared with the control intervention following laparoscopic cholecystectomy, etoricoxib intervention significantly reduced the incidence of shoulder/flank pain (RR=0.65; 95% CI=0.50 to 0.85; P=0.002; **Figure 3**), but showed no notable influence on operation time (Std. MD=-0.18; 95% CI=-0.41 to 0.05; P=0.13; **Figure 4**), nausea and vomiting (RR=0.68; 95% CI=0.42 to 1.10; P=0.11; **Figure 5**), dizziness (RR=0.67; 95% CI=0.42 to 1.06; P=0.09; **Figure 6**), or headache (RR=0.96; 95% CI=0.44 to 2.09; P=0.92; **Figure 7**).

Discussion

Laparoscopic cholecystectomy has become the standard treatment for symptomatic gallstone, but commonly causes moderate or severe pain after the surgery and subsequently results in discomfort and stress responses in many patients [20-23]. The postoperative pain include abdominal pain (visceral pain), incisional pain (trocar site pain), and shoulder or back pain [24-27]. The cause of shoulder pain is not well understood, and may be associated with the overstretching of the diaphragmatic muscle fibers because of the high rate insufflations [12, 27]. Preoperative NSAIDs are a valuable opioid-sparing adjunct to the standard treatment in order to reduce postoperative pain scores [28, 29].

Etoricoxib is known as a COX-2-selective NSAIDs and patients with oral etoricoxib administered about 1 h before laparoscopic cholecystectomy are reported to have significantly reduced pain scores, but show no advantages

of the length of hospital stay [7]. Compared to other NSAIDs, etoricoxib has shown fewer adverse gastrointestinal effects and a reduced tendency to bleed because of platelet dysfunction [30, 31]. Our meta-analysis concludes that administration of etoricoxib before laparoscopic cholecystectomy leads to significantly reduced pain scores and lower incidence of shoulder/flank pain, but demonstrates no remarkable impact on operation time.

The low-pressure pneumoperitoneum may have the potential in reducing the incidence of shoulder or back pain compared to standard-pressure pneumoperitoneum [12, 32]. The combination of low-pressure pneumoperitoneum (7 mmHg) and pre-emptive etoricoxib (120 mg) has been reported to significantly reduce the incidence of shoulder and back pain after laparoscopic cholecystectomy, and no increase in intraoperative complications and incidence of gallbladder perforation is revealed between combination treatment and standard treatment in one included RCT [17]. Consistently, there was no increase in nausea and vomiting, dizziness, or headache after pre-emptive etoricoxib for laparoscopic cholecystectomy based on our meta-analysis.

Several limitations should be taken into account. First, our analysis is based on only four RCTs and two of them have a relatively small sample size (n<100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. The detailed methods of pre-emptive etoricoxib in the included studies are different and they may have an influence on the pooling results. Next, some important index such as patient satisfaction and the length of hospital stay cannot be analyzed based on current included RCTs. Finally, some unpublished and missing data might lead bias to the pooled effect.

Conclusion

Pre-emptive etoricoxib shows some ability to reduce pain scores and the incidence of shoulder/flank pain after laparoscopic cholecystectomy. Pre-emptive etoricoxib is recommended to be cautiously administrated for laparoscopic cholecystectomy.

Disclosure of conflict of interest

None.

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