World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v8.i7.543

World J Gastrointest Oncol 2016 July 15; 8(7): 543-549
ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol

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Author contributions: Lohsiriwat V solely contributed to this article.

Institutional review board statement: The study was reviewed and approved by the Siriraj Institutional Review Board (SIRB COA No. Si014/2013).

Informed consent statement: As the study is a retrospective review, a waiver of informed consent was approved by the Siriraj Institutional Review Board.

Conflict-of-interest statement: Varut Lohsiriwat has received fees for serving as a speaker for Pfizer, MSD and Johnson and Johnson (Thailand) Limited.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at bolloon@hotmail.com.

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Received: February 21, 2016
Peer-review started: March 2, 2016
First decision: April 6, 2016
Revised: April 9, 2016
Accepted: April 21, 2016
Article in press: April 22, 2016
Published online: July 15, 2016

Abstract

AIM: To evaluate the opioid-sparing effect of selective cyclooxygenase-2 (COX-2) inhibitors on short-term surgical outcomes after open colorectal surgery.

METHODS: Patients undergoing open colorectal resection within an enhanced recovery after surgery protocol from 2011 to 2015 were reviewed. Patients with combined general anesthesia and epidural anesthesia, and those with acute colonic obstruction or perforation were excluded. Patients receiving selective COX-2 inhibitor were compared with well-matched individuals without such a drug. Outcome measures included numeric pain score and morphine milligram equivalent (MME) consumption on postoperative day (POD) 1-3, gastrointestinal recovery (time to tolerate solid diet and time to defecate), complications and length of postoperative stay.

RESULTS: There were 75 patients in each group. Pain score on POD 1-3 was not significantly different between two groups. However, MME consumption and MME consumption per kilogram body weight on POD 1-3 was significantly less in patients receiving a selective COX-2 inhibitor ($P < 0.001$). Median MME consumption per kilogram body weight on POD 1-3 was 0.09, 0.06 and nil, respectively in patients receiving a selective COX-2 inhibitor and 0.22, 0.25 and 0.07, respectively in the comparative group ($P < 0.001$), representing at least 59% opioid

reduction. Patients prescribing a selective COX-2 inhibitor had a shorter median time to resumption of solid diet [1 (IQR 1-2) d *vs* 2 (IQR 2-3) d; $P < 0.001$] and time to first defecation [2 (IQR 2-3) d *vs* 3 (IQR 3-4) d; $P < 0.001$]. There was no significant difference in overall postoperative complications between two groups. However, median postoperative stay was significantly 1-d shorter in patients prescribing a selective COX-2 inhibitor [4 (IQR 3-5) d *vs* 5 (IQR 4-6) d; $P < 0.001$].

CONCLUSION: Perioperative administration of oral selective COX-2 inhibitors significantly decreased intravenous opioid consumption, shortened time to gastrointestinal recovery and reduced hospital stay after open colorectal surgery.

Key words: Selective cyclooxygenase-2 inhibitor; Outcome; Colon surgery; Rectal surgery; Enhanced recovery after surgery; Opioid; Ileus; Non-steroidal anti-inflammatory drug; Pain

Core tip: This comparative study validates the effectiveness of perioperative administration of oral selective cyclooxygenase-2 (COX-2) inhibitors as a part of multimodal analgesia in an enhanced recovery after surgery protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. Our findings also indicate that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

Lohsiriwat V. Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol. *World J Gastrointest Oncol* 2016; 8(7): 543-549 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i7/543.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i7.543

INTRODUCTION

Effective pain control for open colorectal surgery plays a crucial role in improving patient's recovery. Various analgesic modalities have been utilized to reduce postoperative pain including epidural analgesia and administration of selective cyclooxygenase-2 (COX-2) inhibitors. However, a recent nationwide analysis of the outcomes of epidural analgesia in open colorectal surgery in the United States has shown that epidural analgesia does not add major clinical benefits over conventional analgesia, but it is associated with longer hospital stay and a higher incidence of ileus[1]. In a large international registry of the enhanced recovery after surgery (ERAS) Compliance Group, prolonged hospitalization was also observed in patients with epidural analgesia[2]. Moreover, epidural analgesia needs to be performed by a qualified anesthesiologist and it could lead to some serious complications such as epidural hematoma and epidural abscess[3]. As a result, the application of epidural analgesia in clinical practice has been limited[1,4,5].

On the other hand, a selective COX-2 inhibitor, a nonsteroidal anti-inflammatory drug (NSAID) directly targeting COX-2 which is an enzyme primarily responsible for inflammation and pain, are widely available in both oral preparation and injectable form[6]. Having little or no effect on platelet aggregation, a selective COX-2 inhibitor has currently been used as a part of multimodal analgesia for several surgical procedures including colorectal surgery - which prefers a non-opioid analgesic regimen[7-9]. Perioperative administration of selective COX-2 inhibitors can reduce opioid requirement[10], facilitate gastrointestinal recovery and shorten hospital stay after colorectal surgery[11]. However, there are a limited number of studies examining these outcome benefits in the setting of an ERAS protocol[10].

In Thailand, an ERAS protocol for colorectal surgery has been introduced into a daily practice since 2011[9,12]. Regarding perioperative analgesia in our ERAS protocol, selective COX-2 inhibitors will be provided based on patient's comorbidities and their healthcare coverage scheme. Meanwhile, thoracic epidural analgesia is seldom applied due to its technical demand and a limited number of physician anesthesiologists[4]. Like many developing and underdeveloped countries, a majority of colorectal procedures in Thailand remains an open surgery because of limited resources and the expense of laparoscopic surgery[13]. The objective of this study was therefore to examine the clinical outcomes of perioperative administration of an oral selective COX-2 inhibitor for open colorectal surgery within an ERAS protocol (without the need of epidural analgesia).

MATERIALS AND METHODS

This non-randomized, comparative, prospective study included adult patients undergoing elective laparotomy for colorectal resection from January 2011 to September 2015 at the Faculty of Medicine Siriraj Hospital. The study was approved by the Siriraj Institutional Review Board (SIRB COA No. Si014/2013). Patients with combined general anesthesia and epidural anesthesia, and those with acute colonic obstruction or perforation were excluded. Clinical outcomes of patients receiving a selective COX-2 inhibitor were compared with those without such a drug, with a ratio of 1 to 1. They were matched for age, gender, body mass index (BMI), the ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (CR-POSSUM)[14], and type of surgical procedure. Of note, all operations were performed by the author under an ERAS protocol. The ERAS protocol has been previously described[9,12,15]. In brief, only patients with left-sided colon or rectal resection received preoperative mechanical bowel preparation. Right-sided colon resection was preferentially

Table 1 Perioperative pain control regimen

Preoperative period	1 tablet of acetaminophen 500 mg
	± 1 tablet of a selective cyclooxygenase-2 inhibitor (either celecoxib 400 mg, etoricoxib 90 mg or etoricoxib 120 mg)
Intraoperative period	Balanced general anesthesia
	Application of atraumatic O-ring wound retractor (if available)
Postoperative period	Infiltration of 0.5% bupivacaine into fascial layer and muscle around the wound edge
	1 tablet of acetaminophen 500 mg every 6 h in the first 3 d
	± 1 tablet of a selective cyclooxygenase-2 inhibitor daily for 5-7 d
	Intravenous patient-controlled morphine (or tramadol) or intermittent intravenous morphine if pain score > 3

done through a transverse incision. Otherwise, a midline laparotomy was performed. No intraabdominal drain or nasogastric tube was used. A diverting stoma was selectively fashioned in cases of coloanal anastomosis and neoadjuvant chemoradiation. Medication for prophylaxis of postoperative nausea and vomiting was administrated based on patient's risk factor[16]. Standard postoperative care was provided including early feeding and scheduled ambulation.

Perioperative analgesia

Approximately 3 h prior to surgery, one tablet of acetaminophen 500 mg with or without one tablet of an oral selective COX-2 inhibitor (either celecoxib 400 mg, etoricoxib 90 mg or etoricoxib 120 mg) were given. Of note, the administration of a selective COX-2 inhibitor was based on patient's co-morbidities, contraindication (*i.e.*, coronary artery disease, ischemic stroke, peripheral arterial disease, uncontrolled hypertension) and their healthcare coverage scheme. An operation was performed under a balanced general anesthesia. An atraumatic O-ring wound retractor was applied during the operation if available[17]. After a closure of abdominal wall muscle, 0.5% bupivacaine (3-4 mg/kg) was infiltrated into fascial layer and muscle around the wound edge. The wound was then closed primarily. Standard protocol for postoperative pain control was followed in all cases. Basically, intravenous morphine (0.03-0.05 mg/kg per dose every 1-2 h) was administered if pain score was > 3 (using a numeric rating scale of 0-10 with 0 = no pain 10 = worst possible pain). Intravenous patient-controlled morphine or intravenous tramadol (an equivalent of 10 mg tramadol to 1 mg morphine) may be used in some cases[18]. During the postoperative period, one tablet of acetaminophen 500 mg was given every 6 h in the first 3 d, with or without daily oral selective COX-2 inhibitor for 5-7 d. Perioperative analgesia protocol was summarized in Table 1.

Outcome measures

Primary outcome measures included average pain score on postoperative day (POD) 1-3, intravenous opioid requirement on POD 1-3, gastrointestinal recovery (time to tolerate solid diet and time to defecate), complication according to the Clavien-Dindo classification system[19], prolonged postoperative ileus[20], and length of postoperative stay. Pain scores were recorded every 4 h by nursing staff. All pain assessments were noted after patients were asked to take a deep breath. Should the patients slept at night during the scheduled time for pain assessment, they were not awakened and the actual time the patients were assessed was noted. Unless intravenous patient-controlled opioid was applied, intermittent intravenous morphine was given if pain score was > 3 as in the aforementioned regimen. Total daily intravenous opioid requirement was reported as morphine milligram equivalent (MME).

All patients were offered a clear liquid diet immediately after surgery providing that they were clinically stable. Once the oral intake exceeded 20 mL/kg body weight without nausea and vomiting, the diet was advanced to a low-residual solid diet. Prolonged postoperative ileus was defined as at least two times of nausea/vomiting, inability to tolerate oral diet and absence of flatus over 24 h, and abdominal distension with radiologic confirmation occurring on or after POD 4[20]. Patients were discharged from the hospital when they had no fever, adequate pain control with oral analgesics, good ambulation, and satisfactory recovery of gastrointestinal function. All patients were scheduled for follow-up at 30 d postoperatively.

Statistical analysis

All data were prepared and compiled using Statistical Package for the Social Sciences (SPSS®) program version 18.0 for Windows (SPSS Inc., Chicago, IL). Values are expressed as median (interquartile range: IQR), mean (SD) or number (%). Continuous variables were compared using the *t*-test or Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test. A *P*-value of less 0.05 was considered statistically significant.

RESULTS

This study included 150 patients (57% male) with the average age of 65 years (range 30-87). There were 75 patients in each group. There was no significant difference in patient's characteristics, intraoperative detail, type of operation and percentage of adherence to the ERAS protocol between the two groups, except patients receiving a selective COX-2 inhibitor had a higher level of preoperative hematocrit and serum albumin (Table 2).

Pain score on POD 1-3 was not significantly different between the two groups. However, MME requirement on POD 1-3 was significantly less in patients receiving

Table 2 Patient characteristics and operative details

	Patients with selective COX-2 inhibitor (n = 75)	Patients without selective COX-2 inhibitor (n = 75)	P-value
Age (yr)	64 (55-73)	65 (59-75)	0.15
Male	43 (57)	42 (56)	0.87
Weight (kg)	68 (51-58)	59 (50-66)	0.93
Body mass index	23.1 (20.9-25.4)	22.5 (20.6-24.6)	0.49
CR-POSSUM predicted mortality	1.8 (1.0-2.5)	1.9 (1.3-3.4)	0.07
Hematocrit (%)	38 (34-41)	35 (31-39)	0.014[1]
Serum albumin (g/L)	4.0 (3.6-4.3)	3.8 (3.4-4.1)	0.013[1]
Operative time (min)	180 (120-220)	160 (120-180)	0.21
Blood loss (mL)	150 (50-250)	150 (50-260)	0.75
Operation for malignancy	67 (89)	68 (91)	0.37
Rectal resection	41 (55)	37 (49)	0.51
Operation without bowel restoration	11 (15)	12 (16)	0.82
Use of atraumatic O-ring retractor	66 (88)	59 (79)	0.13
Adherence to ERAS protocol (%)	88 (82-88)	82 (82-88)	0.28

[1]P < 0.05. COX-2: Cyclooxygenase-2; CR-POSSUM: The ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; ERAS: Enhanced recovery after surgery.

Table 3 Postoperative pain score and intravenous opioid requirement

	Patients with selective COX-2 inhibitor (n = 75)	Patients without selective COX-2 inhibitor (n = 75)	P-value
Pain POD1	1.5 (0.7-2.1)	1.5 (0.5-2.7)	0.78
Pain POD2	0.7 (0-2.0)	0.6 (0-1.5)	0.74
Pain POD3	0.5 (0-1.5)	0.5 (0-1.7)	0.38
MME POD1	6 (2-12)	13 (6-20)	< 0.001[1]
MME POD2	3 (0-17)	20 (4-20)	< 0.001[1]
MME POD3	0 (0-0)	5 (0-15)	< 0.001[1]
MME/KG POD1	0.09 (0.03-0.23)	0.22 (0.11-0.42)	< 0.001[1]
MME/KG POD2	0.06 (0-0.28)	0.25 (0.07-0.37)	< 0.001[1]
MME/KG POD3	0 (0-0)	0.07 (0-0.25)	< 0.001[1]

[1]P < 0.05. COX-2: Cyclooxygenase-2; MME: Morphine milligram equivalent; MME/KG: Morphine milligram equivalent per kilogram body weight; POD: Postoperative day.

a selective COX-2 inhibitor (Table 3). Median MME consumption per kilogram body weight on POD 1-3 was 0.09, 0.06 and nil, respectively in patients receiving a selective COX-2 inhibitor and 0.22, 0.25 and 0.07, respectively in the comparative group (P < 0.001), representing at least 59% opioid reduction.

Patients receiving a selective COX-2 inhibitor had a shorter median time to resumption of solid diet [1 (IQR 1-2) d *vs* 2 (IQR 2-3) d; P < 0.001] and time to first defecation [2 (IQR 2-3) d *vs* 3 (IQR 3-4) d; P < 0.001]. There was no significant difference in the rate of overall postoperative complication and prolonged postoperative ileus between the two groups (Table 4). Of note, there were 1 non-fatal acute myocardial infarction and 1 colorectal anastomotic leakage requiring an operation in patients without selective COX-2 inhibitor. Median and average postoperative stay was significantly 1-d shorter in patients prescribing a selective COX-2 inhibitor; [4 (IQR 3-5) d *vs* 5 (IQR 4-6) d; P < 0.001] and [4.3 (SD 3.0) d *vs* 5.3 (SD 2.5) d; P = 0.023], respectively. Three patients (4%) in the selective COX-2 inhibitor group and 1 patient (1%) in the comparative group required readmission within 30 d after the operation (P = 0.62). No 30-d death was observed in this study.

DISCUSSION

The main findings of this comparative study are that perioperative administration of an oral selective COX-2 inhibitor - as a part of multimodal analgesic regimen - reduces intravenous opioid requirement, shortens time to gastrointestinal recovery and decreases the length of hospital stay after open colorectal surgery within an ERAS protocol. These results were consistent with a report from a prospective randomized, double-blind, placebo-controlled study examining the influence of pre- and post-administration of a selective COX-2 inhibitor (valdecoxib 40 mg) in major colorectal surgery within a non or partial ERAS protocol[11]. The randomized clinical trial indicated that patients treated with valdecoxib had a one-third opioid reduction, a 12-h quicker time to first bowel movement and a 2-d shorter hospital stay. However, valdecoxib has been off the market since 2005 due to its potentially life-threatening skin reaction and lack of adequate data on its long-term cardiovascular safety[21].

Many studies have shown that preemptive analgesia is more effective than postoperative analgesia[22-24]. A combination of preoperative and postoperative admini-

Table 4 Gastrointestinal recovery, complication and hospital stay

	Patients with selective COX-2 inhibitor (n = 75)	Patients without selective COX-2 inhibitor (n = 75)	P-value
Time to tolerate solid diet (d)	1 (1-2)	2 (2-3)	< 0.001[1]
Time to defecate (d)	2 (2-3)	3 (3-4)	< 0.001[1]
Overall complication	9 (11)	17 (23)	0.08
Grade Ⅰ	4	7	
Grade Ⅱ	5	7	
Grade Ⅲ	0	2	
Grade Ⅳ	0	1	
Prolonged postoperative ileus	4 (5)	6 (8)	0.75
Postoperative stay (d)			
Median (IQR)	4 (3-5)	5 (4-6)	< 0.001[1]
Mean (SD)	4.3 (3.0)	5.3 (2.5)	0.023[1]
Readmission within 30 d	3 (4)	1 (1)	0.62

[1]P < 0.05. If a patient had more than one complication, the highest Clavien-Dindo grade was reported. COX-2: Cyclooxygenase-2.

stration of analgesics would have a better pain control. A beneficial outcome effect of perioperative administration of currently available selective COX-2 inhibitors including celecoxib and etoricoxib may be attributed to adequate perioperative nociceptive afferent blockage and to minimize central sensitization (as a preoperative use), and to maintain anti-inflammatory effect after an operation (as a postoperative use). Unlike conventional NSAIDs, a selective COX-2 inhibitor has little or no effect on platelet aggregation and gastrointestinal irritation[25,26]. These characteristics of selective COX-2 inhibitors are therefore favorable to perioperative administration.

Although there was no difference in postoperative pain score between the two groups, this study showed that a regimen of perioperative pain control in both groups was very effective - which achieved a reasonable level of comfort in the postoperative period (with a median pain score of < 2). However, patients receiving a selective COX-2 inhibitor required less parenteral opioid. Since opioid is well known to cause postoperative nausea/vomiting and gastrointestinal dysfunction[27], as a result, in part, shorter gastrointestinal convalescence was observed in patients prescribing a selective COX-2 inhibitor. While a reduction in opioid consumption may be responsible for shorter time to gastrointestinal recovery, a selective COX-2 inhibitor alone was shown to diminish a local inflammatory response of the small bowel to surgical manipulation, thus leading to quicker recovery of postoperative intestinal dysfunction[28]. In animal studies, selective COX-2 inhibitors induced duodenal motility and improved small bowel propulsion in rats subjected to abdominal surgery[29,30].

In this study, there was a non-significant trend in decreased rates of overall complication and prolonged postoperative ileus in patients receiving a selective COX-2 inhibitor. The clinical relevant of NSAID-induced opioid sparing on favorable postoperative outcomes, including less incidence of postoperative gastrointestinal dysfunction and other complications, has been shown in several studies of non-colorectal surgery[31-35] and colorectal surgery[11]. Apart from its opioid-sparing effects, selective COX-2 inhibitors may be associated with a reduction in postoperative complication by minimizing both inflammatory response and endocrine-metabolic response to surgery[36].

While it seems clear that a selective COX-2 inhibitor has a positive impact on opioid consumption and gastrointestinal recovery in this study, patients prescribing a selective COX-2 inhibitor are generally at a higher risk for cardiovascular and thromboembolic events compared with a control or placebo drug[37]. Therefore, selective COX-2 inhibitors should not be used in individuals at increased risk for vascular thrombosis, *e.g.*, coronary artery disease, cerebrovascular disease and peripheral arterial disease. The physicians are also encouraged to use the lowest effective dose for the shortest duration of a selective COX-2 inhibitor. In surgical point of view, the use of any NSAIDs including selective COX-2 inhibitors in the setting of gastrointestinal anastomosis has been concerned because some studies have suggested that NSAIDs may impair anastomotic healing[38-40]. Recently, a meta-analysis of clinical and experimental studies in 2014 has indicated a strong link between anastomotic leakage and the use of non-selective NSAIDs, but not the use of selective COX-2 inhibitors[41]. So far, the ERAS society guidelines include NSAIDs and selective COX-2 inhibitors as a component of multimodal analgesia in elective colorectal surgery[7,8].

Limitations of this study include the fact that it is a non-randomized study. Selective bias and performance bias could occur in the study. However, all patients were operated on by the same surgeon with a relatively high adherence to the ERAS protocol (> 80% compliance in both groups). Moreover, the patients were systematically assessed with a pre-defined objective measurement. It should be noted that not all patients received intravenous patient-controlled analgesia due to a limited number of equipment. To overcome this problem, a standardized protocol for postoperative pain control has been adopted in our institute since 2004. Another limitation is that only patients undergoing open colorectal surgery were included in this study. Whether patients undergoing minimally

invasive surgery, who will have a less inflammatory and metabolic response to surgery compared with open surgery[42], will be beneficial to the administration of selective COX-2 inhibitors are not investigated.

In conclusion, this study validates the effectiveness of perioperative administration of currently available oral selective COX-2 inhibitors as a part of multimodal analgesia in an ERAS protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. Our findings also indicate that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

COMMENTS

Background

Effective perioperative pain control plays a crucial role in improving patient's recovery especially for an open abdominal surgery. Opioid is very effective analgesia but it has several undesired side effects such as sedation, itching, nausea, vomiting and constipation. Non-opioid analgesia has been recommended as a part of multimodal analgesia in an enhanced recovery after surgery (ERAS) protocol. Selective cyclooxygenase-2 (COX-2) inhibitors have some advantages over conventional non-steroidal anti-inflammatory drugs because they have little or no effect on platelet aggregation and gastrointestinal irritation.

Research frontiers

Several studies have shown perioperative administration of selective COX-2 inhibitors can reduce opioid requirement, facilitate gastrointestinal recovery and shorten hospital stay after colorectal surgery. However, there are a limited number of studies examining these outcome benefits in the setting of an ERAS protocol.

Innovations and breakthroughs

The present study validates the effectiveness of perioperative administration of currently available oral selective COX-2 inhibitors as a part of multimodal analgesia in an ERAS protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. This study also indicates that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

Applications

The study results suggest that perioperative administration of selective COX-2 inhibitors is an effective perioperative pain control regimen - which could be used as a part of multimodal analgesia for open colorectal surgery if no contraindication.

Peer-review

This is a good article.

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