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Oral etodolac, a COX-2 inhibitor, reduces postoperative pain immediately after fast-track cardiac surgery

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Abstract
Purpose. The present study was designed to evaluate the efficacy of a cyclooxygenase (COX)-2 inhibitor, etodolac, on postoperative pain after fast-track cardiac surgery, and to examine the changes in plasma etodolac concentration after oral administration.
Methods. Thirty patients scheduled for elective coronary artery bypass grafting (CABG) surgery were randomly assigned preoperatively in a double-blind fashion to receive either vehicle ($n = 15$) or etodolac 400 mg ($n = 15$) via a gastric tube at the end of the surgery. Standardized fast-track cardiac anesthesia was used. In both groups, postoperative pain was treated with buprenorphine suppository. Visual analogue pain scores (VASs) were recorded immediately after extubation and at 24 h after surgery. Plasma etodolac concentration was measured at 1, 2, and 6 h after administration ($n = 8$).
Results. No difference was detected in time to extubation between the etodolac group (209 ± 85 min, mean ± SD) and the vehicle group (207 ± 98 min). VASs were significantly lower in the etodolac (2.3 ± 2.1) vs the vehicle group (5.8 ± 2.0) immediately after extubation ($P = 0.009$), but no difference was detected in pain scores at 24 h after surgery, or in the amount of buprenorphine administered in the intensive care unit (ICU), or in the incidence of side effects. Plasma etodolac concentration was within the pharmaceutically recommended range at 1 h, 2 h, and 6 h after administration.
Conclusion. The oral use of etodolac with rectal buprenorphine reduces pain scores immediately after cardiac surgery without an increase in side effects.

Key words COX-2 inhibitor · Postoperative pain · Fast-track cardiac surgery

Introduction

Fast-track cardiac anesthesia requires lower doses of opioids in the peri- and postoperative period. Good postoperative pain control is essential to ensure adequate breathing, as well as to reduce the number of ischemic episodes after surgery, especially for patients receiving painful median sternotomy, which is performed in the majority of patients requiring coronary artery bypass grafting (CABG) and harvesting of the internal mammary artery [1–5].

Currently, opioids remain the mainstay of postoperative pain management after major surgery [6]. Although the use of opioids can provide excellent analgesia, the doses necessary to provide effective pain relief may lead to undesirable side effects such as respiratory depression, sedation, and nausea.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent analgesics [7], but are inadequate for postoperative analgesia after major surgery when used alone [6,7]. These drugs have side effects on gastrointestinal function and coagulation resulting from the inhibition of the constitutive cyclooxygenase (COX)-1 isoform [8]. NSAIDs in conjunction with opioids for postoperative analgesia have been shown to improve pain scores and reduce opioid consumption [6,9]. Furthermore, this opioid-sparing effect may reduce the incidence of drowsiness and the need for antiemetic therapy [9,10].

Recently, selective COX-2 inhibitors have become available. These types of NSAIDs mainly act on COX-2, which is primarily upregulated in response to inflammation [8,11]. Until now, two reports have studied the risk of serious coronary heart disease associated with the selective COX-2 inhibitor, rofecoxib [12,13]. However, there has been only one report which studied the effects of a COX-2 inhibitor in the acute phase of postoperative pain, especially after cardiac surgery [14].

The aim of this study was to evaluate the efficacy of a selective COX-2 inhibitor, etodolac, on postoperative pain immediately after CABG, and to observe the changes in plasma etodolac concentration at 1 h, 2 h, and 6 h after oral administration in patients with cardiac surgery with cardiopulmonary bypass (CPB).

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Table 1. Preoperative exclusion criteria

Age >75 years
Weight >80 kg or <50 kg
Previous cardiac surgery
Ejection fraction <40%
Previous history of peptic ulcer disease or gastrointestinal bleeding
Renal or hepatic insufficiency
Allergy to any NSAIDs

NSAID, nonsteroidal anti-inflammatory drug

Subjects and methods

After Institutional Ethics Committee approval was granted, 30 patients scheduled to undergo elective CABG consented to participate in this study. Patients were instructed preoperatively on how to use a visual analogue scale (VAS) for recording pain intensity. Preoperative exclusion criteria are shown in Table 1.

Anesthetic management

Preoperatively, all patients received standard premedication of 5–10 mg diazepam p.o. Anesthesia was induced with 6–8 $\mu g \cdot kg^{-1}$ fentanyl, midazolam 0.1–0.2 $mg \cdot kg^{-1}$, and 0.2 $mg \cdot kg^{-1}$ vecuronium. Anesthesia was maintained by propofol infusion of 3–5 $mg \cdot mk^{-1} \cdot h^{-1}$ with sevoflurane in a 60% oxygen and air mixture. Supplemental doses of vecuronium were used for muscle relaxation as required. Additional fentanyl was given up to a maximum of 10 $\mu g \cdot kg^{-1}$ before CPB. All patients received methylprednisolone 1000 mg after anesthesia induction, as per routine at our institution. Patients underwent a median sternotomy. Saphenous veins, internal thoracic artery, gastroepiploic artery, and/or radial artery were selected according to each patient's vascular condition, as grafts for the coronary artery bypass. Patients were randomly allocated to receive 400 mg etodolac with 20 ml normal saline or vehicle only (20 ml normal saline), via a gastric tube at the time of sternal closure ($n = 15$ in each group). The gastric tube was clamped until tracheal tube extubation. The dose of etodolac was selected by referring to the standard daily dose of the drug [15]. All patients received a buprenorphine suppository (0.2 mg) at the end of surgery.

Management in the intensive care unit (ICU)

On arrival in the ICU, the patients were taken in charge by a doctor and a nurse who were unaware of the groups in this study. No reversal of muscle relaxants was employed. The relief of anxiety and agitation was treated with diazepam, given intravenously. Inotropes (dopamine/dobutamine 0–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and a vasodilator (nitroglycerin 0.5–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were administered following our routine protocol. Once the patients were awake, normothermic, and hemodynamically stable with satisfactory arterial blood gases (pH 7.32–7.48; P_{O_2} 80 mmHg with $F_{I_{O_2}} < 0.6$ while receiving 3 cmH_2O continuous positive airway pressure for 30 min), extubation of the trachea was performed after discharging the gastric contents. Immediately after extubation, the consciousness level of the patients was evaluated. After confirming the patients' orientation (that they gave their name, age, and location), the VAS was collected from the patients to define the intensity of early postoperative pain. The VAS was again recorded 24 h after surgery. An additional buprenorphine suppository (0.2 mg) was used when requested by the patients. Total buprenorphine consumption during the first 24 h, chest-tube blood loss during the first 12 h, and the incidence of nausea and vomiting were recorded. Nausea was treated with 10 mg metoclopramide i.v.

Plasma etodolac concentration

Serial venous blood samples were taken preadministration, and 1, 2, and 6 h after the administration of etodolac from the first eight patients who participated in this study. Blood was immediately separated, and plasma was frozen and kept at −80°C until analysis. Etodolac concentration was measured with high-performance liquid chromatography.

Statistical analysis

Data values are presented as means ± SD unless indicated otherwise. Continuous variables were treated with a univariate analysis of variance (ANOVA) for between-group differences. VAS scores were analyzed by Mann-Whitney's U-test. Binary variables were compared using χ^2 statistics. A P value of less than 0.05 was considered significant.

Results

Thirty patients consented to participate and were enrolled in the study. Four patients were withdrawn from this study. In one patient in the etodolac group, postoperative blood loss exceeded 100 $ml \cdot h^{-1}$ in the first 3 h after surgery. The bleeding was managed conservatively. In another patient in the etodolac group and two patients in the vehicle group, the tracheas were not extubated within 6 h, and they were withdrawn from the data analysis.

There were no intraoperative awakenings. Two patients in the etodolac group and one in the vehicle group

Table 2. Demographics and preoperative and intraoperative clinical data (mean ± SD or number)

	Etodolac (n = 13)	Vehicle (n = 13)
Age (years)	62.0 ± 7.9	65.2 ± 6.8
Sex (male/female)	9/4	11/2
Weight (kg)	64.7 ± 6.5	64.4 ± 6.7
Ejection fraction (%)	65.7 ± 9.9	63.4 ± 12.2
History of myocardial infarction (n)	8	5
Fentanyl dose (μg/kg)	8.38 ± 0.85	7.89 ± 0.88
Operation duration (min)	300 ± 38	298 ± 40
CPB duration (min)	103 ± 18	107 ± 32
AC duration (min)	58 ± 17	60 ± 20
Bleeding (ml)	462 ± 148	454 ± 214
Type of bypass graft (n)		
Left internal mammary artery	13	12
Saphenous vein	4	4
Gastroepiploic artery	7	9
Right internal mammary artery	4	6
Left radial artery	3	2
Number of grafts (mean)	2.4	2.5

P, not significant (NS)
CPB, cardiopulmonary bypass; AC, aorta cross-clamp

Table 3. Postoperative data (mean ± SD or number)

	Etodolac (n = 13)	Vehicle (n = 13)
Time from arrival at ICU to extubation (min)	209 ± 85	207 ± 98
Time from administration of etodolac to first VAS measurement (min)	260 ± 111	254 ± 98
Blood loss, first 12 h (ml)	181 ± 87	186 ± 71
Nausea, first 12 h (n)	2	2
Vomiting, first 12 h (n)	1	1
Total dose of buprenorphine in first 12 h (mg)	0.12 ± 1.10	0.25 ± 0.25

P, NS
ICU, intensive care unit; VAS, visual analogue pain score

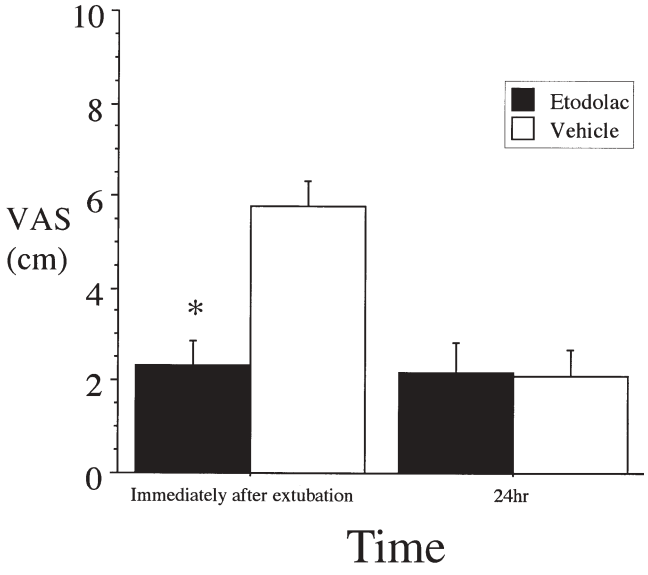

Fig. 1. Postoperative pain scores. Scores were measured with a visual analogue scale (*VAS*) (0–10 cm: 0, no pain; 10, worst possible pain). Pain scores are expressed as means ± SD for each group. *P = 0.009 compared with vehicle

were treated with diazepam for anxiety and agitation while in the ICU.

The two groups were comparable in terms of demographics and clinical preoperative and intraoperative data (Table 2). Postoperatively, no difference between the groups was detected in time to tracheal extubation (209 ± 85 min vs 207 ± 98 min; etodolac vs vehicle), time from administration of etodolac to first VAS measurement (260 ± 111 min vs 254 ± 98 min), 12-h chest-tube blood loss (181 ± 87 ml vs 186 ± 71 ml), or the incidence of nausea and vomiting (Table 3).

Pain scores immediately after extubation were lower in the etodolac (2.3 ± 2.1) than in the vehicle group (5.8 ± 2.0; P = 0.009; Fig. 1). However, no difference was detected in pain scores at 24 h after surgery (Fig. 1), nor was any difference detected in the amount of buprenorphine administered in the ICU (Table 3).

The plasma concentration of etodolac was within the pharmaceutically recommended range at 1 h, 2 h, and 6 h after administration (3.0 ± 1.6 to 4.4 ± 2.2 μg/ml; Table 4).

No major postoperative complications were reported in either group. None of the study subjects developed perioperative myocardial infarction, bleeding gastric ulcer, renal dysfunction, or aspiration pneumonia.

Discussion

This study has demonstrated that the combination of etodolac with buprenorphine resulted in reduced pain scores in the immediate postoperative period after cardiac surgery. A similar observation had already been reported by others in patients treated with etodolac after coronary artery bypass operation, although the design of that study was different from ours [14]; that study demonstrated that etodolac given on postoperative days 2 and 3 reduced postoperative pain after CABG.

NSAIDs effectively provide analgesia and suppress inflammation by inhibiting the COX enzyme, with a consequent decrease in prostaglandin synthesis. However, COX inhibition may lead to undesired side effects by inhibiting the synthesis of prostaglandins that serve

Table 4. Plasma concentrations of etodolac (mean ± SD)

Time after administration (h)	Preoperation	1	2	6
Plasma concentration (μg/ml)	ND	3.0 ± 1.6	3.3 ± 1.3	4.4 ± 2.2

ND, not detected

important functions in other organs. This may promote complications, including upper gastrointestinal ulcer formation and hemorrhage, renal insufficiency, and platelet dysfunction, resulting in increased postoperative blood loss [8].

However, when a COX-2 inhibitor is used, side effects such as gastrointestinal events are significantly lower, as Bombardier and colleagues [17] reported in a large randomized trial of 8076 patients with rheumatoid arthritis treated with rofecoxib (a selective COX-2 inhibtor) compared with patients treated with naproxen (a nonselective inhibitor).

In our study, patients given etodolac orally did not have a difference in postoperative surgical blood loss, compared with patients given vehicle, for the first 12 h after surgery. Although one patient who had a large chest-tube blood loss after surgery was excluded from our data analysis, the large blood loss was explained by a surgical problem. In addition, we did not observe an increase in the incidence of nausea and vomiting in the patients receiving etodolac, and none of them developed peptic ulcer or gastrointestinal bleeding.

When a COX-2 inhibitor is used for a long period, the relative risk of the development of a thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks) may be higher, as Mukherjee and colleagues [12] reported in a large randomized trial of patients with arthritis and musculoskeletal pain treated with rofecoxib compared with patients treated with naproxen. However, the risk of cardiovascular events in the perioperative period associated with using a COX-2 inhibitor is unknown. It was thought that there was a little danger of thrombotic cardiovascular events in our study for the following reasons. First, the drugs were administered short-term rather than long-term. Second, the patients developed a bleeding tendency because of decreased and dysfunctional platelets and a decrease in coagulation factors caused by hemodilution after CPB. Third, the patients received medication after myocardial revascularization using grafts.

Currently, the pharmacokinetics of etodolac administered orally in patients undergoing cardiac surgery with CPB is unknown. In regard to the pharmaco-kinetics, it has been described that the plasma concentration started to increase approximately 30 min after oral administration, and peaked at about 60 min after oral intake [15]. An effective plasma concentration (about 3–20 $\mu g \cdot ml^{-1}$) is maintained for about 360 min when 400 mg etodolac is orally administered. In our study, the plasma concentration of etodolac increased gradually until 6 h after administration. It is possible that the absorption of etodolac in our study was delayed by the slow gastric emptying during anesthesia and cardiac surgery [18,19]. In the present study, we were not able to determine when the blood concentration reached its peak and how it was lowered after the peak. Further study with longer follow up may be necessary to determine the pharmacokinetics of orally administered etodolac in patients undergoing cardiac surgery.

Because COX-2 inhibitors are available only for oral use in Japan, we administered the drug via a gastric tube in this study. It was thought that there was little danger of aspiration, because patients had been tracheally intubated at the time of administration of the drug and were extubated after discharging the gastric contents.

The limitation of this study was that the VAS was measured at only two points after surgery (immediately after extubation and 24 h after surgery). Several physiological assessments scheduled on the first day after surgery, and a staff shortage, did not allow for more frequent assessment of pain in a calm atmosphere. More frequent assessment of pain may be necessary to clarify the effects of etodolac precisely.

In conclusion, etodolac, a COX-2 inhibitor, may be used as an adjunct for analgesia management in fast-track cardiac surgery. The oral use of etodolac reduced pain scores immediately after surgery without producing side effects. Further study on a larger scale and with various doses may be necessary to establish the most effective analgesic regimen with a COX-2 inhibitor after cardiac surgery.

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