ORIGINAL PAPER

EFFICACY AND SAFETY OF CELECOXIB COMPARED WITH PLACEBO AND ETODOLAC FOR ACUTE POSTOPERATIVE PAIN: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, CONTROLLED TRIAL

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ABSTRACT

Celecoxib is a nonsteroidal anti-inflammatory drug (selective cyclooxygenase-2 inhibitor) that is widely used. The efficacy and safety of celecoxib for treatment of acute postoperative pain were evaluated in Japanese patients. The objective was to assess whether celecoxib showed superiority over placebo treatment and non-inferiority versus etodolac (another selective cyclooxygenase-2 inhibitor) that has been widely used for the management of acute pain. A multicenter, double-blind, randomized, parallel-group, controlled study was performed, in which 616 patients with postoperative pain received celecoxib, etodolac, or placebo. Their impressions of study drug efficacy (overall assessment) and pain intensity were evaluated. Based on each patient's overall assessment of pain, the efficacy rate was 63.7% in the placebo group, 76.2% in the celecoxib group, and 68.0% in the etodolac group, with these results demonstrating superiority of celecoxib to placebo and noninferiority versus etodolac. The efficacy rate was significantly higher in the celecoxib group than in the etodolac group. There were no adverse events specific to celecoxib, and the safety of celecoxib was similar to that of placebo. Celecoxib was superior to etodolac for controlling acute postoperative pain.

Key Words: Celecoxib, Clinical study, Placebo, Etodolac, Postoperative pain

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory, analgesic and antipyretic effects by inhibiting cyclooxygenase-2 (COX-2) and thus blocking the production of inflammatory mediators such as prostaglandin (PG) E2. These drugs are widely used for the treatment of chronic diseases such as rheumatoid arthritis (RA), osteoarthritis (OA), and back pain, as well as for the control of acute pain such as postoperative pain, posttraumatic pain, and pain after dental surgery.[1] Conventional NSAIDs also inhibit cyclooxygenase-1 (COX-1),

and thus block the biosynthesis of PGs that are important for maintaining the integrity of the upper gastrointestinal tract mucosa or are involved in platelet and kidney function, leading to adverse reactions such as gastrointestinal tract disorders, impaired platelet aggregation, and renal impairment.[2-5]

Postoperative pain is caused by nociceptive stimuli due to tissue damage. Characteristically, postoperative pain is most intense immediately after surgery, and often diminishes in a relatively short period.[6] NSAIDs are widely used to control postoperative pain. However, NSAIDs can cause acute gastric mucosal lesions, along with surgical stress and trauma. Moreover, platelet aggregation is reduced by NSAIDs and this may lead to postoperative bleeding.[7] In view of these risks, any NSAID that is selected for the control of acute postoperative pain must have a superior safety profile even though the administration period is likely to be short.

Celecoxib is a selective COX-2 inhibitor, with an inhibitory effect on COX-2 that is 375 times stronger than its effect on COX-1.[8-10] In various models of inflammation and pain, celecoxib causes less damage to the gastrointestinal mucosa and less impairment of platelet function than conventional NSAIDs at doses showing a similar anti-inflammatory/analgesic effect.[10] In clinical studies, the incidence of endoscopic gastroduodenal ulcers was found to be significantly lower in patients given celecoxib than in those treated with conventional NSAIDs, and was similar to the incidence in the placebo group, indicating that celecoxib is safer for the upper gastrointestinal tract compared with conventional NSAIDs.[11-12]

Currently, celecoxib has been approved for various indications in approximately 140 countries around the world, and it is used for the treatment of acute pain in approximately 60 countries. We conducted the present clinical study in Japanese patients undergoing different types of surgery to evaluate the efficacy and safety of celecoxib for acute postoperative pain. Our objective was to assess whether celecoxib showed superiority over placebo treatment and non-inferiority versus etodolac, another selective COX-2 inhibitor that has been widely used for the management of acute pain. This was the first head-to-head study of two commercially available selective COX-2 inhibitors for acute postoperative pain (excluding patients undergoing oral surgery).

MATERIALS AND METHODS

This multicenter double-blind, randomized, parallel-group controlled trial was conducted at 79 centers in Japan from February to November 2010. The study was approved by each institution's investigational review board. This study was registered at http://www.clinicaltrials. gov (NCT01118572).

Subjects

The subjects were patients undergoing osteosynthetic implant removal, osteosynthesis, ligament reconstruction, arthroscopic meniscectomy or meniscal repair, tendon repair, removal of benign tumors, and surgery for carpal tunnel syndrome, cubital tunnel syndrome, ingrown toenail, inguinal hernia, and varicose veins. Only patients whose postoperative pain was judged to be controllable with oral NSAIDs alone were eligible, provided that they were ≥20 years old and gave written informed consent to this study. Patients who required general anesthesia were excluded, as were patients with risk factors for cerebrovascular/cardiovascular disease, patients with gastrointestinal bleeding/peptic ulcer, and patients using prohibited concomitant medications.

Study drug administration

Celecoxib, etodolac, or placebo was administered if patients had spontaneous pain within 24

hours after surgery that met the following criteria:
1) "Moderate" or "severe" pain on a 4-grade pain intensity scale ("none", "mild", "moderate", and "severe").
2) Pain with a 100 mm visual analogue scale (VAS) score≥45.0 mm.

Patients were randomized to the celecoxib, etodolac, and placebo groups at the ratio of 2:2:1, using dynamic allocation with the type of surgery (osteosynthetic implant removal, inguinal hernia, benign tumor removal, and others) as a factor. A computerized randomization system (block size five; generated by Adjust, an independent allocation company) was used, with concealed allocation of study drugs to consecutively numbered subjects. Patients and investigators were masked to treatment throughout the study. The initial dose of celecoxib was 400 mg, with subsequent doses being 200 mg each. Etodolac was administered at 200 mg per dose throughout the study. Each study drug was administered orally twice a day for two days at intervals of six hours or longer.

If postoperative pain could not be controlled by the study drug and rescue analgesia was required, the study was discontinued and another analgesic (not etodolac or celecoxib) was administered.

Prior and concomitant treatments

The following concomitant medications were prohibited: analgesics apart from aspirin, anesthetics, other anti-inflammatory drugs, hypnotics, antiepileptic drugs, antipsychotic drugs, antidepressants, anti-mania drugs, anxiolytics, analeptics, antiparkinson drugs, antihistamines, and corticosteroids. However, use of ultra-short-acting sedative-hypnotics before surgery was permitted, as was use of midazolam and propofol for sedation during surgery under local anesthesia and use of anesthetics during surgery.

Concomitant therapy for postoperative pain, such as immobilization, could be provided as long as it was not changed during the study. Concomitant drugs that could interact with the investigational drugs were prohibited.

Efficacy assessment

Pain intensity was assessed on the VAS before treatment, at 2, 4, and 6 hours after the initial dose, at bedtime on day 1, on awakening and at bedtime on day 2, and at discontinuation (if the study was discontinued). Each subject assessed the study drug on a 4-grade scale ("very effective", "effective", "slightly effective", or "not effective") at 6 hours after the initial dose, before bedtime on day 1, before bedtime on day 2, and at discontinuation (if relevant).

The primary endpoint was each patient's overall assessment throughout the treatment period (from the initial dose to before bedtime on day 2 or at discontinuation). The efficacy rate was the percentage of "effective" plus "very effective" evaluations.

Safety

An adverse event was defined as any untoward medical event in a subject who had received any of the study drugs, and information on adverse events was collected. At the start and end of the observation period, laboratory tests (red cell count, hemoglobin, hematocrit, white cell count, platelets, total protein, A/G ratio, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, CPK, BUN, creatinine, total cholesterol, Na, K, Cl, Ca, inorganic phosphorus, urinalysis (protein, glucose, urobilinogen, and blood), urinary β-N-acetyl-D-glucosaminidase, β₂-microglobulin, and creatinine, and fecal occult blood) were performed and the vital signs (systolic/diastolic blood pressure and pulse rate) were recorded.

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Statistical analysis

To determine the target sample size, it was assumed that the efficacy rate would be 85% in the celecoxib and etodolac groups versus 56% in the placebo group, with an effect size of approximately 30% and a noninferiority margin of 10% (1/3 of the effect size). Accordingly, the ratio of subjects in the placebo group versus the active drug groups was set at 1:2, and the number of subjects necessary to assess the superiority of celecoxib over placebo and its noninferiority to etodolac at $p<0.05$ (two-sided) with a power of 80% was calculated. The required number of subjects was 553 (221 subjects in each of the celecoxib and etodolac groups, and 111 in the placebo group), so the target sample size was set at 600 subjects to allow for dropouts.

For statistical analysis, SAS Data Integration Studio (version 3.4), SAS Drug Development (version 3.4), and PC-SAS (version 8.2) software were used. The level of significance was set at $p<0.05$ (two-sided), and 95% confidence intervals (two-sided) were calculated. MedDRA/J (version 13.1) was used for the tabulation of diseases and adverse events.

If a patient discontinued the study, data obtained until the time of discontinuation were used. Missing data were replaced by the nearest values available using the last observation carried forward approach.

The analysis population was the full analysis set (FAS), which was defined as subjects with one or more of the efficacy endpoints who received an investigational drug.

The efficacy rate was the primary endpoint and its two-sided 95% confidence interval was calculated. The confidence interval of the difference in efficacy was calculated by the Mantel-Haenszel method with adjustment for the type of surgery. In addition, the superiority of celecoxib over placebo and its noninferiority to etodolac were investigated by a closed testing procedure, in which noninferiority to etodolac was only assessed if superiority over placebo was initially confirmed. The cumulative rate of discontinuation due to lack of efficacy was calculated by the Kaplan-Meier method and the log-rank test was conducted.

RESULTS

Written informed consent was obtained from 1,024 subjects. Patients were randomized two days before surgery since the study treatment needed to be started immediately when patients complained of postoperative pain. Patients whose pain did not reach the specified level were excluded from the study, and the remaining 616 patients received a study drug. The disposition of the subjects is shown in Figure 1. In the placebo group, 96 out of 124 patients (77.4%) completed the study, as did 221 out of 248 patients (89.1%) in the celecoxib group and 205 out of 224 patients (84.0%) in the etodolac group. The reasons for withdrawal before randomization were violation of the inclusion/exclusion criteria (n=90), withdrawal of consent (n=25), and others (n=5). The reasons for withdrawal after randomization were violation of the inclusion/exclusion criteria (n=281, including patients in whom pain intensity did not reach the specified level), withdrawal of consent (n=3), protocol violation (n=1 case), and others (n=3).

The demographic and baseline characteristics of the subjects are shown in Table 1. Although the percentage of women was slightly lower in the celecoxib group than in the other two groups, there were no significant differences of the mean age, body weight, and body mass index (BMI) among the groups. There were also no differences in the site or type of surgery and the level of surgical invasion.

The efficacy rate based on each patient's overall assessment of the investigational drug was the primary endpoint of this study; it was 63.7% in the placebo group, 76.2% in the celecoxib group, and 68.0% in the etodolac group. The efficacy rate was significantly higher in the

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│      1,024 patients         │
│   giving informed consent   │
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              │                     ┌─────────────────────────┐
              ├─────────────────────│  120 withdrawals before │
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│       904 patients          │
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              ├─────────────────────│  288 withdrawals after  │
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│       616 patients          │
│         treated             │
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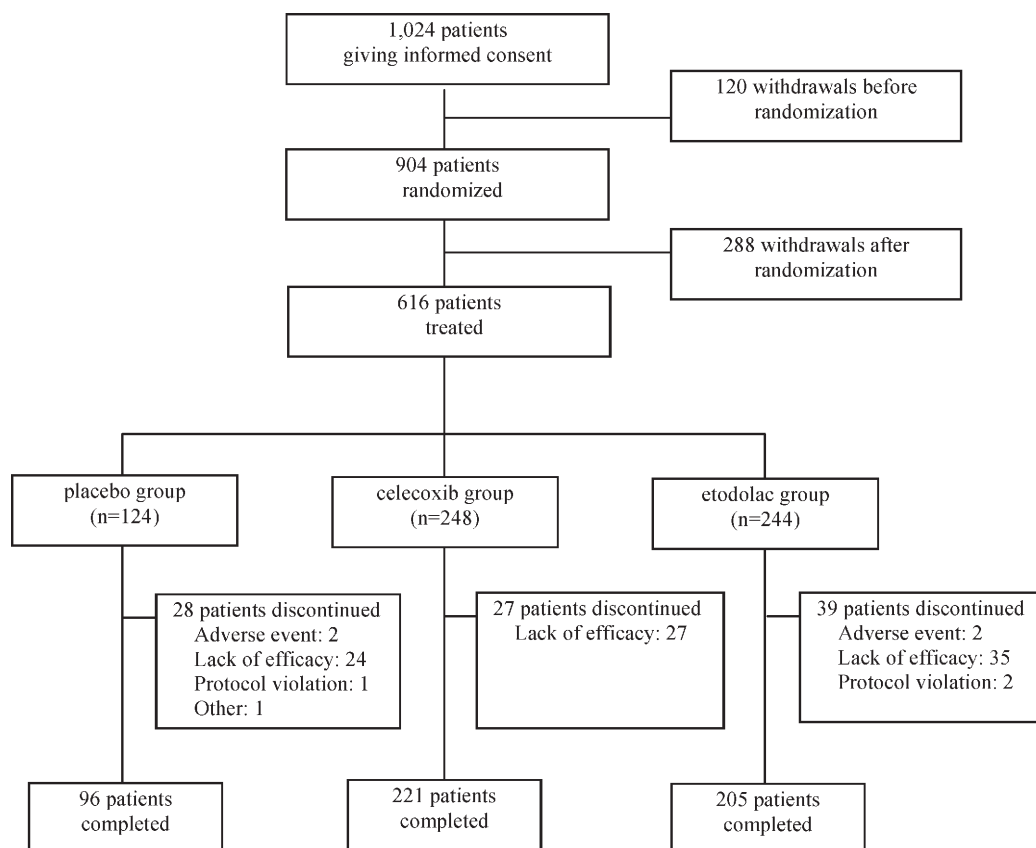| placebo group (n=124)	celecoxib group (n=248)	etodolac group (n=244)
28 patients discontinued Adverse event: 2 Lack of efficacy: 24 Protocol violation: 1 Other: 1	27 patients discontinued Lack of efficacy: 27	39 patients discontinued Adverse event: 2 Lack of efficacy: 35 Protocol violation: 2
96 patients completed	221 patients completed	205 patients completed

Fig. 1 Disposition of the subjects

celecoxib group than the placebo group, while no significant difference was observed between the etodolac and placebo groups. The efficacy rate was also significantly higher in the celecoxib group than the etodolac group (Figure 2). Since the lower limit of the 95% confidence interval for the difference in efficacy rate between celecoxib and etodolac was 0.32% and this value was larger by −10%, noninferiority of celecoxib relative to etodolac was demonstrated.

The results of subgroup analysis are shown in Figure 3. Subgroup analysis was performed with stratification by the surgical procedure, level of surgical invasiveness, and baseline pain intensity. In relation to the type of surgery, the efficacy rate was calculated for groups undergoing osteosynthetic implant removal, inguinal hernia, removal of benign tumors, and other procedures. In relation to surgical invasiveness, this was evaluated as mild, moderate, or severe by the investigator. In relation to baseline pain intensity, the intensity of spontaneous pain immediately before the first dose of the investigational drug was assessed by the subjects (none, mild, moderate, or severe). Only subjects with moderate or severe pain were included in the study. The efficacy rate was calculated as the percentage of patients who evaluated the study drug as "effective" or "very effective". Efficacy rates (%) with 95% confidence intervals are shown, together with numbers in parentheses indicating the number of subjects. The efficacy rate was 55.2–70.6% for inguinal hernia, 60.0–77.6% for osteosynthetic implant removal, and 77.8–86.5% for removal of benign tumors, showing some differences between the different operations. In addition, the efficacy rate

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Table 1 Demographic and baseline data of the full analysis set

	Placebo n=124	Celecoxib n=248	Etodolac n=244
Sex			
Male	68(54.8%)	157(63.3%)	138(56.6%)
Female	56(45.2%)	91(36.7%)	106(43.4%)
Age (Years, Mean±SD, Min-Max)	53.7±14.8, 20–90	50.2±16.3, 20–82	53.2±15.7, 20–91
Body weight (kg, Mean±SD, Min-Max)	61.6±11.5, 40.0–113.8	62.2±11.3, 40.0–111.0	62.7±11.8, 39.0–114.5
BMI[a)] (kg/m^2, Mean±SD, Min-Max)	23.4±3.5, 16.5–38.8	23.2±3.6, 15.9–37.5	23.5±3.3, 17.2–34.9
Surgical site			
Upper extremity	36(29.0%)	64(25.8%)	60(24.6%)
Lower extremity	42(33.9%)	88(35.5%)	89(36.5%)
Trunk	42(33.9%)	83(33.5%)	87(35.7%)
Others	4(3.2%)	13(5.2%)	8(3.3%)
Type of surgery			
Nail extraction	25(20.2%)	50(20.2%)	49(20.1%)
Inguinal hernia	34(27.4%)	68(27.4%)	67(27.5%)
Removal of benign tumor	18(14.5%)	37(14.9%)	36(14.8%)
Others	47(37.9%)	93(37.5%)	92(37.7%)
Invasiveness			
Mild	82(66.1%)	151(60.9%)	161(66.0%)
Moderate	42(33.9%)	96(38.7%)	83(34.0%)
Severe	0	1(0.4%)	0
Baseline pain intensity			
No pain	0	0	0
Mild pain	0	0	0
Moderate pain	111(89.5%)	224(90.3%)	226(92.6%)
Severe pain	13(10.5%)	24(9.7%)	18(7.4%)
Baseline pain intensity (VAS[b)]) (mm, Mean±SD, Min-Max)	63.2±11.6, 46.6–99.0	62.7±10.6, 45.0–100.0	60.7±11.2, 45.1–100.0

a) BMI : Body Mass Index b) VAS : Visual Analog Scale

was higher in patients who underwent less invasive surgery than in those who underwent more invasive surgery (67.1–79.5% vs.57.1–71.9%). Furthermore, the efficacy rate was higher in patients with moderate pain than in those with severe pain (69.4–78.1% vs. 15.4–58.3%). The placebo group showed the lowest efficacy rate and the celecoxib group had the highest efficacy rate in most of these subgroup analyses.
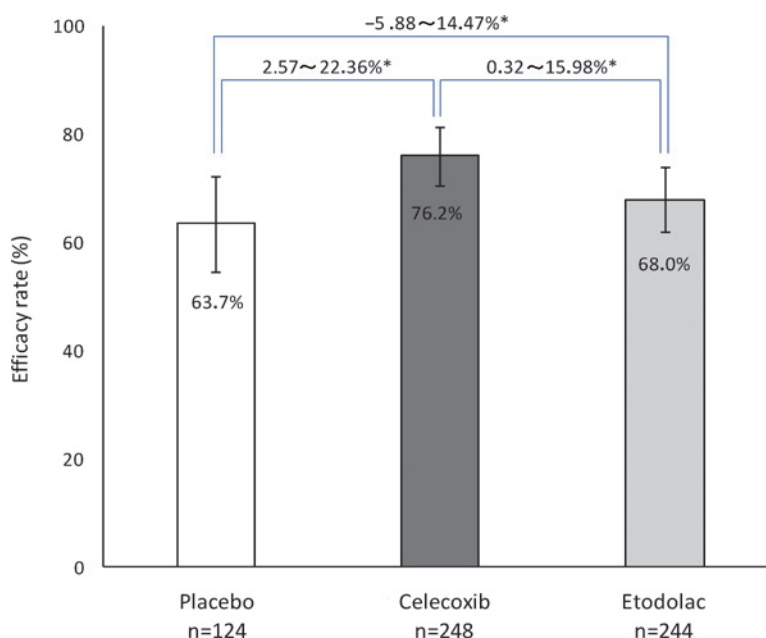
Fig. 2 Efficacy rate in the full analysis set
*: 95% confidence interval (CI) of the difference between groups by the Mantel-Haenszel test.
The efficacy rate and 95% CI are shown.

The changes of pain intensity determined from the VAS data are shown in Figure 4. In all groups, pain intensity decreased over time, but it was significantly lower in the celecoxib and etodolac groups than in the placebo group at all times of assessment (2, 4, and 6 hours) after the initial dose. (Not tested at baseline/before bedtime on day 1/at waking on day 2/ before bedtime on day 2.)

The discontinuation rate due to unsatisfactory efficacy is shown in Figure 5. It was 19.4% in the placebo group, 10.9% in the celecoxib group, and 14.3% in the etodolac group. A time to event analysis with the Kaplan Meier method revealed a significant difference between the celecoxib group and the placebo group (log-rank test: p=0.0231). There was no significant difference between the etodolac group and the placebo group or between the celecoxib group and the etodolac group.

No deaths occurred during this study. The incidence of adverse events was 33.1% (41/124 patients) in the placebo group, 30.2% (75/248 patients) in the celecoxib group, and 34.4% (84/244 patients) in the etodolac group, being similar in all three groups. Serious adverse events occurred in two patients, which were pyrexia in one patient from the placebo group and headache in one patient from the celecoxib group. However, the headache was judged as mild in severity by the investigator and the relationship with celecoxib was excluded. Adverse events leading to discontinuation of treatment occurred in two patients from the placebo group (pyrexia in both patients) and two patients from the etodolac group (nausea and back pain).

A classification of adverse events by system organ class/symptom is shown in Table 2. Adverse events with an incidence of 2% or higher were occult blood positive (12.5%), β_2 microglobulin urine increased (4.4%), blood urine present (3.2%), blood creatine phosphokinase increased (2.4%), headache (2.4%), and urine β-N-acetyl-D-glucosaminidase increased (2.0%). The incidence
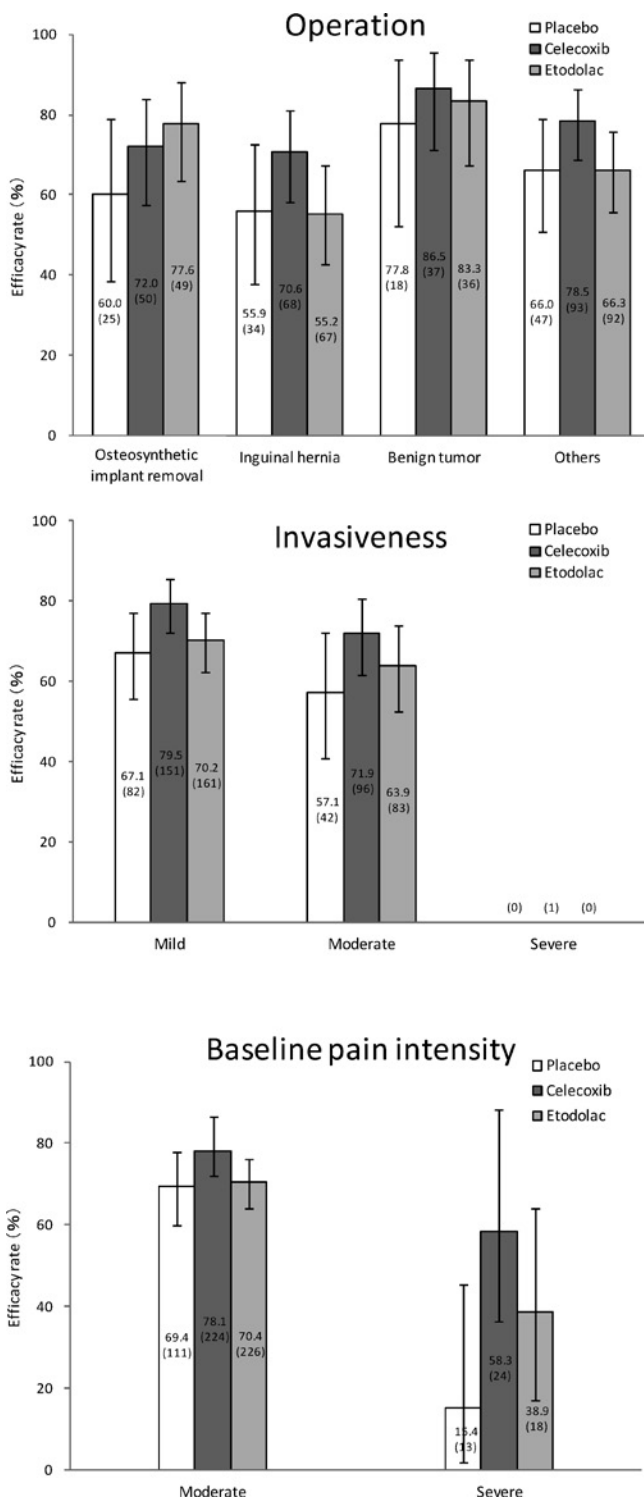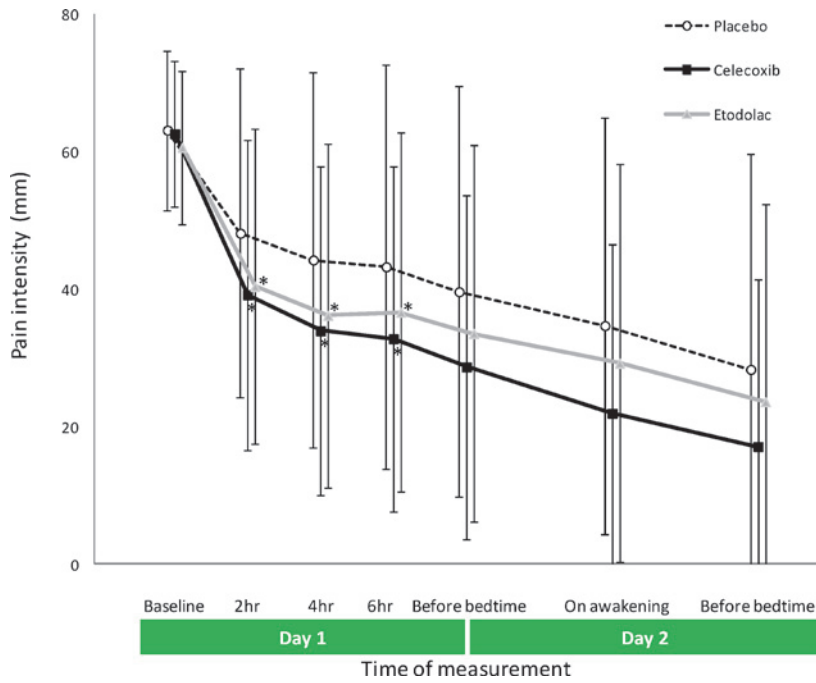
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Fig. 3 Subgroup analysis of efficacy

Fig. 4 Changes of VAS pain intensity in the full analysis set
Data are shown as the mean and standard deviation.
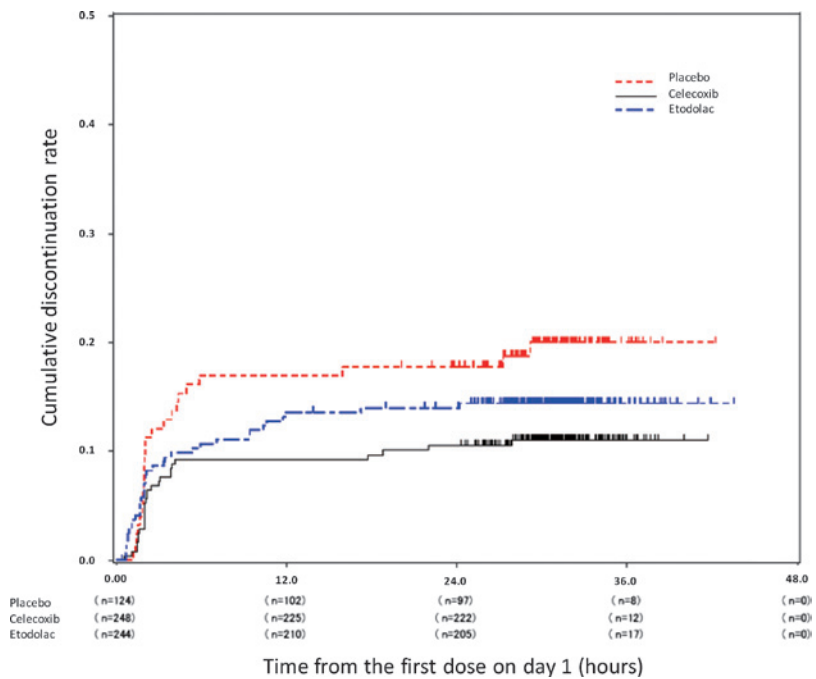*: $p < 0.05$ versus placebo (t-test).

Fig. 5 Cumulative discontinuation rate for lack of efficacy in the full analysis set.

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Table 2 Adverse events with an incidence ≥1% in any group

	Placebo n=124	Celecoxib n=248	Etodolac n=244
All adverse events[a]	41(33.1%)	75(30.2%)	84(34.4%)
Gastrointestinal disorders	6(4.8%)	6(2.4%)	10(4.1%)
Constipation	1(0.8%)	3(1.2%)	3(1.2%)
Diarrhea	2(1.6%)	1(0.4%)	1(0.4%)
Nausea	1(0.8%)	0	4(1.6%)
General disorders and administration site conditions	6(4.8%)	2(0.8%)	3(1.2%)
Pyrexia	4(3.2%)	2(0.8%)	3(1.2%)
Investigations	30(24.2%)	56(22.6%)	68(27.9%)
Alanine aminotransferase increased	0	2(0.8%)	3(1.2%)
Aspartate aminotransferase increased	1(0.8%)	2(0.8%)	3(1.2%)
Beta 2 microglobulin urine increased	5(4.0%)	11(4.4%)	16(6.6%)
Beta-N-acetyl-D-glucosaminidase increased	6(4.8%)	5(2.0%)	8(3.3%)
Blood bilirubin increased	2(1.6%)	3(1.2%)	2(0.8%)
Blood creatine phosphokinase increased	1(0.8%)	6(2.4%)	4(1.6%)
Glucose urine present	5(4.0%)	4(1.6%)	6(2.5%)
Blood urine present	3(2.4%)	8(3.2%)	5(2.0%)
Occult blood positive	21(16.9%)	31(12.5%)	39(16.0%)
Urobilinogen urine increased	0	3(1.2%)	2(0.8%)
Nervous system disorders	2(1.6%)	7(2.8%)	8(3.3%)
Headache	2(1.6%)	6(2.4%)	8(3.3%)

a) Adverse events (MedDRA/J ver.13.1) with an incidence of 1% or higher in any group are listed for the safety analysis set. Data are shown as the number (%) of patients.

of a positive occult blood test was 16.9% in the placebo group and 16.0% in the etodolac group, while the incidence of increased urine β_2-microglobulin was 4.0% and 6.6%, and the incidence of hematuria was 2.4% and 2.0%, respectively. None of the adverse events showed a higher incidence in the celecoxib group and all adverse events observed in the celecoxib group were mild. Moderate adverse events were pyrexia in one patient from the placebo group and headache in one patient from the etodolac group.

DISCUSSION

This was the first head-to-head study of two commercially available COX-2 inhibitors for acute postoperative pain in patients undergoing surgery (excluding oral surgery). Efficacy of both celecoxib and etodolac for acute postoperative pain has already been demonstrated by comparison with other active agents or placebo,[13-20] but this was the first direct comparison of the two drugs for acute pain after surgery. Our results showed that celecoxib was more effective for postoperative pain than etodolac, while showing similar safety to placebo.

Acute postoperative pain decreases over time, but providing effective early pain control is essential for rapid recovery and for improving patient satisfaction.[6,21] The expected decrease of pain intensity over time may account for the high efficacy rate observed in the placebo group in the present study, and the large placebo effect is probably one reason that etodolac showed no significant difference in efficacy from placebo. On the other hand, celecoxib was significantly more effective than placebo, and the efficacy of celecoxib can be inferred.

We considered that patients with postoperative pain would be an appropriate population for assessing the efficacy of a drug for acute pain, since their demographic profile can be standardized more easily than that of general patients with acute pain. To ensure the enrollment of patients who had a certain level of pain, the types of surgery were specified in this study so that the extent of surgical invasion was similar. This still allowed us to assess not only orthopedic surgery but also other types of surgery in the minor to moderate categories, in which patients are able to take oral medications postoperatively. The number of patients who received study treatment was smaller than the number giving informed consent because we excluded patients who only had mild postoperative pain. Subjects were dynamically allocated to each group in order to minimize any bias of baseline pain intensity.

The initial dose of celecoxib was 400 mg, with subsequent doses of 200 mg, while etodolac was always administered at 200 mg per dose. These are approved dosages in Japan, and were also considered to be standard dosages on a global basis,[20] making it unlikely that the dose of etodolac was insufficient for comparison of efficacy. The initial dose of celecoxib (400 mg) was reasonable in view of the need for rapid control of acute postoperative pain. After a single 100 mg dose of celecoxib, C_{max} was 553±212.2 ng/mL, while this concentration was reached at approximately 30 minutes after a single dose of 400 mg.[21] The present study demonstrated that celecoxib was useful for postoperative pain since the incidence of adverse events was not increased by administration soon after surgery. An adequate early analgesic effect may have contributed to the higher efficacy of celecoxib, as well as to the low discontinuation rate for lack of efficacy (Figure 5).

The lower efficacy of placebo compared with celecoxib and etodolac in subjects with "severe" baseline pain indicated that the placebo effect was smaller in patients who required more pain control, supporting the validity of this study.

No marked difference in safety was seen among the three groups. In particular, the frequency of gastrointestinal symptoms and positive fecal occult blood tests in the celecoxib group and the etodolac group was similar to that of the placebo group.

In conclusion, this study showed the safety of COX-2 inhibitors for postoperative pain control, with celecoxib being more effective than etodolac for this indication.

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CONFLICT OF INTEREST

Ishigro Naoki was a medical adviser to the study and was paid an advisory fee by Astellas Pharma. Ishigro Naoki have also received honoraria from Abbott Japan, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical, Kaken Pharmaceutical, Ono Pharmaceutical, Pfizer Japan, Takeda Pharmaceutical, Mitsubishi Tanabe Pharmaceutical, Taisho Toyama Pharmaceutical, Hisamitsu Pharmaceutical, Daiichi Sankyo Pharmaceutical. Hanaoka Akio, Okada Toshiyuki and Ito Masanori are currently employees of Astellas Pharma.

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