

The Efficacy of Celecoxib Premedication on Postoperative Pain and Recovery Times After Ambulatory Surgery: A Dose-Ranging Study

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Recently, the Food and Drug Administration increased the celecoxib dosage recommendation from 200 mg to 400 mg for acute pain management. No studies have directly compared the analgesic efficacy of different doses of celecoxib for the prevention of postoperative pain. In this prospective, double-blinded, placebo-controlled study, we compared oral celecoxib 200 mg to 400 mg when administered for premedication of outpatients undergoing minor ear-nose-throat surgery. A total of 93 healthy outpatients were assigned to 1 of 3 study groups: control (placebo; $n = 30$), celecoxib 200 mg ($n = 30$), or celecoxib 400 mg ($n = 33$). The study drug was given orally 30–45 min before surgery, and all patients received a standardized general anesthetic technique. During the postoperative period, pain scores (0–10), recovery times, the need for rescue analgesics, quality of recovery (0–100), patient satisfaction with pain management (0–100), and side effects were recorded. Pain was assessed at 30-min intervals using a verbal rating scale, with 0 = no pain to 10 = worst pain imaginable, in the postanesthesia care unit and day surgery unit recovery areas and at 24 h after surgery.

Celecoxib 400 mg was significantly more effective than 200 mg (and placebo) in reducing postoperative pain. Both celecoxib 200 mg and 400 mg were more effective than placebo in reducing the postoperative fentanyl requirement ($74 \pm 67 \mu\text{g}$ and $56 \pm 62 \mu\text{g}$ versus $120 \pm 86 \mu\text{g}$, respectively). The larger dose of celecoxib significantly reduced the percentage of patients with severe pain at discharge (6% versus 37% and 30% in the celecoxib 200 mg and control groups, respectively). The median number of doses of oral analgesic medication after discharge was also significantly reduced in the celecoxib 400 mg group (0 versus 2 and 2 in the celecoxib 200 mg and control groups, respectively). However, no differences were found among the three study groups with respect to recovery times and secondary outcome variables (e.g., patient satisfaction and quality of recovery). We conclude that oral premedication with celecoxib 400 mg was more effective than 200 mg in reducing severe postoperative pain and the need for rescue analgesic medication in the postoperative period.

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Nonsteroidal antiinflammatory drugs (NSAIDs) are increasingly used as part of a multimodal approach to improve the management of pain after ambulatory surgery (1). However, there is still controversy regarding the use of the traditional nonselective NSAIDs (2). These classical NSAIDs block the synthesis of prostaglandins by inhibiting both cyclooxygenase type-1 (COX-1) and the inducible COX type-2 (COX-2)

enzymes. As a result, the use of NSAIDs in the perioperative setting has been limited because of concerns regarding their potential adverse effects on platelet function (e.g., operative site bleeding), gastrointestinal mucosa (3,4), and renal tubular function (5).

COX-2 selective drugs have been introduced into clinical practice as alternatives to the nonselective NSAIDs because they are alleged to produce comparable analgesia without adverse effects on platelet, gastrointestinal mucosal, and renal function (6,7). Celecoxib, a COX-2 inhibitor, has been found to be comparable to acetaminophen (8) but less effective than rofecoxib in the prevention of pain after surgery (7–10). However, all of these studies compared a 200-mg dose of celecoxib to 50 mg of rofecoxib. The Food and Drug Administration increased the celecoxib dosage recommendation for acute postoperative

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pain to 400 mg. No published controlled studies have directly compared the analgesic efficacy of the two doses of celecoxib for the prevention of postoperative pain.

Therefore, this prospective, double-blinded, placebo-controlled study was designed to compare oral celecoxib 200 mg and 400 mg when administered for premedication in outpatients undergoing minor ear-nose-throat (ENT) surgery. We tested the hypothesis that a larger dose of celecoxib (400 mg) would more effectively reduce postoperative pain and the need for opioid-containing analgesics than the 200-mg dose. A secondary objective was to assess the effect of the celecoxib dose on the recovery process and patient satisfaction with their pain management and quality of recovery.

Methods

After obtaining IRB approval at the University of Texas Southwestern Medical Center at Dallas, written informed consent was obtained from 93 ASA physical status I and II outpatients (aged 19–75 yr) undergoing minor ENT procedures. These patients were studied according to a randomized, double-blinded, placebo-controlled protocol. Patients were excluded if they had received any analgesic medication within 12 h before surgery, were pregnant, breast-feeding, had a history of drug or alcohol abuse, clinically significant cardiovascular, renal, hepatic, or gastrointestinal disease, or had experienced an adverse reaction to the study medication.

In the preoperative holding area, patients completed baseline verbal rating scales (VRS) for pain and nausea, with 0 = none to 10 = worst imaginable. Patients were randomly assigned to one of the three treatment groups: control (Vitamin C; $n = 30$), celecoxib 200 mg ($n = 30$), or celecoxib 400 mg ($n = 33$). The study drugs were prepared by the operating room pharmacist according to a computer-generated random number schedule and were given by a staff nurse 30–45 min before surgery. The patients, the researchers, and those involved in the anesthetic care of the patients were blinded to the contents of the oral premedication.

Before leaving the preoperative holding area, all patients were also premedicated with midazolam 20 $\mu\text{g}/\text{kg}$ IV. On arrival in the operating room, anesthesia was induced with propofol 2 mg/kg IV and remifentanyl 0.5 $\mu\text{g}/\text{kg}$ IV, and tracheal intubation was facilitated with rocuronium 0.6 mg/kg. Droperidol, 0.625 mg IV, was given to all patients for antiemetic prophylaxis. Anesthesia was initially maintained with desflurane 4% inspired concentration in combination with air (0.5 L/min) and oxygen (0.5 L/min) and an infusion of remifentanyl 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The inspired concentration of desflurane and the remifentanyl infusion rate were subsequently varied from 2% to 6% and 0.06 to 0.2

$\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, to maintain the mean arterial blood pressure and heart rate values within 15% of the baseline values. At the end of the surgical procedure, residual neuromuscular block was reversed with edrophonium 50–80 mg IV and atropine 0.5–0.8 mg IV, and the maintenance anesthetic drugs were discontinued.

During the postoperative period, a blinded observer (TI) determined recovery times to awakening (e.g., opening eyes in response to a verbal command) and orientation to person, date, and place at 1-min intervals after discontinuation of the maintenance anesthetics. Patients rated their pain (and nausea) scores on the 11-point VRS. These scores were recorded at 30-min intervals and immediately before receiving any rescue analgesic (or antiemetic) medication in the postanesthesia care unit (PACU) and in the day surgery unit (DSU). Patients with pain VRS scores of 6 or larger were considered to have severe pain. Patients complaining of moderate-to-severe pain (VRS >3) were treated with fentanyl 25- μg IV boluses. In keeping with our standard nursing practices, the nurses were not required to titrate fentanyl to achieve a specific VRS value. Patients with pain scores of 2–3 received a combination of oral hydrocodone (5 mg) and acetaminophen (500 mg). If the patient complained of nausea or experienced repeated episodes of vomiting (or retching), they were treated with dolasetron 12.5 mg IV, and if the emetic symptoms persisted, promethazine 6.25-mg IV boluses were administered to a total dose of 25 mg.

Postoperative side effects (e.g., pain, dizziness, nausea, and vomiting) and the requirements for rescue analgesic and antiemetic drugs were recorded along with the duration of their stay in the Phase I (PACU) and Phase II (DSU) recovery units, as well as the times until the patient was considered fit for discharge. The criteria used to determine fitness for discharge were that the patient be awake, alert, with stable vital signs on standing, experiencing no intractable postoperative side effects, and able to walk without assistance (8).

Finally, a follow-up telephone evaluation was performed at 24 h after surgery, and the patients were asked to report the number of doses of oral analgesic medications consumed after discharge. The occurrence of postdischarge nausea and vomiting, the need for rescue antiemetic therapy, and other side effects were also recorded. Finally, patient satisfaction with their postoperative pain management and the quality of their recovery were assessed using a VRS, with 0 = poor to 100 = excellent.

This study was designed to assess the ability of celecoxib 200 or 400 mg orally given preoperatively to reduce postoperative pain. Hence, the end-points of pain intensity difference, pain relief over time, and time to onset of pain relief were not used. The analgesic efficacy of the study drugs was also assessed by

comparing the dose of rescue analgesic medications required in each group.

The primary end-points of this study were the dose of fentanyl required for rescue analgesia in the immediate postoperative period and the maximum pain score before rescue with an opioid-containing analgesic. The secondary end-points included recovery times and patient satisfaction with their pain management and quality of recovery. An *a priori* power analysis estimated that 30 patients would be required in each group. This was based on the following assumptions:

1. The mean and SD of the rescue dose of fentanyl in the placebo group would be similar to that in previously published studies with two similar patient populations where the same anesthetic regimen was used (8,9,11).
2. A clinically important reduction in the rescue dose of fentanyl with celecoxib 400 mg would be similar to that reported with the preoperative use of oral rofecoxib 50 mg in this patient population when a similar anesthetic regimen was used (9).
3. A Type I error of 0.0167 (two-sided test adjusted for multiple comparisons with three groups).
4. Power = 80%.

Data analyses were performed using Statview[®] for Windows Version 5.0.1 (SAS Institute, Cary, NC). Normally distributed continuous data were analyzed using one-way analysis of variance, and if significant differences were noted, a Student-Newman-Keuls test was used for intergroup comparisons. Continuous data not normally distributed (e.g., pain scores) were analyzed by a Kruskal-Wallis analysis of variance, and if significant differences were noted, a Mann-Whitney *U*-test was used for intergroup differences. Categorical data were analyzed using the χ^2 test with Yates' continuity correction or Fisher's exact test where appropriate. Data are presented as mean values \pm SD for normally distributed data, medians with interquartile ranges for data not normally distributed, numbers, or percentages. A *P* value of <0.05 was considered statistically significant.

Results

There were no significant differences among the three treatment groups with respect to age, weight, sex, type and durations of surgery and anesthesia, and the total doses of desflurane and remifentanyl administered during surgery (Table 1). Baseline pain and nausea VRS scores were similar in all three study groups. There were also no significant differences in the times from the end of anesthesia to eye opening, response to verbal commands, and orientation (Table 2). In addition, there were no differences in the time spent in the PACU and DSU or in the time to achieve fitness for discharge (Table 2).

The total dose of fentanyl used for rescue in the PACU was significantly decreased in both celecoxib groups compared with placebo and in the celecoxib 400-mg group compared with the celecoxib 200-mg group (Table 2). The proportion of patients with severe pain scores (VRS >6) during the postoperative period was also significantly decreased in the celecoxib 400 mg group compared with the other treatment groups. In addition, the peak pain scores were also significantly decreased in the celecoxib 400-mg group compared with the placebo group. However, the differences in peak pain scores between the celecoxib 200 mg and the other groups failed to achieve statistical significance. There were no significant differences among the study groups in the time to first rescue analgesia or in the nausea scores before discharge (Table 2).

The peak pain scores after discharge did not differ significantly among the three study groups (Table 3). However, the total number of doses of oral analgesics consumed during the first 24 h after surgery was significantly reduced in the celecoxib 400-mg group compared with the other two study groups. Unfortunately, the reductions in pain scores and the need for rescue analgesic medication did not lead to significant differences in the time to achieve fitness for discharge, patient satisfaction with pain management, or the quality of recovery among the three study groups (Tables 2 and 3).

Discussion

This study has demonstrated that the preoperative administration of oral celecoxib 400 mg provided better postoperative analgesia than celecoxib 200 mg but without altering times to discharge or improving patient satisfaction after minor ENT surgery. Whereas celecoxib 200 mg was also effective in reducing postoperative fentanyl consumption (the primary end-point of the study), it did not exert a statistically significant influence on other outcome measures such as the peak pain scores, oral analgesic consumption, recovery times, or patient satisfaction. Although the mean intraoperative anesthetic (desflurane) and analgesic (remifentanyl) requirements were slightly reduced in the large-dose celecoxib group, these differences were not statistically significant. Furthermore, these differences failed to significantly reduce emergence or recovery times. Even if these differences were to become statistically significant by enlarging the group sizes, they would probably not be clinically significant (e.g., time to home readiness).

This dose-ranging study was not really designed to achieve statistically significant results for all the secondary outcome variables, and the findings suggest a smaller power to detect these differences. It is interesting that a similar divergence between pain scores and opioid consumption was noted by Hyllested et al. (12) in 6 of 33 studies included in a recent systematic review comparing the analgesic efficacy of acetaminophen and

Table 1. Patient Characteristics, Surgery Type, Anesthesia and Surgery Times, Intraoperative Analgesic, and Anesthetic Dosages in the Three Study Groups

	Placebo	Celecoxib (200 mg)	Celecoxib (400 mg)
Number (n)	30	30	33
Age (yr)	46 ± 13	39 ± 13	42 ± 15
Weight (kg)	80 ± 22	78 ± 22	88 ± 20
Sex (M/F) (n)	18/12	15/15	22/11
Surgical procedures (n)			
Ethmoidectomy	8	7	7
Adenoidectomy	9	11	11
Panendoscopy and biopsy	13	12	15
Surgery time (min)	72 ± 35	69 ± 39	64 ± 42
Anesthesia time (min)	91 ± 36	90 ± 40	86 ± 44
Intraoperative remifentanyl (μg)	1007 ± 459	836 ± 430	837 ± 511
End-tidal desflurane concentration (%)	4.3 ± 0.8	4.2 ± 1.2	3.9 ± 0.7

Values are mean ± SD, numbers (n), or percentage (%).

Table 2. Recovery Times, Recovery Units Length of Stay, Time to First Analgesic Rescue Medication, and Postoperative Pain and Nausea Scores in the Three Study Groups

	Placebo	Celecoxib (200 mg)	Celecoxib (400 mg)
Recovery time (min) from end of surgery to			
Eyes opening (min)	8 ± 5	8 ± 5	6 ± 4
Obeys commands (min)	11 ± 6	13 ± 7	8 ± 4
Orientation (min)	14 ± 8	15 ± 9	12 ± 5
Recovery unit stay			
PACU (min)	69 ± 24	62 ± 27	62 ± 26
DSU (min)	85 ± 39	90 ± 60	81 ± 68
Time to first analgesic (min)	40 ± 39	41 ± 20	34 ± 36
Peak pain scores in PACU (0-10) (n)	5 (2-8)	5 (0-10)	4 (2-6)*
Patients with severe pre-discharge pain [n (%)]	9 (30)	11 (37)	2 (6)*†
Maximum nausea score (0-10) (n)	2 ± 2	2 ± 2	2 ± 2
Fentanyl in PACU (μg)	120 ± 86	74 ± 67*	56 ± 62*†
Satisfied discharge criteria (min)	141 ± 50	128 ± 26	119 ± 48

Values are mean ± SD, medians (interquartile range), and percentages (%).

PACU = postanesthesia care unit; DSU = day-surgery unit.

* $P < 0.05$, versus placebo group; † $P < 0.05$, versus celecoxib 200 mg group.

Table 3. Pain, Analgesic Requirements, Patient Satisfaction, and the Quality of Recovery at 24 h after Surgery in the Three Study Groups

	Placebo	Celecoxib (200 mg)	Celecoxib (400 mg)
Peak VRS pain scores after discharge (n)	2 (0-10)	2 (0-6)	2 (0-5)
Median doses of oral analgesics			
after hospital discharge (n)	2 (0-6)	2 (0-5)	0 (0-2.5)*
during first 24 h after surgery (n)	3 (0-7)	2.5 (0-5.5)	1 (0-3)*†
Patient satisfaction with pain management (n) ^a	93 ± 7	93 ± 8	95 ± 6
Quality of recovery score (n) ^b	90 ± 12	91 ± 14	94 ± 5

Values are mean ± SD, medians (interquartile range), and numbers.

VRS = verbal rating scale, with 0 = no pain to 10 = worst pain imaginable.

^a Patient satisfaction (0 = highly dissatisfied to 100 = highly satisfied).

^b Quality of recovery score (0 = poor to 100 = excellent).

* $P < 0.05$ vs Placebo group.

† $P < 0.05$ vs Celecoxib 200 mg group.

NSAIDs. However, the findings of this study clearly support the recent decision by the Food and Drug Administration to increase the initial dosage of celecoxib

from 200 mg to 400 mg when it is used for acute pain management. Subsequent 200-mg doses of celecoxib have been recommended, and it is possible that a second

dose of celecoxib at the time of discharge (or on the morning after surgery) may have led to an improvement in pain management after discharge. It is also unclear if similar analgesia can be achieved with nonselective NSAIDs such as ibuprofen, diclofenac, and ketorolac.

The proponents of the use of selective COX-2 drugs for postoperative analgesia suggest that there will be a decreased incidence of side effects such as operative site bleeding. Whereas a limited number of relatively small studies in pediatric patients have reported increased bleeding after tonsillectomy procedures when the nonselective COX-1 inhibitor ketorolac was used (3,4), a large multicenter study involving 11,245 adult patients found no differences in the incidence of bleeding from either the surgical site or the gastrointestinal tract with ketorolac, ketoprofen, or diclofenac (13). In the latter study, there was increased bleeding in all ENT patients compared with those undergoing other operations, but the combination of ENT surgery and ketorolac therapy was not associated with increased operative site bleeding (13).

Interestingly, a study by Pickering et al. (14) involving children undergoing adeno-tonsillectomy procedures failed to detect a difference in blood loss between rofecoxib and ibuprofen pretreatment groups. However, these authors stated that the study had limited power to demonstrate a difference seen between the groups because of the large variation in blood loss (14). Obviously, additional large-scale studies involving a wide variety of surgical procedures are required to determine if the preferential use of COX-2 inhibitors like celecoxib will be associated with reduced perioperative bleeding compared with the nonselective NSAIDs ketorolac and ibuprofen.

In the current study, we administered oral celecoxib 30–45 minutes before surgical procedures lasting an average of 68 (± 38) minutes. Because peak blood levels of celecoxib occur within two hours after oral administration on an empty stomach (15), patients should have had adequate time to achieve analgesic blood levels in the early recovery period. There are also data indicating an onset of analgesic action within 90 minutes after oral administration (7–15) and a lack of correlation between blood levels and analgesic efficacy (16). Therefore, it would seem that there was adequate time for the onset of the analgesic action of celecoxib in our study population.

The results of this study differ somewhat from our earlier study (8) because this outpatient population only included minor ENT procedures. It is possible that this subset of ENT patients experienced less postoperative pain than in the earlier study involving a more diverse ENT population. As a result, the current study population may have been more responsive to the analgesic effects of this COX-2 inhibitor. Because NSAIDs are known to have a ceiling effect with respect to analgesia, these drugs may be less beneficial in reducing pain and

opioid consumption after more extensive surgical procedures. In contrast to our earlier ENT study involving premedication with oral rofecoxib 50 mg (9), the improved postoperative analgesia with celecoxib 400 mg failed to influence recovery times or patient satisfaction with their pain management and quality of recovery. The failure to demonstrate an improvement in these outcome variables may reflect patient satisfaction with the prompt administration of rescue analgesic medication by the nurses in the PACU and DSU (as evidenced by the high degree of patient satisfaction in the control group).

In conclusion, oral premedication with celecoxib 400 mg was more effective than 200 mg in reducing the severity of postoperative pain and the need for rescue analgesic medication in the early postoperative period and in the postdischarge period after ENT surgery.

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