EFFECT OF PERIOPERATIVE CELECOXIB ON PATIENT OUTCOMES

AFTER MAJOR PLASTIC SURGERY PROCEDURES

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Sun T, Sacan O, White PF, Coleman J, Rohrich RJ, Kenkel JM. Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. *Anesth Analg* 2008;106:950-8

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ABSTRACT

EFFECT OF PERIOPERATIVE CELECOXIB ON PATIENT OUTCOMES AFTER MAJOR PLASTIC SURGERY PROCEDURES

TIFFANY B. SUN

The University of Texas Southwestern Medical Center at Dallas, 2008

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Background: Controversy continues to surround the use of COX-2 inhibitors in the perioperative period. This randomized, double-blind, placebo-controlled study was designed to examine the hypothesis that administration of celecoxib preoperatively or postoperatively and for a total of 4 days after major plastic surgery would improve pain control and clinically-important patient outcomes. Another objective of the study was to determine if perioperative administration of celecoxib offered any advantages over postoperative administration alone.

Methods: One hundred and twenty healthy consenting patients undergoing major plastic surgery (e.g., breast augmentation, abdominoplasty procedures) utilizing a standardized general anesthetic technique were randomized to one of three treatment groups: (1) Control group (n=40) received two placebos orally before and after surgery, as well as one placebo BID for three days after surgery (2) Postoperative group (n=40) received two placebos before surgery and two celecoxib 200 mg po after surgery, followed by one celecoxib 200 mg po BID on POD #1, #2 and #3, and (3) Perioperative group (n=40) received two celecoxib 200 mg po 30-90 minutes before surgery and two placebos after surgery, followed by one celecoxib 200 mg po BID on POD #1, #2 and #3. Pain scores, the need for "rescue" analgesics, and side effects were recorded at specific time intervals

in the postoperative period. Follow-up evaluations were performed at 24 h, 48 h, 72 h and 7 d after surgery to assess post-discharge pain, analgesic requirements, return of bowel function, resumption of normal daily activities, quality of recovery, and patients' satisfaction with their pain management.

Results: Compared to the Control group, the two celecoxib groups had similarly significant reductions in postoperative pain and need for opioid analgesics during the first three postoperative days ($p<0.01$). Patients recovered bowel function 1 d earlier and resumed normal activities 2 d earlier in the celecoxib groups. In addition, patient satisfaction with pain management and quality of recovery were significantly improved in the celecoxib (vs. control) groups ($p<0.05$).

Conclusion: Celecoxib (400 mg po) administered on the day of surgery and for three days postoperatively is effective in improving postoperative pain management, as well as the speed and quality of recovery after major plastic surgery. However, perioperative administration offers no advantages over simply giving the drug after surgery.

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LIST OF ABBREVIATIONS

ANOVA: Analysis of variance

ASA: American Society of Anesthesiologists

BID: *bis in die,* twice a day

COX: Cyclooxygenase

DVT: Deep venous thrombosis

IRB: Institutional Review Board

IV: Intravenous

kg: Kilogram

mg: Milligram

NSAIDs: Non-steroidal anti-inflammatory drugs

PACU: Post anesthesia care unit

po: *per os,* by mouth

PONV: Post operative nausea and vomiting

POD: Postoperative day

PCA: Patient controlled analgesia

prn: *pro re nata,* as needed

QID: *quater in die,* four times a day

QD: *quaque die,* daily

SD: Standard deviation

μg: Microgram

VRS: Verbal rating scale

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Chapter 1: INTRODUCTION

The goal in optimizing postoperative pain management should be to reduce pain symptoms, improve the quality of the patients' recovery, and facilitate resumption of normal activities of daily living (1). Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly administered as a part of multimodal analgesic regimens for preventing pain after fast-track surgery (2,3). For example, ketorolac has been found to reduce postoperative pain and the need for opioid analgesics after laparoscopic surgery (4) and facilitated an earlier discharge after superficial surgery procedures (5). Nevertheless, concerns persist regarding the use of non-selective NSAIDs (e.g., ketorolac and diclofenac) during the perioperative period in patients undergoing major plastic surgery procedures due to the risk of operative site and gastrointestinal mucosal bleeding from blockade of prostaglandin synthesis at the cyclooxygenase (COX)-1 receptor (6-8). The more selective COX-2 inhibitors appear to be as efficacious as the non–selective NSAIDs for the prevention of postoperative pain with a lower risk of operative site bleeding (9-11).

Although pre-emptive analgesia utilizing the COX-2 inhibitors has been recommended for the prevention of postoperative pain (12), the benefits of pre-emptive vs. postoperative analgesia have been questioned (13). Perioperative administration (i.e., before and after surgery) of COX-2 inhibitors reduces pain and opioid-related side effects in the early postoperative period (14); however, improvements in clinically-relevant recovery outcomes appear to require a more sustained period of drug administration after surgery (15-18). Of concern, recent studies involving perioperative administration of COX-2 inhibitors for 10-14 days after cardiac surgery demonstrated that these

compounds could increase postoperative wound infections (19) and cardiovascular complications (20).

We designed this randomized, double-blind, placebo-controlled study to test the hypothesis that short-term administration of celecoxib, 400 mg po, would improve pain control and lead to an earlier resumption of normal activities of daily living after major plastic surgery without increasing wound complications. The secondary objective was to compare peri- vs. postoperative administration of celecoxib with respect to postoperative pain management, the need for rescue analgesics, and resumption of normal physical activities.

CHAPTER 2: METHODS AND MATERIALS

After obtaining IRB approval at UT Southwestern Medical Center, a total of 179 ASA physical status I-III patients (18-75 yr) undergoing major plastic surgery procedures (e.g., breast augmentation or abdominoplasty with or without liposuction involving abdomen, buttocks, and lower extremities) were screened for participation in this placebo-controlled protocol. Patients were excluded if they had an allergy or contraindication to NSAIDs, chronically used NSAIDs, had received any analgesic medication within a 12 h period prior to the operation, were pregnant or breast-feeding, had a history of alcohol or drug abuse, had a bleeding disorder, unstable neurologic, cardiovascular, renal, hepatic or gastrointestinal diseases, or were unwilling to complete the follow-up evaluations.

After obtaining written informed consent, 120 patients were randomly assigned to one of three treatment groups: (1) *Control* group (n=40) received two placebo capsules orally 30-90 min prior to surgery, followed by two placebo capsules 1 h postoperatively in the recovery room, (2) *Postoperative* group (n=40) received two placebo capsules orally 30-90 min before surgery and two celecoxib 200 mg capsules 1 h after surgery, and (3) *Perioperative* group (n=40) received two celecoxib 200 mg capsules 30-90 min prior to surgery and two placebo capsules 1 h after surgery. On the first three postoperative days, patients in the *Control* group received one placebo capsule po BID, while the *Postoperative* and *Perioperative* groups received celecoxib 200 mg po BID. The study medication was prepared by a hospital pharmacist in identical-appearing capsules according to a computer-generated random number schedule. The patients, nurses,

surgeons, and anesthesiologists directly involved in the patients' care were blinded as to the content of the oral study medication capsules.

In the preoperative holding area, patients completed baseline 11-point verbal rating scales (VRS) for pain, with scores of 0 = "no pain" to 10 = "worst pain imaginable." All patients received midazolam, 20 μg/kg IV, immediately prior to leaving the preoperative holding area. Upon arrival in the operating room, standard monitoring devices were applied. The mean arterial pressure, heart rate, and hemoglobin oxygen saturation were recorded at 5 min intervals during surgery. Anesthesia was induced with propofol, 1.5-2.5 mg/kg IV, and fentanyl, 100 μg IV. Following loss of consciousness, rocuronium, 0.6 mg/kg IV, was given for tracheal intubation. Desflurane 4% in combination with air 50% in oxygen as well as a sufentanil infusion, 0.005-0.015 μg/kg/min, was administered for maintenance of anesthesia. After endotracheal intubation, all patients were mechanically ventilated to maintain the end-expiratory CO_2 value between 34-36 mmHg. A local anesthetic solution containing 20 ml of 0.5 % bupivacaine was injected at the incision at the end of surgery in all cases. In addition, ondansetron, 4 mg, and dexamethasone, 4 mg, were administered for routine antiemetic prophylaxis. Upon completion of surgery, the combination of neostigmine, 2-5 mg IV, and glycopyrrolate, 0.2-0.8 mg IV, was administered for reversal of residual neuromuscular blockade, the desflurane was discontinued, and the inspired oxygen flow rate was increased to 5 L/min. Tracheal extubation was performed when the patients could open their eyes or obey simple commands (e.g., squeeze hand). After applying the surgical dressing, all patients were transferred directly to the postanesthesia care unit (PACU).

Anesthesia (from induction of anesthesia to discontinuation of the desflurane) and surgery (from incision to placement of the surgical dressing) times were recorded. The discharge criteria from the PACU required that patients be awake and alert with stable vital signs and not experiencing side effects related to surgery or anesthesia. The hospital discharge criteria required that the patients be able to ambulate without assistance, tolerate oral intake, void, and control their pain with oral analgesics. In addition, patients could not be experiencing any drug-related side effects or surgical complications. All patients were asked to assess their quality of recovery using a validated 9-item questionnaire (Figure 1) (21) at 24 h intervals after surgery.

Patients rated their pain and nausea on the 11-point VRS at 30-min intervals and immediately prior to receiving any rescue analgesic medication in the PACU. Patients with VRS pain scores of 3-6 were considered to be in moderate pain and scores of ≥7 were considered to have severe pain. Patients complaining of moderate to severe pain in the PACU were treated with fentanyl, 25 μg IV boluses. However, the nurses were not required to titrate fentanyl to achieve a specific VRS pain score. Patients with pain scores of ≤2 received a combination of oral hydrocodone, 5 mg, and acetaminophen, 500 mg. For patients who were being admitted to the hospital, a patient-controlled analgesia (PCA) device was provided, and patients were allowed to self-administer morphine 2 mg IV bolus injections with a lockout interval of 10 min and a 4 h limit of 40 mg. The incremental bolus dosage was increased to 3 mg if pain relief was inadequate (VRS pain score ≥7) after 1 h of use. When the patients were discharged, they were prescribed a combination of oral hydrocodone (5 mg) and acetaminophen (500 mg) po QID, prn for pain control. Patients who complained of nausea or experienced repeated episodes of

vomiting after surgery were treated with promethazine, 6.25 mg IV boluses, administered to a total dose of 25 mg.

A trained interviewer who was also blinded to the study medication contacted each patient at 24 h, 48 h, and 72 h postoperatively to inquire about their maximum VRS pain score. Patients who were still hospitalized were visited by one of the investigators, and the opioid medications administered were determined from the medication administration record. Patients who had been discharged home were contacted by telephone and asked about their use of oral opioid-containing analgesic medication (i.e., number of pills consumed). To compare the opioid consumption of the three groups, morphine equivalents were calculated using a standardized conversion table (22). The patients were only admitted to the hospital if they experienced post-surgical bleeding complications or pain requiring parenteral opioid analgesics for >24 h.

Patient satisfaction with postoperative pain management and the times to tolerate normal fluids and solid food, have a bowel movement, and resume their normal activities of daily living after surgery were recorded at the 24 h, 48 h, 72 h, and 7 d follow-up evaluations. The occurrence of any wound complications (e.g., hematoma, infection) was also noted at the time of the first follow-up visit to the plastic surgery clinic, and at the long-term follow-up visits 1 and 3 months postoperatively.

Statistical analysis

Data were analyzed using analysis of variance (ANOVA) and Chi-square analysis as appropriate. Based on the assumption that the Control group would self-administer 50 mg of morphine (with a standard deviation of 10 mg), a sample size of 35 patients per

group was calculated to detect a difference of 20% or more in PCA morphine consumption (usage) with a power of 80% and a significance level of 0.05 for a two-sided test. Additionally, repeated measure ANOVA was used to analyze pain scores, early recovery times, and quality of recovery data over time for the three treatment groups. Continuous variables were evaluated utilizing ANOVA. Levene's test for homogeneity of variance was used to determine if ANOVA was appropriate. Welch's ANOVA was applied where heterogeneity of variance was indicated. The Student Newman Keuls multiple comparisons test was applied for pairwise comparisons of means between the given treatments. When multiple comparisons of continuous data (e.g., pain scores) were performed between the three treatment groups, a Bonferonni correction was applied. Categorical variables were evaluated utilizing Chi-square contingency table analysis. Fisher's exact test was employed where cell values were low, therefore not satisfying the assumptions for a valid Chi-square contingency table analysis. Statistical partitioning was used to investigate source of variability. For all statistical analyses, p-values <0.05 were considered to be statistically significant.

Figure 1. Questionnaire used to assess the patients' quality of recovery score (21)

		Not at all	**Some of the time**	**Most of the time**
1	Have you had a feeling of general well-being?	0	1	2
2	Have you had support from others (especially doctors & nurses)?	0	1	2
3	Have you been able to understand instructions and advice given to you?	0	1	2
4	Have you been able to look after personal toilet and hygiene needs unaided?	0	1	2
5	Have you been able to pass urine ("waterworks") and have no trouble with bowel function?	0	1	2
6	Have you been able to breathe easily?	0	1	2
7	Have you been free from headache, backache or muscle pains?	0	1	2
8	Have you been free from nausea, dry-retching or vomiting?	0	1	2
9	Have you been free from experiencing severe pain or constant moderate pain?	0	1	2

Summary Score: 0 -18

CHAPTER 3: RESULTS

Of the 120 patients entered into the study, a total of 112 patients successfully completed the entire protocol (Fig. 2). The eight patients who did not complete the treatment protocol (e.g., did not take their study medication or refused to complete all the postoperative assessments) had their data included up until the time they withdrew from the study. There were no significant differences between the three study groups with respect to age, ASA physical status, weight, height, gender, or durations of surgery and anesthesia (Table 1). In addition, the total dosages of propofol and sufentanil administered during the operative period were similar in the three treatment groups.

Although the total morphine equivalents administered in the PACU were similar in the three groups, the need for opioid analgesics on the first three postoperative days was significantly less in the Postoperative and Perioperative groups compared to the Control group (18 and 23 mg vs. 68 mg; 5 and 13 mg vs. 40 mg; and 3 and 3 mg vs. 32 mg, respectively, $p<0.05$) (Fig. 3). There were no between-group differences in the pain scores at PACU discharge. However, the average pain scores on the first, second, and third PODs were significantly lower in the Postoperative and Perioperative groups (Fig. 4). There were no statistically significant differences in pain scores or opioid analgesic requirements between the two celecoxib groups at any of the assessment intervals.

Patient satisfaction with pain management was significantly higher in the Postoperative and Perioperative (vs. Control) groups (Table 2). In addition, quality of recovery scores on the first, second, and third POD were significantly higher in the Postoperative and Perioperative (vs. the Control) groups. Return of bowel function

occurred earlier 1(1-2), 1(1-2) vs. 2(1-3) days, respectively, $p<0.05$, and more importantly, the time to resumption of normal activities of daily living after surgery was shorter in the Perioperative and Postoperative groups (vs. Control) groups 2(1-3), 2(1-3), vs. 3(2-5) days, respectively, $p<0.05$ (Table 2). Again, there were no statistically significant differences between the Peri- vs. Postoperative groups.

Postoperative emetic symptoms did not differ significantly between the three treatment groups (Table 2). One patient in the Postoperative group had a deep venous thrombosis (DVT), leading to a prolonged 7 d hospital stay. There was no significant difference in the number of wound complications at the seven day and three month follow-up evaluations (Table 3).

Figure 2: Enrollment and outcomes of enrolled patients. Patients who discontinued study drug administration prior to the end of the third postoperative day were included in the efficacy analysis up until the time they withdrew from the study.

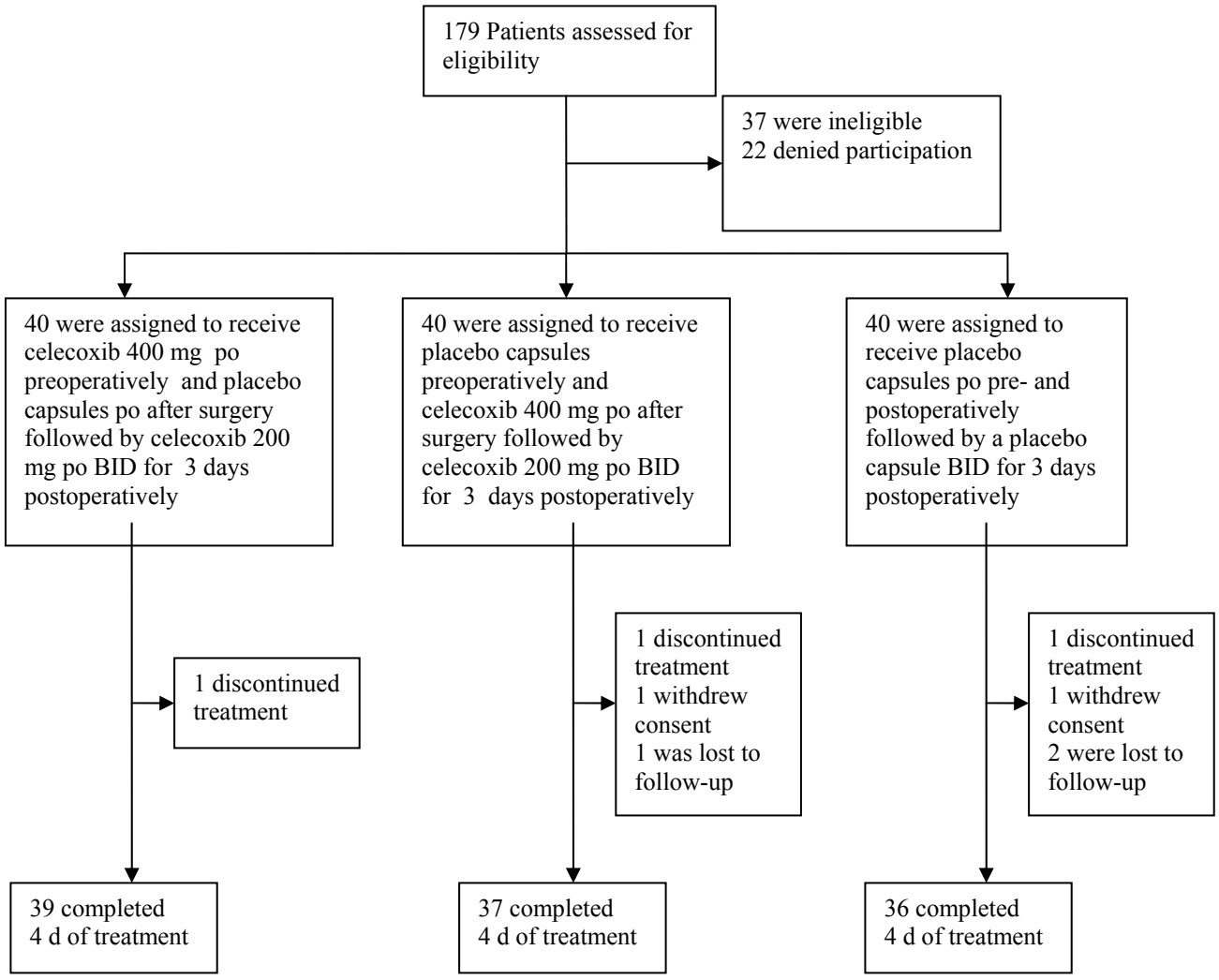
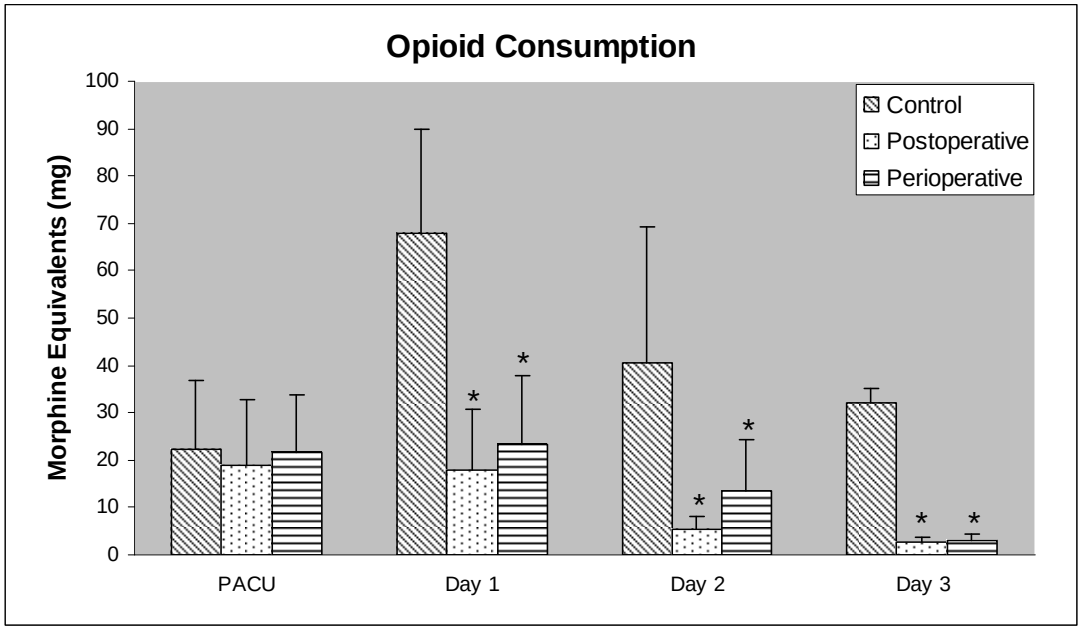


Table 1. Demographic characteristics and intraoperative conditions in the three treatment groups †

	Control (n = 36)	**Postoperative (n = 37)**	**Perioperative (n = 39)**
Demographics			
Age (yr)	42 ± 12	42 ± 14	43 ± 14
Height (cm)	164 ± 10	165 ± 7	165 ± 7
Weight (kg)	69 ± 18	74 ± 17	71 ± 16
Gender (M/F) (n)	2/34	0/37	4/35
ASA physical status (I/II/III) (n)	12/24/2	13/20/4	12/24/3
Pre-existing conditions n (%)			
Chronic hypertension	5 (14)	6 (16)	4 (10)
Coronary artery disease	0	0	1 (3)
Asthma	3 (8)	3 (8)	3 (8)
Diabetes	3 (8)	2 (5)	1 (3)
Types of Procedures n (%)			
Abdominoplasty	5 (14)	6 (16)	6 (15)
Breast augmentation	21 (58)	21 (57)	23 (59)
Combination ‡	10 (28)	10 (27)	10 (26)
Intra-operative Data			
Duration of anesthesia (min)	206 ± 88	216 ± 123	175 ± 78
Duration of surgery (min)	175 ± 88	178 ± 119	157 ± 77
Propofol (mg)	138 ± 33	139 ± 28	136 ± 28
Sufentanil (μg)	49 ± 25	46 ± 25	43 ± 23
Blood loss (ml)	172 ± 109	155 ± 123	133 ± 113
Fluid intake (ml)	2049 ± 1003	1842 ± 991	1876 ± 790

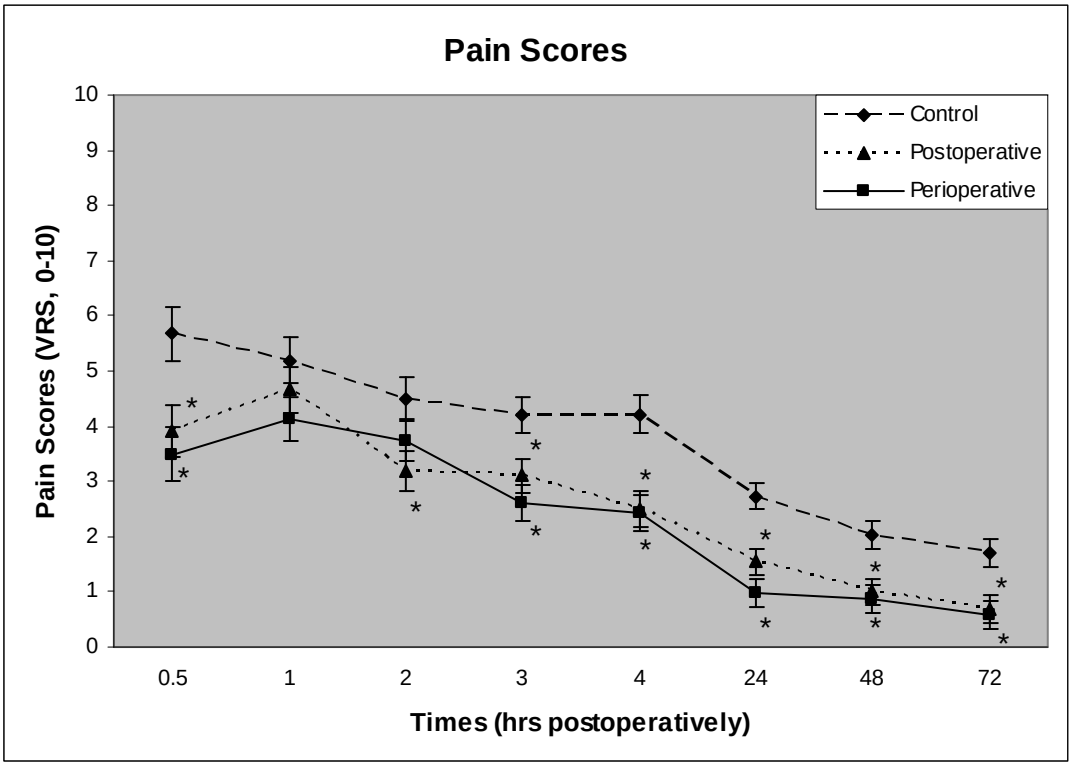
† Values are means ± SD, percentages (%), and numbers of patients (n)
‡ Breast augmentation or abdominoplasty with the addition of liposuction
ASA, American Society of Anesthesiologists

Figure 3: Opioid consumption in converted morphine equivalents (mg) of the three groups during the PACU stay and on POD #1, #2, and #3. Values are means ± standard deviations.



*p<0.05 vs. Control group

Figure 4: Postoperative pain scores of patients in the three groups. Patients rated their pain on an 11-point verbal rating scale (VRS), with 0 = "no pain" to 10 = "worst pain imaginable." Values are means ± standard deviations.



*p<0.05 vs. Control group

Table 2. Rescue analgesic and antiemetic requirements in the PACU; mean times to resumption of normal diet, bowel function, and physical activity; patient satisfaction scores regarding pain management; and quality of recovery scores in the three study groups.†

	Control (n = 36)	**Postoperative (n = 37)**	**Perioperative (n = 39)**
Required rescue analgesic in PACU (n, %)	34 (94)	35 (95)	32 (82)
Required morphine dosage in PACU (mg)	9.5 ± 8.0	6.0 ± 5.5	5.0 ± 3.9
Required fentanyl dosage in PACU (μg)	102 ± 45	107 ± 61	115 ± 67
Time to first rescue analgesic (min)	17 ± 12	23 ± 20	26 ± 20
Postoperative nausea and/or vomiting (n, %)	8 (22)	6 (16)	8 (21)
Required rescue antiemetic in PACU (n, %)	8 (22)	6 (16)	7 (18)
Primary outcome variables			
PACU stay (min)	97 ± 36	90 ± 48	85 ± 45
Resume normal diet (d)	2 (1-3)	1 (1-2)*	1 (1-2)*
Return of normal bowel function (d)	3 (2-5)	2 (1-3)*	2 (1-3)*
Resume normal physical activity (d)	6 (3-7)	4 (2-6)*	4 (2-6)*
Patient satisfaction	91 ± 10	97 ± 5*	97 ± 5*
Quality of recovery scores (VRS, 0-18)			
24 hr	16 (15-18)	17 (16-18)*	17 (16-18)*
48 hr	16 (15-18)	18 (17-18)*	18 (17-18)*
72 hr	17 (16-18)	18 (17-18)*	18 (17-18)*

† Values are means ± SD, medians (inter-quartile ranges), numbers (n), and percentages (%)
*$p<0.05$ vs. Control group
VRS, verbal rating scale

Table 3. Cardiovascular and surgical wound complications at the 7 d and 30 d follow-up evaluations in the three treatment groups. †

	Control (n = 36)	**Postoperative (n = 37)**	**Perioperative (n = 39)**
Deep venous thrombosis	0	1	0
Pulmonary emboli	0	0	0
Myocardial infarction	0	0	0
Wound complications			
Ecchymoses	2	3	3
Dermatitis	0	1	0
Skin necrosis	1	1	0
Delayed wound healing	4	4	1
Wound infection	3	0	0
Hematoma	2	0	0
Keloid formation	1	0	0

† Values are numbers (n)

CHAPTER 4: DISCUSSION

Patients undergoing major plastic surgery procedures are at risk of developing opioid-induced side effects (e.g., sedation, postoperative nausea and vomiting [PONV], urinary retention, pruritis, ileus, constipation). Rather than emphasizing the use of opioid analgesics for preventing acute postoperative pain, a more balanced view that utilizes non-opioid analgesics as the primary agents for preventing postoperative pain is recommended (2,3,23). In fact, some authors have suggested that opioid analgesics should only be used when other analgesic techniques have failed to provide adequate pain relief (2,23). After implementing a multimodal analgesic regimen that includes COX-2 inhibitors in patients undergoing total joint arthroplasty procedures, Peters et al. (24) reported earlier mobilization, shortened length of stay, and improved pain control with less opioid analgesic medication. Although non-selective NSAIDs can produce significant opioid-sparing effects, they can also produce side effects (e.g., bleeding complications, renal dysfunction, gastrointestinal distress) (6).

In plastic surgery patients receiving diclofenac, a reduction in the number of platelets and prolongation of the bleeding time was reported (25). Not surprisingly, in women undergoing breast surgery, use of diclofenac was associated with significantly more postoperative bleeding (26). Due to the occurrence of unexpected postoperative hemorrhages in women receiving ketorolac after plastic surgery, it is considered to be contraindicated for this type of surgery (27). Although a systematic review of the risk of operative site bleeding after tonsillectomy with non-selective NSAIDS reported "equivocal results" (28), Marret et al. (29) suggested that these drugs were contraindicated due to an increased risk of re-operation for hemostasis. Of interest,

Pickering et al. (30) found no difference in intraoperative blood loss when a non-selective NSAID, ibuprofen, was compared to a COX-2 inhibitor in this same patient population. Placebo-controlled studies evaluating the effects of preoperative administration of a COX-2 inhibitor in patients undergoing spinal fusion surgery reported no significant increase in intraoperative bleeding or in the likelihood of a re-operation due to hematoma formation (9,31).

In the current clinical investigation involving adults undergoing major plastic surgery procedures, the preoperative administration of 400 mg oral celecoxib 30-90 min prior to the start of the operation did not produce an increase in intraoperative blood loss or wound complications. However, the primary benefits of celecoxib administration with respect to improving pain management and facilitating recovery of clinically-relevant outcome measures appears to be related to its administration over the 4 day period. These findings are consistent with earlier studies in patients undergoing orthopedic (15), general (32), gynecologic (17), and laparoscopic (16,18) surgery procedures. In the most recent study involving patients undergoing laparoscopic surgery, celecoxib, 400 mg po, for four days not only decreased postoperative pain and the need for opioid-containing analgesic medication, but more importantly led to an improved quality of recovery and earlier resumption of activities of daily living (18).

In contrast to Reuben et al. (12), we found that preemptive administration of this COX-2 inhibitor was no more effective than giving the same dose after the operation followed by daily use for the first three PODs with respect to pain scores, opioid usage and resumption of normal activities of daily living. The negative findings in the comparison of perioperative (vs. postoperative) drug administration may be related in

part to inadequate absorption due to the short interval from drug administration to induction of anesthesia (i.e., 30-90 min) and the length of the surgical procedures (i.e., 2-4 h). However, these findings support the conclusions of the meta-analysis by Moiniche et al. (13).

The perioperative use of the COX-2 selective inhibitors has become increasingly controversial following the withdrawal of rofecoxib (Vioxx®) and valdecoxib (Bextra®) from the market due to concerns regarding the occurrence of an increased cardiovascular and other complications (e.g., Stevens-Johnson syndrome) with long-term administration of these NSAIDs (33). Of even greater concern to anesthesiologists are the reports describing an increase in postoperative complications in patients undergoing cardiac surgery (19, 20) following relatively short-term (10-14 d) administration of COX-2 inhibitors. In the study by Nussmeier et al. (20), the perioperative use of COX-2 inhibitors parecoxib and valdecoxib was associated with an increased incidence of cardiovascular events within the 30 day follow-up period after cardiac surgery. Despite these reports, many non-cardiac surgery studies have confirmed that the administration of COX-2 inhibitors before and for up to five days after surgery provides beneficial effects with respect to improving postoperative pain management without producing any serious complications (15-18, 34).

Of interest, a recent meta-analysis by Zhang et al. (35) reported that rofecoxib was associated with an increased risk of renal and cardiac complications, but a COX-2 inhibitor "class" effect was not demonstrated. It has been suggested that the less highly selective COX-2 inhibitors (e.g., celecoxib) may be devoid of significantly increased cardiovascular complications even with prolonged administration. Despite extensive

worldwide use of COX-2 inhibitors in the immediate perioperative period, there have been no reports of serious cardiovascular complications associated with short-term use of COX-2 inhibitors in non-cardiac surgery patients (33). The current study is underpowered to examine serious cardiovascular complications. However, one patient in the Postoperative group did develop a deep venous thrombosis, a well-known complication after major plastic surgery procedures (36). A recent report by Al-Sukhun et al. (37) also suggested that the use of COX-2 inhibitors was associated with early failure of free vascular flaps due to their ability to inhibit production of prostacyclin.

Due to ongoing concerns regarding the potential for non-selective NSAIDs to increase operative site bleeding (6) and COX-2 inhibitors to increase prothrombotic complications after major surgery, non-opioid analgesics which are devoid of these side effects are being investigated as alternatives to these compounds as part of multimodal analgesic regimens (38). Preliminary studies utilizing the gabapentinoid compounds gabapentin (39, 40) and pregabalin (41) have reported similar beneficial effects to the COX-2 inhibitors with respect to improving patient satisfaction and facilitating the recovery process after elective surgery procedures. These studies also suggest that use of the gabapentinoids in combination with COX-2 inhibitors produces additive (or even synergistic) effects with respect to improving postoperative pain management (41). A recent meta-analysis confirmed the analgesic efficacy of the gabapentinoid compounds in the postoperative period. However, their use may also be associated with an increased incidence of side effects (e.g., sedation, dizziness) (42, 43).

The primary deficiencies of this investigation relate to the limited power of this study to detect differences in all secondary outcomes (e.g., wound complications, major

cardiovascular events). As a result of the ongoing controversy regarding the perioperative risk of COX-2 inhibitors in patients with pre-existing cardiac disease (33), we excluded all patients with unstable cardiovascular disease. Additional perceived deficiencies of the study may relate to the celecoxib dosage regimen, the timing of its administration, and the possibility of delayed gastric emptying and drug absorption following induction of anesthesia. Although these operations lasted 2-4 h, it is possible that surgery and anesthesia interfered with the oral uptake of preoperative celecoxib from the gastrointestinal tract. The celecoxib dose (400 mg QD) (44) and the dosing intervals (18) have previously been reported to be effective in improving postoperative pain control and facilitating recovery after a wide variety of surgical procedures (33). Furthermore, most outpatients undergoing elective surgery procedures typically arrive in the preoperative preparation area only 60-120 min prior to the start of surgery, precluding earlier administration of the study drug. Clearly, additional large-scale studies are needed to confirm the safety of the perioperative use of COX-2 inhibitors in patients at increased risk of cardiovascular complications (45).

In conclusion, postoperative administration of celecoxib (400 mg po BID) for a total of four days in patients undergoing major plastic surgery procedures decreased postoperative pain and the need for analgesic rescue medication, contributing to improved patient satisfaction with their quality of recovery. The short-term use of the COX-2 inhibitor in the postoperative period also facilitated the resumption of normal activities of daily living after discharge. Celecoxib administration 30-90 minutes before surgery offers no significant advantages over simply giving the drug after surgery.

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VITAE

Tiffany B. Sun was born in China on August 13, 1984 to Michael and Grace Sun and immigrated to the United States at age six. At age fifteen she began full-time college coursework at the Texas Academy of Math and Science, an early college entrance program for gifted and talented high school students. It was here that Tiffany first fell in love with science, working in a developmental physiology laboratory under the supervision of Dr. Warren Burggren.

After graduating from the Academy, she continued her studies at Cornell University and graduated Cum Laude with a Bachelor of Science in Neurobiology in 2004. In June 2004, Tiffany began the first of two summers participating in the Medical Student Summer Research Program at UT Southwestern, working under the direction of Dr. Paul F. White in the Department of Anesthesiology & Pain Management. Since that time, she has presented research posters at the Medical Student Research Forum in 2005 and 2006, and in 2006 was chosen to be an oral presenter.

In addition, as a first year medical student, Tiffany was the first UT Southwestern student to win the Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship, allowing her to continue her research during her second and third years of medical school. In April of 2008, Tiffany was inducted into the Gamma Texas Chapter of Alpha Omega Alpha Medical Honor Society. After graduation from medical school, Tiffany will perform her residency training in the field of Anesthesiology & Pain Management at the University of California, San Francisco in preparation for her career as an academic anesthesiologist.