EFFECT OF SHORT-TERM POSTOPERATIVE CELECOXIB ADMINISTRATION ON PATIENT OUTCOME AFTER OUTPATIENT LAPAROSCOPIC SURGERY

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EFFECT OF SHORT-TERM POSTOPERATIVE CELECOXIB ADMINISTRATION ON PATIENT OUTCOME AFTER OUTPATIENT LAPAROSCOPIC SURGERY

by

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ABSTRACT

EFFECT OF SHORT-TERM POSTOPERATIVE CELECOXIB ADMINISTRATION ON PATIENT OUTCOME AFTER OUTPATIENT LAPAROSCOPIC SURGERY

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The University of Texas Southwestern Medical Center at Dallas, 2009

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Purpose: Non-opioid analgesics are increasingly used as part of a multimodal regimen for pain management. This prospective, randomized, double-blinded, placebo-controlled study was designed to evaluate the effect of short-term postoperative administration of celecoxib on pain management and recovery outcomes following laparoscopic surgery.

Methods: Eighty consenting ASA I–III outpatients undergoing laparoscopic surgery were randomly assigned to one of two treatment groups: Control (placebo) or Celecoxib (celecoxib, 400 mg·day^{-1}). The initial dose (celecoxib 400 mg or placebo *po*) was administered in the recovery room, and celecoxib 200 mg (or a placebo) *po* bid was continued for three additional days after surgery. Postoperative pain scores and the need for opioid- containing analgesics were recorded at specific intervals in the recovery room. Follow-up evaluations were performed at 24 hr, 48 hr, 72 hr and seven days and one month after surgery to assess post-discharge pain, analgesic requirements, complications, quality of recovery, and resumption of normal activities, as well as patient satisfaction with their pain management.

Results: Celecoxib reduced mean pain scores and the need for analgesics at 24 hr and 48 hr postoperatively. Patient satisfaction with their postoperative pain management was also higher in the Celecoxib group (94 ± 8 *vs* 80 ± 25, $P < 0.05$). Quality of recovery scores were significantly higher in the Celecoxib group on the first and second postoperative days (17 ± 1 *vs* 15 ± 2, and 18 ± 1 *vs* 16 ± 2, respectively). Finally, bowel function recovered an average of one day earlier and patients resumed activities of daily living two days earlier in the Celecoxib group ($P < 0.05$).

Conclusion: Short-term administration of celecoxib, 400 mg·day^{-1} *po*, decreased postoperative pain and the need for opioid-containing analgesic medication, leading to an improved quality of recovery after outpatient laparoscopic surgery.

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PRIOR LIST OF PUBLICATIONS AND PRESENTATIONS

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White PF, Sacan O, Nuangchamnong N, Sun T, Eng MR. The relationship between patient risk factors and early versus late postoperative emetic symptoms. Anesthesia Analgesia. 2008 Aug; 107(2): 459-463.

White PF, Eng MR. Fast-track anesthetic techniques for ambulatory surgery. Current Opinion in Anaesthesiology. 2007 Dec; 20(6): 545-557.

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Presentations:

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LIST OF ABBREVIATIONS

ASA: American Society of Anesthesiologists

BID: *bis in die,* twice a day

COX: Cyclooxygenase

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

prn: *pro re nata,* as needed

QD: *quaque die,* daily

SD: Standard deviation

μg: Microgram

VRS: Verbal rating scale

List of Tables

Table 1. Patient demographic characteristics, durations of surgery and anesthesia, and anesthetic drug dosages in the two study groups[†]

	Control	Celecoxib
† Number (n)	38	39
Age (yr)	38±12	36±10
Sex (M/F) (n)	6/31	4/35
Weight (kg)	88±31	79±25
Height (cm)	137±61	147±47
ASA physical status (I / II/ III) (n)	14/20/3	17/19/3
Duration of surgery (min)	112±76	97±51
Duration of anesthesia (min)	145±78	124±56
Propofol (mg)	158±39	159±58
Fentanyl (μg)	261±118	285±116
Desflurane (end-tidal %)	4.9±0.9	4.8±0.9

[†] Values are means ± SD, percentages (%) and numbers of patients (n)

Table 2. Pain scores, need for rescue analgesic medication in the postanesthesia care unit (PACU), as well as on postoperative day 1 (<24 h), day 2 (<48 h), and day 3 (<72 h), and patient satisfaction with their pain management in the two study groups[†]

	Control (n=38)	Celecoxib (n=39)
Pain scores (0-10)[Ŧ]		
Preoperative baseline (n)	0±0	0±0
at PACU Discharge	5±3	4±4
at 24 h	5±3	3±2*
at 48 h	4±3	3±2*
at 72h	3±3	2±2*
Required rescue analgesic medication		
at PACU (%, n)	70 (26)	54 (21)
at 24 h (%, n)	90 (30)	54 (21)*
at 48 h (%, n)	88 (29)	39 (15)*
at 72 h (%, n)	84 (27)	31 (12)*
Analgesic medication in PACU		
Patients receiving pain medication (%, n)	71 (27)	54 (21)
Total fentanyl dosage (μg, %)	127±58, 32	84±45*, 36
Hydrocodone/acetaminophen (number of pills, %)	2 (0.5), 42	1 (1), 28
Patient satisfaction with pain management (0-100)	80±25	94±8*

† Values are means ± SD, medians (IQR), number of patients (n), percentages (%).

Ŧ Verbal rating scale: 0 = no pain to 10 = maximal pain

* $p<0.05$ vs Control group

Table 3: Quality of recovery scores, postoperative nausea and vomiting, and primary outcome variables in the two study groups †

	Control (n=38)	Celecoxib (n=39)
Quality of recovery scores		
at 24 h	15±2	17±1*
at 48 h	16±2	18±1*
at 72 h	17±1	18±0*
Postoperative nausea and vomiting		
Vomiting in PACU (n, %)	8, 22	11, 28
Rescue antiemetic in PACU (n, %)	8, 22	9, 23
Post-discharge nausea vomiting (n, %)	3, 9	5, 15
Post-discharge vomiting (n, %)	4, 11	2, 5
Primary outcome variables		
Normal diet (days)	3±2	2±2
Normal bowel functions (days)	3±2	2±1*
Resume normal activities (days)	6±3	4±2*

† Values are means ± SD, percentages (%) and numbers of patients (n)

*****$p<0.05$ vs Control group

CHAPTER 1: INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as part of a multimodal analgesic regimen for preventing pain after ambulatory surgery.[1] Ketorolac has been found to reduce postoperative pain and the need for opioid analgesics after laparoscopic surgery,[2] and facilitate an earlier discharge after anorectal surgery.[3] Nevertheless, concerns persist regarding the use of non-selective NSAIDs like ketorolac during the perioperative period because of the risk of operative site and gastrointestinal mucosal bleeding due to blockade of prostaglandin synthesis at the cyclooxygenase-1 (COX-1) receptor.[4,5]

Studies involving COX-2 selective inhibitors have demonstrated that they can improve pain control after a wide variety of ambulatory surgery procedures.[6-12] Nevertheless, questions remained regarding the efficacy of perioperative administration of COX-2 inhibitors in improving the later recovery processes (e.g., recovery of bowel function, resumption of normal activities of daily living). For example, perioperative administration of rofecoxib improved the quality of recovery in the early postoperative period after outpatient hernia surgery, but failed to facilitate resumption of normal activities of daily living.[10] Similarly, it was shown that perioperative celecoxib reduced postoperative pain and opioid-related side effects (e.g., constipation) after ambulatory arthroscopic knee surgery without improving late recovery events.[12] Preoperative parecoxib followed by short-term postoperative valdecoxib improved recovery after laparoscopic cholecystectomy procedures.[11] However, studies involving perioperative administration of these two COX-2 inhibitors in patients undergoing cardiac surgery found an increased incidence of postoperative wound infections[13] and cardiovascular complications.[14]

Since both valdecoxib and rofecoxib have been withdrawn from the market because of patient safety concerns, we designed this randomized, double-blinded, placebo-controlled study to test the hypothesis that postoperative administration of oral celecoxib (400 mg·day^{1} for four days) would lead to an improved quality of recovery and earlier resumption of normal activities of daily living after laparoscopic surgery.

Chapter 2: METHODS AND MATERIALS

After obtaining Institutional Review Board approval at the University of Texas Southwestern Medical Center at Dallas and written informed consent, 80 American Society of Anesthesiologists (ASA) physical status I–III outpatients undergoing laparoscopic surgery (e.g., tubal ligation, cholecystectomy, diagnostic) at Parkland Memorial Hospital were enrolled in this randomized, double-blinded, placebo-controlled clinical study. Patients were excluded if they had difficulty understanding English, had an allergy or contraindication to taking NSAIDs, chronically used NSAIDs, had received an opioid analgesic medication within a 12-hr period prior to the operation, were pregnant or breast-feeding, had a history of alcohol or drug abuse, had a bleeding disorder, or had clinically-significant neurologic, cardiovascular, renal, hepatic or gastrointestinal diseases. Patients meeting the inclusion criteria were assigned to one of two treatment groups, Control (placebo) or Celecoxib 400 $mg \cdot day^{-1}$, based on a computer-generated randomization table.

In the preoperative holding area, patients were asked to complete baseline verbal rating scales (VRS) for pain and nausea using an 11-point VRS, with 0 = none to 10 = maximum. Immediately prior to leaving the preoperative holding area, patients were premedicated with midazolam, 20 $\mu g \cdot kg^{-1}$ IV. Upon arrival in the operating room, standard monitoring devices were applied and non-invasive arterial blood pressure, heart rate, hemoglobin oxygen saturation, and end-tidal concentrations of carbon dioxide and desflurane were monitored throughout the operation.

Anesthesia was induced with propofol 2 mg·kg^{-1} IV, and fentanyl 1 µg·k^{g-}1 IV, and tracheal intubation was facilitated with rocuronium 0.6 mg·kg^{-1} IV. Anesthesia was maintained with desflurane 4–6% in combination with air (1 L·min^{-1}) and oxygen (1 L·min^{-1}). A combination of droperidol, 0.625 mg IV, and dexamethasone, 4 mg IV, was administered after induction of anesthesia for antiemetic prophylaxis. Bupivacaine 0.25% was locally infiltrated at the incision sites prior to wound closure. At the end of the surgical procedure, residual neuromuscular block was reversed with neostigmine, 2–5 mg IV, and glycopyrrolate, 0.3–1 mg IV, the desflurane was discontinued, and the inspired oxygen flow was increased to 5 L·min^{-1}. Upon awakening from anesthesia, patients were extubated and transferred directly to the postanesthesia care unit (PACU).

The study medication (i.e., placebo or Celecoxib 200 mg) was prepared in identical-appearing capsules by the manufacturer of celecoxib (Pfizer, Inc., New York, NY, USA). The initial dose of study medication was administered by mouth 10–20 min after patients arrived in the PACU (i.e., either two celecoxib 200 mg or two placebo capsules). The patients were given a numbered envelope containing six additional capsules, and they were instructed to take one capsule twice a day for the subsequent three postoperative days (PODs). The patients, observers, and anesthesiologists directly involved in the patients' care were all "blinded" as to the content of the study medication.

Patients were asked to evaluate their pain and nausea on the 11-point VRS at 30, 60, 120 and 240 min intervals after surgery, as well as immediately prior to receiving any "rescue" analgesic medication. Patients complaining of moderate-to-severe pain (VRS > 3) were treated with fentanyl, 25 µg IV boluses. In accordance with the standard hospital PACU nursing practice, the nurses were not required to titrate fentanyl to achieve a specific VRS pain score. Patients requesting analgesic medication 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 retching or vomiting in the PACU, they were treated with promethazine, 6.25 mg IV boluses, administered to a maximum (total) dose of 25 mg. "Home readiness" was determined using standardized postanesthetic discharge criteria.[15]

A "blinded" interviewer contacted each patient by telephone at 24 hr, 48 hr and 72 hr after discharge to inquire about their maximum VRS pain score, use of oral opioid-containing analgesic medication (i.e., number of pills), occurrence of any emetic symptoms, and use of rescue antiemetic therapy. The patient quality of recovery scores were also assessed using a standardized nine-item questionnaire.[16] Patient satisfaction with postoperative pain management (using a 100-point scale from 1 = highly dissatisfied to 100 = highly satisfied), the times (i.e., number of days after surgery) to tolerate normal fluids and solid food, have a bowel movement, and to resume their normal activities of daily living after surgery were recorded at the 72 hr and/or seven-day follow-up evaluation. The presence of wound (e.g., hematomas, infections) and cardiovascular complications were assessed at the time of the initial postsurgical clinic visit and at the one month follow-up telephone interview, respectively.

The group sizes (n = 40) were calculated to detect a one-day reduction in the times to resume normal dietary, bowel and physical activities after surgery in the Celecoxib (vs Control) group, with a power of 80% and a significance level of 0.05. The statistical analysis was performed using SPSS Software (Chicago, IL, USA). For continuous variables, the Student's t test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the 2 test. A repeated measures of analysis of variance was performed to examine differences in the VRS pain and quality of recovery scores over time, with a Bonferroni correction applied for multiple comparisons. Data are expressed as mean ± standard deviation, medians (interquartile ranges), percentages (%), and numbers (n), and a P-value < 0.05 was considered statistically significant.

Chapter 3: RESULTS

Of 133 patients who were initially screened, 39 were excluded due to difficulty understanding English, and 14 refused to sign the consent form. Eighty patients met the inclusion criteria, and were subsequently enrolled and randomized to receive the initial dose of the study medication or placebo. Follow-up evaluations were incomplete in three patients (two in group Control, and one in grup Celcoxib); none of the data from these patients was included in the final statistical evaluation. The groups were similar with respect to age, weight, height, gender, ASA physical status, and durations of surgery and anesthesia (Table I). The mean amount of propofol, end-tidal desflurane, and fentanyl administered during the operative period did not differ between the two treatment groups.

Even though the percentage of the patients requiring rescue analgesics in the PACU was similar in the two treatment groups, the amount of fentanyl administered was less in the Celecoxib group compared to the Control group (84 ± 45 µg *vs* 127 ± 58 µg *iv*, respectively, $P < 0.05$). There were no between-group differences in the mean pain scores at PACU discharge; however, the average pain scores on the first,second and third PODs were significantly lower in the Celecoxib group (Table II). Furthermore, the percentages of patients who required "rescue" analgesic medication at 24 hr, 48 hr, and 72 hr after discharge was significantly reduced in the Celecoxib (*vs* Control) group (54 *vs* 90%, 39 *vs* 88%, 31 *vs* 84%, respectively, all $P < 0.05$).

Patient satisfaction with their pain management and the quality of recovery scores on the first, second, and third PODs were significantly higher in the Celecoxib group (Table III).

Recovery of the bowel function occurred earlier (2 ± 1 *vs* 3 ± 2 days, $P < 0.05$), and more importantly, the time to resumption of normal daily living activities after surgery was shorter in the Celecoxib (*vs* Control) group (4 ± 2 *vs* 6 ± 3, respectively, $P < 0.05$) (Table III).

Postoperative emetic symptoms did not differ significantly between the two treatment groups (Table III). No patient in either group experienced either wound or cardiovascular complications at the seventh day and one-month follow-up periods after discharge from the hospital.

Chapter 4: DISCUSSION

Effective pain management has been reported to facilitate the recovery process and enhance patient satisfaction after outpatient surgery.[1] In the current study involving an adult ambulatory surgery population undergoing laparoscopic surgery, the postoperative administration of celecoxib (400 mg/d) for 4 days immediately after surgery was found to be effective in reducing pain, improving patient satisfaction with their pain management and facilitating the recovery process. These findings are of clinical importance because it has been recently suggested that inadequately treated acute postoperative pain can lead to chronic pain even in patients undergoing minor surgery.[17]

The use of COX-2 selective inhibitors has become increasingly controversial following the withdrawal of rofecoxib and valdecoxib from the market due to concerns regarding the occurrence of cardiovascular complications even after relatively short-term (10-14 d) administration in "at risk" surgical populations.[12,13] In the study by Nussmeier et. al.,[13] the perioperative use of the 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 this observation, many non-cardiac surgery studies[6-11] have confirmed that administration of COX-2 inhibitors before and/or immediately after surgery has beneficial effects with respect to improving postoperative pain management without causing these serious complications.[18]

In contrast to their short-term use in the perioperative period, long-term use of celecoxib[19] and rofecoxib[20] for chronic pain conditions has been reported to increase the incidence of cardiovascular adverse events. In a recent meta-analysis, Zhang et al[21] reported that rofecoxib was associated with an increased risk of renal and cardiac complications, but a COX-2 inhibitor "class" effect was not demonstrated. Despite extensive world-wide use of COX-2 inhibitors in the perioperative period, there have been no reports of serious cardiovascular complications associated with short-term use of COX2 inhibitors in non-cardiac surgery patients.[22]

The concerns about the potential for COX-2 inhibitors to increase prothrombotic complications have lead to the search for “alternative” non-opioid analgesics.[23] The gabapentinoid compounds, gabapentin[24] and pregabalin[25] are an interesting class of non-opioid analgesics which appear to possess similar benefits to the COX-2 inhibitors in improving patient satisfaction and facilitating the recovery process after surgery. Other non-opioid compounds (e.g., IV acetaminophen, longer-acting local anesthetics) are also being evaluated as alternatives to the COX-2 inhibitors for minimizing the opioid analgesic requirement and improving patient outcomes after surgery.[26]

In contrast to the study by Buvanendran et al[27] in patients undergoing knee replacement surgery, the patients in our current study only received the COX-2 inhibitor after their operation. The benefits of short-term postoperative administration of celecoxib in this laparoscopic surgery population were similar to those reported after knee replacement surgery with respect to improved pain management and outcome measures. Our rationale for administering celecoxib only in the postoperative period was because we have found no advantage with peri-vs postoperative celecoxib administration with respect to reducing pain or improving patient outcomes after major plastic surgery procedures.[28] A qualitative and quantitative systematic review of the peer-reviewed literature has questioned the importance of the administration of a COX-2 inhibitor before vs after surgery.[29]

Despite the opioid-sparing effect of the COX-2 inhibitor in this outpatient surgery population, the overall incidence of postoperative nausea and vomiting was not significantly reduced. The routine administration of droperiodol and dexamethasone for antiemetic prophylaxis and the avoidance of nitrous oxide during the maintenance period clearly contributed to the low incidence of postoperative emetic symptoms in both treatment groups. Additionally, the study was insufficiently powered to find a difference between the groups with respect to this secondary outcome variable. This study can also be criticized for failing to include a non-selective NSAID comparator (e.g., ketorolac or ibuprofen) or acetaminophen as an active comparator. Pharmacoeconomic studies are clearly needed to compare the analgesic efficacy and safety of celecoxib with less costly non-opioid analgesics (e.g., ibuprofen, acetaminophen) after outpatient surgery.

In conclusion, administration of celecoxib (400 mg/d po) for four days after laparoscopic surgery 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 did not result in any postoperative wound (e.g., hematoma formation, infections) or cardiovascular complications. Therefore, celecoxib (400 mg/d po) facilitated the resumption of normal activities of daily living after discharge in patients undergoing laparoscopic surgery without any serious complications.

Chapter 5: CONCLUSIONS AND RECOMMENDATIONS

The administration of celecoxib (400 mg/d po) for four days after laparoscopic surgery decreased postoperative pain and the need for analgesic rescue medication, contributing to improved patient satisfaction and their quality of recovery. These data suggest that celecoxib appears to be an acceptable alternative to the parecoxib-valdecoxib combination[11] in this surgical population. The short-term use of the COX-2 inhibitor did not result in any postoperative wound (e.g., hematoma formation, infections) or cardiovascular complications. Therefore, celecoxib (400 mg/d po) facilitated the resumption of normal activities of daily living after discharge in patients undergoing laparoscopic surgery without any serious complications.

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VITAE

Matthew R. Eng was born in Dallas, Texas on March 20, 1980 to Bob and Mary Eng. He graduated from L.V. Berkner High School (Richardson, Texas) in May 1998. He attended The University of Texas at Austin and graduated in May 2002 with a Bachelor of Science in Electrical Engineering with Honors. After college, Matthew moved to Dallas, where he worked as an electrical engineer for Raytheon and British Petroleum. In June 2004, Matthew returned to The University of Texas at Austin to complete premedical post-baccalaureate work.

Matthew matriculated at The University of Texas Southwestern Medical School in July 2005. During summer 2006, he participated 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, he has presented research posters at the Medical Student Research Forum in 2007 and 2009, and in 2007 was chosen to be an oral presenter. Through the guidance of Dr. White, Matthew co-authored three peer-reviewed publications on new analgesic and antiemetic techniques. In addition, he co-authored two book chapters for the latest editions of the two major anesthesia textbooks, namely Miller et. al (Ambulatory [Outpatient] Anesthesia) and Barash et. al (Intravenous Anesthesia). He also authored a published review article on postoperative nausea and vomiting.

After graduation from medical school, Matthew will perform his residency training in the field of Anesthesiology & Pain Management at the Cedars Sinai Medical Center, Los Angeles, CA in preparation for his career as an academic anesthesiologist.