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Effect of preoperative intravenous vs oral acetaminophen on postoperative opioid consumption in an enhanced recovery after surgery (ERAS) program in patients undergoing open gynecologic oncology surgery

Katherine E. Cain, PharmD[1], **Maria D. Iniesta, MD, PhD**[2], **Bryan M. Fellman, MS**[3], **Tina S. Suki, BS**[2], **Ashley Siverand, MBA**[2], **Camila Corzo, MD**[2], **Javier D. Lasala, MD**[4,5], **Juan P. Cata, MD**[4,5], **Gabriel E. Mena, MD**[4], **Larissa A. Meyer, MD, MPH**[2], **Pedro T. Ramirez, MD**[2]

[1]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2]Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4]Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[5]Anesthesiology and Surgical Oncology Research Group. Houston, TX, USA

Abstract

Objective: Both intravenous (IV) and oral acetaminophen provide effective opioid-sparing analgesia after surgery when used as part of a multimodal preemptive pain management strategy. The purpose of this study was to compare postoperative opioid consumption in patients undergoing open gynecologic oncology surgery who received preoperative IV vs oral acetaminophen within an enhanced recovery after surgery (ERAS) program.

Methods: Retrospective data were collected on consecutive patients undergoing open gynecologic oncology surgery from May 1, 2016 to February 28, 2018 in patients receiving either

Corresponding author: Katherine E. Cain, PharmD, Division of Pharmacy, Unit 0090, The University of Texas MD Anderson Cancer Center, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: (713) 745-8239. Fax: (713) 794-4399. kecain@mdanderson.org.

Authors' contributions:

Katherine E. Cain: This author helped in manuscript preparation and led the study. Maria D. Iniesta: This author helped in database management and manuscript preparation.

Bryan M. Fellman: This author helped in data analysis and manuscript preparation. Tina S. Suki: This author helped in data collection and database management. Ashley Siverand: This author helped in data collection and database management. Camila Corzo: This author helped in data collection and database management. Javier D. Lasala; This author helped in manuscript preparation and data analysis. Juan P. Cata: This author helped in manuscript preparation and data analysis. Gabriel E. Mena: This author helped in manuscript preparation and data analysis. Larissa A. Meyer: This author helped in manuscript preparation and data analysis. Pedro T. Ramirez: This author helped in manuscript preparation and data analysis.

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1 gram IV or oral acetaminophen preoperatively. Patients were given a preoperative multimodal analgesia regimen including acetaminophen, celecoxib, pregabalin and tramadol. The primary outcomes were morphine equivalent daily doses (MEDD) on postoperative days (POD) 0 and 1. Secondary outcomes included highest patient-reported pain score in the post-anesthesia care unit (PACU) and intraoperative MEDD. Regression models adjusted by matched pairs were fit to estimate the average treatment effect of IV vs oral acetaminophen on MEDD.

Results: Of 353 patients, 178 (50.4%) received IV acetaminophen and 175 (49.6%) received oral acetaminophen. When balancing across the matched samples, there was no difference in postoperative MEDD for POD 0 between the IV and oral acetaminophen groups (Beta = −1.11; 95% CI: −4.83 to 2.60; p=0.56). On POD 1, there was no difference between the IV and oral groups (Beta = 2.24; 95% CI: −2.76 to 7.25; p=0.38).

Conclusions: There was no difference in postoperative opioid consumption between patients receiving preoperative IV or oral acetaminophen within an ERAS program for patients undergoing open gynecologic oncology surgery.

Introduction

One of the key components of an enhanced recovery after surgery (ERAS) program is opioid-sparing multimodal perioperative pain management.[1] Multimodal techniques for pain management require the use of multiple pharmacologic agents with different analgesic mechanisms of action. ERAS guidelines strongly recommend a combination of acetaminophen, nonsteroidal anti-inflammatory drugs, and a gabapentinoid, for gynecologic oncology surgery in order to reduce postoperative opioid requirements, when no contraindications exist.[2] These guidelines also recommend acetaminophen oral route vs intravenous (IV) when tolerated by patients. Both IV and oral acetaminophen, alone or in combination with other nonopioid analgesics, provide an opioid-sparing effect.[3,4]

The peak concentration of IV acetaminophen occurs 30 minutes faster than that of oral acetaminophen and results in higher peak concentrations in both plasma and cerebrospinal fluid than equivalent oral doses.[5] However, higher IV acetaminophen peak concentrations at a faster rate have not been shown to provide better analgesia in patients undergoing arthroscopy of the knee.[6]

The average wholesale price of 1 gram of IV acetaminophen is $56.84, while the average wholesale price of 1 gram (2 500-mg tablets) of oral acetaminophen is $0.10 (range, $0.02–0.33).[7] Thus, because the cost of IV acetaminophen is almost 600 times higher than that of the oral formulation, there needs to be a significant clinical benefit to justify using the IV formulation in this setting. The use of IV acetaminophen is appropriate when a patient is unable to tolerate the oral route. In the setting of postoperative pain management, few studies have compared the effects of preoperative administration of IV vs oral acetaminophen and, to our knowledge, no published studies exist comparing preoperative acetaminophen administration routes in patients undergoing open gynecologic oncology surgery.[8,9] The hypothesis of this study was that there would be no difference in postoperative opioid consumption in patients receiving IV vs oral acetaminophen within an ERAS program for patients undergoing open gynecologic oncology surgery.

Methods

This study was approved by our Institutional Review Board (IRB) (PA18–0677). The requirement for written consent was waived by the IRB. Data were collected retrospectively on consecutive patients undergoing open gynecologic oncology surgery receiving preoperative IV acetaminophen (surgery date May 1, 2016 to February 28, 2017) or oral acetaminophen (surgery date May 1, 2017 to February 28, 2018). IV acetaminophen was used exclusively as part of our multimodal preoperative pain regimen when our ERAS program began in November 2014, but in March 2017 the gynecologic oncology surgery service decided to switch to oral acetaminophen in order to decrease costs. The same ERAS protocol was followed during both time periods. Thus, our study period included data for 10 months of IV acetaminophen use and 10 months of oral acetaminophen use. During the months of March and April 2017 it was observed that some patients still received preoperative IV acetaminophen. We excluded patients treated during this transition period. Additionally, patients who received both IV and oral acetaminophen preoperatively were excluded. We also excluded any patient taking scheduled long-acting opioids at the time of the preoperative visit. Additionally, patients whose procedures were converted from minimally invasive to open surgery were excluded because these patients only receive acetaminophen and celecoxib premedications preoperatively. Patients admitted to the intensive care unit (ICU) from the operating room where excluded since patients would be unable to maintain greater than 70% of ERAS compliance[10]. Patients were also excluded if they received postoperative IV acetaminophen.

Patients received acetaminophen, either 1 gram IV at the time of anesthesia induction or 1 gram oral approximately 1 hour prior to induction, depending on the date of surgery (as outlined above). Other standard preoperative medications included 400 mg celecoxib, 75 mg pregabalin, 300 mg tramadol extended release (ER), based upon standard safety and practice guidelines for our institutional ERAS program (Table 1). Intraoperative IV opioids were administered at the anesthesiologist's discretion. General anesthesia agents varied between inhalational anesthetics, total intravenous anesthesia (TIVA), or a combination of the 2 approaches per the anesthesiologist's judgment. Patients received local wound infiltration with standard bupivacaine at the end of the case. No patients received a transversus abdominis plane nerve block or intraoperative epidurals. Postoperatively, patients were transferred to the post-anesthesia care unit (PACU), while in the PACU patients received IV opioids as needed for pain scores above 4. From the PACU patients were transferred to an inpatient ward, here patients received scheduled oral acetaminophen 1 gram every 6 hours (starting 6 hours from last dose administered), ibuprofen 800 mg 3 times daily with meals (starting morning of POD 1), and pregabalin 75 mg twice daily for 4 doses (starting evening of POD 0), with rescue oral oxycodone and IV hydromorphone as needed.[11] Rescue oral oxycodone was available in both 5 mg and 10 mg doses for pain score of 4–6 and 7–10 every 4 hours as needed, respectively. If a patient reported pain unrelieved by oxycodone, then 0.5 mg IV hydromorphone was administered.

The primary outcome was total daily opioid consumption during postoperative days (POD) 0 and 1 in order to evaluate the effectiveness of preoperative acetaminophen administration. We hypothesized that if a difference between preoperative IV and oral acetaminophen exists

the biggest difference would most likely manifest within the first 24 hours. POD 0 was defined as the time from arrival in the PACU to midnight of POD 0. Total daily opioid consumption was calculated in morphine equivalent daily dose (MEDD) using institutional standard conversions. Administration of rescue opioids was based on patients' reported pain levels as described above. Secondary outcomes included intraoperative MEDD and the highest patient-reported pain level in the PACU. Pain intensity was assessed using a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain). Compliance with scheduled postoperative medication was also assessed. Demographic and clinical data collected included age, Charlson Comorbidity Index, length of hospital stay, surgical time, time in PACU, body mass index (BMI), ERAS compliance, American Society of Anesthesiologists (ASA) physical status class, benign vs malignant indication for surgery, rate of compliance with standard preoperative medication (celecoxib, pregabalin, and tramadol ER), dexamethasone dose, compliance with wound infiltration, and general anesthesia technique.

Statistical Analysis

We used descriptive statistics to summarize variables of interest separately for those patients who received IV vs oral acetaminophen. Continuous measures were compared using a 2-sample *t*-test or Wilcoxon rank-sum test, and categorical variables were compared using Fisher's exact or chi-squared test. A number of variables were identified as potential confounders: age at surgery, dexamethasone dose, preoperative celecoxib, preoperative tramadol, preoperative pregabalin, wound infiltrations, general anesthesia technique, and surgical time. To correct for possible bias with regard to MEDD outcomes, nearest-neighbor matched pairs were first obtained. Regression models with adjusted estimates by the matched pairs were fit to estimate the average treatment effect of IV versus oral acetaminophen on MEDD outcomes. The nearest-neighbor matching distance metric used was Mahalanobis. Standardized differences and variance ratios for the raw data and the matched samples were used as diagnostic statistics to check for covariate balance over the treatment groups after estimation. All statistical analyses were performed using Stata/MP v15.0 (College Station, TX).

Results

A total of 423 patients were reviewed for inclusion in the study. One patient was excluded for receiving both IV and oral acetaminophen preoperatively. Eight patients were excluded due to preoperative long-acting opioid use. Additionally, 19 patients were excluded due to conversion from minimally invasive surgery to an open procedure. Two patients were excluded for postoperative ICU admission. Forty patients were excluded because they received IV acetaminophen doses postoperatively. A total of 353 patients were included in the analysis, with 178 (50.4%) patients receiving preoperative IV acetaminophen and 175 (49.6%) patients receiving preoperative oral acetaminophen. There was no difference in median age, comorbidities, length of hospital stay, time in PACU, BMI, ASA score, indication for surgery, or wound infiltration compliance between the 2 groups (Table 2). Specifically, the clinical and baseline demographics for IV acetaminophen and oral acetaminophen respectively included: the median age (years) 59.5 [range, 22–82] vs 60

[range, 20–86]; p=0.79, median comorbidity score 3 vs 3; p=0.89, median length of hospital stay (days) 3 vs 3; p=0.82, median time in PACU (hours) 3.4 [1.2–9.8] vs 3.22 [1.1–7.7]; p=0.56, median BMI (kg/m^2) 27 [19.3–62.7] vs 28.2 [15.8–54]; p=0.89. Prior to the matched-pair analysis, the data were unbalanced for surgical time (favoring IV), intraoperative dexamethasone dose (favoring IV), and general anesthesia technique (favoring IV) (Table 2). Surgical time was shorter in the IV acetaminophen group (202.5 minutes vs 217 minutes; p=0.032). The IV acetaminophen group had a higher median dexamethasone dose intraoperatively than did the oral group (10 mg vs. 8 mg; p=0.004). We also found significant differences in general anesthesia technique between the IV and oral acetaminophen groups (p<0.001). Patients who received IV acetaminophen most often received combined anesthesia (42.7%), followed by inhalational anesthesia (30.3%) and TIVA (27%), whereas patients in the oral acetaminophen group most often received inhalational (54.9%) anesthetic agents, followed by combined anesthesia (32.6%) and TIVA (12.6%). Overall compliance with ERAS pathway was 75% [range, 45–90%]. ERAS compliance was found to be higher in the oral acetaminophen group 80% vs 70%, p<0.001. The overall rate of standard preoperative medication compliance (celecoxib, pregabalin, and tramadol ER) administration in patients receiving all preoperative medications was 67.1%. However, standard preoperative medication compliance was significantly higher in the IV acetaminophen group than in the oral acetaminophen group (73.6% vs. 60.6%; p=0.009).

The oral acetaminophen group had, on average, 11.07 lower MEDDs intraoperatively than did the IV group (95% CI: −16.25 to −5.88; p< 0.001). The highest median pain score reported in the PACU was higher in the oral acetaminophen group than in the IV group (5 vs. 4; p=0.004). When balancing across the matched samples, there was no difference in postoperative MEDD for POD 0 between the IV and oral acetaminophen groups (Beta = −1.11; 95% CI: −4.83 to 2.60; p=0.56). On POD 1, there was also no difference between the IV and oral groups (Beta = 2.24; 95% CI: −2.76 to 7.25; p=0.38) (Table 3). There was no difference found between IV and oral acetaminophen groups receiving a patient controlled analgesia (PCA) pump (3.4% vs 2.3%; p=0.75).

Discussion

Our study showed that there was no difference in postoperative opioid consumption between patients given preoperative IV or oral acetaminophen within POD 0 or POD 1. Lombardi et al.[12] conducted a double-blind randomized trial in women undergoing robotic-assisted laparoscopic hysterectomy for benign indications and observed no difference in the primary outcome of pain at 2 hours postoperatively between patients receiving preoperative IV or oral acetaminophen (Visual Analog Scale (VAS) = 36 vs 35; p=0.86), nor was there a difference at 4 or 24 hours. Most other published studies comparing preoperative IV and oral acetaminophen are in the orthopedic surgery literature. Politi et al.[8] found that in patients undergoing hip or knee arthroplasty, there were no differences in VAS scores except at the first postoperative 4-hour interval, which favored IV acetaminophen (VAS = 4.4 vs 3.4; p=0.03). Additionally, there were no differences in 24-hour average or 4-hour interval hydromorphone equivalents. Another study in patients undergoing knee arthroscopy found no statistically significant differences in fentanyl requirements, mean pain score at 30 minutes, overall mean pain score, or total time in recovery area between patients who

received 1 gram of preoperative oral acetaminophen and those who received 1 gram of intraoperative IV acetaminophen.[6] Similarly, Hickman et al.[9] reported equivalent pain control in patients undergoing hip or knee arthroplasty within the 24 hours postoperatively. In a randomized, double-blind, placebo-controlled study, Konstantatos et al.[13] compared outcomes of IV and oral acetaminophen use in 142 outpatient surgery patients. The study population consisted primarily of healthy patients having orthopedic or plastic surgery. Patients received one of the following regimens: 1 gram intraoperative IV acetaminophen with postoperative oral acetaminophen vs 1 gram preoperative oral acetaminophen dose with postoperative oral acetaminophen vs or placebos. There were no statistically significant differences in terms of mean 24-hour pain score, pain intensity coming out of anesthesia, time to discharge from PACU, and opioid requirements in the PACU among the 3 groups. A systematic review of six randomized controlled trials published by Jibril et al. concluded as a major finding the absence of strong evidence suggesting superiority of IV acetaminophen administration over oral routes.[14]

In our study, patients who received oral acetaminophen received less intraoperative opioids than did patients who received IV acetaminophen. This difference might explain the higher reported PACU pain in the oral group. However, this difference in reported pain did not translate into increased opioid administration on POD 0 or 1. It is worth noting that although a statistically significant difference in PACU pain score was observed, it is questionable whether this difference was clinically significant. A 30% reduction in pain is the most commonly used benchmark for a clinically significant reduction, which would correspond to 2 points on a 0-to-10 numerical rating scale.[15] Since we found only a 1-point difference, it is unlikely to be clinically meaningful.

It is important to discuss factors that contribute to the opioid-sparing effect and minimize possible bias. We identified many variables that could potentially confound the results, so we used a matched-pair analysis. We did identify unbalanced differences prior to matching. First, surgical time was shorter in the IV acetaminophen group (202.5 minutes vs 217 minutes; p=0.032). Despite the shorter surgical time, patients in the IV acetaminophen group received more intraoperative opioids than the oral acetaminophen group. Second, the IV acetaminophen group received a higher median intraoperative dexamethasone dose (10 mg vs 8 mg; p=0.002). Dexamethasone at both of these doses is opioid sparing, but some studies have shown a dose-dependent relationship for postoperative pain.[16,17] Nonetheless, after matched-pair analysis there was no difference in postoperative MEDD between patients receiving preoperative IV and oral acetaminophen. Third, the general anesthetic technique used was unbalanced between the IV and oral acetaminophen groups. In this study, despite the IV acetaminophen group’s having more patients who underwent the TIVA technique, after matching the IV acetaminophen group had higher intraoperative opioid administration. After matching, there was no difference in MEDD postoperatively. This finding could be explained by the fact that multiple anesthesiologists were involved in the intraoperative period, potentially decreasing internal validity and increasing variability in the practice. Finally, premedication compliance for patients receiving all three medications (tramadol ER, celecoxib, and pregabalin) was higher in the IV acetaminophen group than in the oral group. Although not statistically significant more patients in the IV acetaminophen group received preoperative pregabalin. The reason for this difference is likely a May 2017 institutional

change in preoperative medication guidelines advising caution in administering preoperative pregabalin to patients aged 75 or older because of possible dizziness and sedation. Prior to this recommendation, age was not an exclusion factor for administration of pregabalin. However, even after the matched-pair analysis, there was no difference in postoperative MEDD between patients who received preoperative IV vs oral acetaminophen.

Our study differs from others in the literature in that it is the first to evaluate IV vs oral acetaminophen within an ERAS program for patients undergoing open gynecologic oncology surgery. A strength of this study is that our ERAS program was well established before the start of this study. In addition, we attempted to correct for possible bias by matching the cohorts. We do recognize several limitations of our study, such as its retrospective nature and the small number of patients, which might have underpowered our analysis. Additionally, when evaluating one element (i.e. acetaminophen) of a bundled approach (i.e. ERAS as a whole) we are less likely to find a difference between elements even after matching the cohorts. All potential confounding variables may not have been assessed. We also cannot generalize our results to minimally invasive surgery due to their exclusion in the study. External validity is lacking in programs that do not have ERAS established. Finally, there was no set criteria for opioids given intraoperatively.

Our ERAS program has successfully reduced our patients' opioid consumption without compromising patient-reported pain.[18] As we continue to expand and reevaluate our program, we are focusing on value-based care. According to our own data, if a patient has a functioning gastrointestinal tract and is able to take oral formulations, IV formulations are not indicated. The significantly higher cost associated with the preoperative IV acetaminophen formulation and the lack of clinical benefit favors the use of oral acetaminophen when possible. Future studies should include both efficacy and safety outcomes and assess multiple dosing rather than single dosing to determine more precisely differences associated to the dosage forms used in current practice.

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Highlights:

- In matched samples, there was no difference in POD 0 or 1 MEDD between preoperative IV and oral acetaminophen
- Oral acetaminophen reduced opioid consumption without compromising patient-reported pain
- Preoperative oral acetaminophen should be utilized when oral administration is possible

Table 1.

ERAS Premedication Ordering Guidelines

Medication	Guidelines
Pregabalin	• CI if hypersensitivity • Avoid in patients older than 75 years of age
Celecoxib	• CI if hypersensitivity (not sulfa allergy) • CI if active GI bleeding • CI with CrCI < 30 mL/min • CI if Child-Pugh Class C • CI in patients with NYHA functional classification II and above • Decrease dose to 200 mg for Child-Pugh Class B
Tramadol ER	• CI if hypersensitivity • CI if CrCI < 30 mL/min • CI if Child-Pugh Class C • CI with concurrent MAOI therapy • Decrease dose to 200 mg for Child-Pugh Class B
Acetaminophen	• CI if hypersensitivity • Decrease dose if patient weight < 50 kg (dose 15 mg/kg) • Decrease dose to 500 mg if hepatic impairment/active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or CrCI < 30 mL/min

CI: contraindicated, GI: gastrointestinal, NYHA: New York Heart Association, ER: extended release, MAOI: monoamine oxidase inhibitor, CrCl: creatinine clearance

Table 2.

Clinical and demographic characteristics by acetaminophen status[a]

Characteristic	Overall N = 353	Intravenous n = 178 (50.4%)	Oral n = 175 (49.6%)	p-value
Age, median (Min, Max)	60 (20, 86)	59.5 (22, 82)	60 (20, 86)	0.79
Charlson Comorbidity Index, median (Min, Max)	3 (0, 9)	3 (0, 9)	3 (0, 8)	0.89
Length of stay (days), median (Min, Max)	3 (1, 25)	3 (1, 25)	3 (1, 12)	0.82
Surgical time (minutes), median (Min, Max)	212 (46, 846)	202.5 (46, 840)	217 (72, 619)	0.032
Time in PACU (hours), median (Min, Max)	3.33 (1.1, 9.8)	3.4 (1.2, 9.8)	3.22 (1.1, 7.72)	0.56
BMI (kg/m^2), median (Min, Max)	27.7 (15.8, 62.7)	27 (19.3, 62.7)	28.2 (15.8, 54)	0.89
ASA physical status				0.11
I/II	21 (6%)	7 (3.9%)	14 (8%)	
III/IV	332 (94%)	171 (96.1%)	161 (92%)	
Indication for surgery				0.96
Malignant	276 (78.2%)	139 (78.1%)	137 (78.3%)	
Benign	77 (21.8%)	39 (21.9%)	38 (21.7%)	
Intraoperative dexamethasone dose (mg), median (Min, Max)	8 (0, 20)	10 (0, 20)	8 (0, 10)	0.004
Wound infiltration compliance	346 (98%)	176 (98.9%)	170 (97.1%)	0.28
General Anesthesia Technique				0.001
Volatile (inhaled)	150 (42.4%)	54 (30.3%)	96 (54.9%)	
Total intravenous	70 (19.8%)	48 (27%)	22 (12.6%)	
Combined	133 (37.7%)	76 (42.7%)	57 (32.6%)	
ERAS compliance %, median (Min, Max)	75 (45, 90)	70 (55, 85)	80 (45, 90)	<0.001
Standard premedication compliance[b]				0.009
No	116 (32.9%)	47 (26.4%)	69 (39.4%)	
Yes	237 (67.1%)	131 (73.6%)	106 (60.6%)	

[a] N (%) reported unless indicated otherwise; missing values not included in p-value calculation.

[b] Patients receiving all premedication medications (pregabalin, celecoxib, and tramadol)

ASA: American Society of Anesthesiologists, BMI: body mass index

Table 3.

Nearest-neighbor matched-pair analysis

Characteristic		Beta	95% LB	95% UB	p-value
MEDD Total (Intraop)	oral (ref IV)	−11.07	−16.25	−5.88	< 0.001
MEDD Total (POD0)		−1.11	−4.83	2.6	0.56
MEDD Total (POD1)		2.24	−2.76	7.25	0.38

LB: lower bound, UB: upper bound, MEDD: morphine equivalent daily dose, POD: postoperative day; IV: intravenous