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Patient characteristics and opioid use prior to discharge after open gynecologic surgery in an enhanced recovery after surgery (ERAS) program

R. Tyler Hillman [a], Amalia Sanchez-Migallon [b], Larissa A. Meyer [a], Maria D. Iniesta [a], Katherine E. Cain [c], Ashley M. Siverand [a], Simone P.L. Veum [a], Tina S. Suki [a], Javier D. Lasala [d], Pedro T. Ramirez [a,*]

[a] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Gynecology and Obstetrics, Dexeus University Hospital, Barcelona, Spain
[c] Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

HIGHLIGHTS

- Nearly half of patients undergoing open gynecologic surgery in an ERAS program are opioid-free prior to discharge.
- Age, smoking status, and race are independently associated with opioid-free pain control prior to discharge.
- Surgical indication, complexity and operative time, are not associated with opioid-free pain control prior to discharge.

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ABSTRACT

Objective. To identify clinical and demographic characteristics associated with the absence of opioid usage on the day before discharge among patients undergoing open gynecologic surgery within an enhanced recovery after surgery (ERAS) program.

Methods. This was a single institution retrospective cohort study including all patients who underwent elective open gynecologic surgery as part of an ERAS program between November 1, 2014 and September 30, 2018 and who were discharged between post-operative day 2 and 7. Patients were excluded if they reported pre-existing chronic opioid use or underwent total pelvic exenteration. Descriptive statistics were used and multivariable logistic regression was used to identify factors associated with the absence of opioid usage on the day before discharge, after adjustment for relevant covariates.

Results. A total of 971 were included with a median length of stay of 3 days, and of these 526 (54.2%) used opioids on day before discharge and 445 (45.8%) did not. Absence of opioid use on the day before discharge was associated with age ($P < .001$), race ($P = .04$), Charlson Co-morbidity Index ($P < .001$), marital status ($P = .004$), and smoking status ($P = .002$) by univariate analysis. In a multivariable model, older age (adjusted OR 1.04; 95% CI 1.02–1.06; $P < .001$), current smoker status (adjusted OR 0.42; 95% CI 0.20–0.81; $P = .01$), and white or Caucasian race (adjusted OR 0.59; 95% CI 0.38–0.91; $P = .02$) were significantly associated with the absence of opioid use on the day prior to discharge.

Conclusions. Nearly half of patients undergoing open gynecologic surgery within an established ERAS program did not consume any opioids on day before discharge. Safe, evidence-based reductions in post-operative opioid prescribing may be feasible for a subset of gynecologic surgery patients.

1. Introduction

The rate of accidental death from fatal drug overdose has increased dramatically over the past two decades in the United States, due in large part to a four-fold increase in prescription opioid overdose deaths between 1999 and 2017 [1,2]. The opioid abuse crisis in this country is fueled in part by physician prescribing patterns since per capita daily

* Corresponding author at: Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA.
E-mail address: peramire@mdanderson.org (P.T. Ramirez).

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consumption of prescription opioids in the United States is nearly double that of Canada and western Europe [3]. Trends in the use of opioids for post-operative pain management mirror these increases: both the rate of new opioid prescriptions after surgery as well as the average total morphine equivalent dose prescribed have increased between 2004 and 2014 among patients undergoing common general and gynecologic surgical procedures in the United States [4,5].

Reports from across surgical sub-specialties suggest that the amount of opioids prescribed after elective surgery is often excessive, which can lead to misuse and addiction [6–9]. The harm posed by new post-operative chronic opioid use is becoming better defined, with new evidence indicating that this rate is approximately 6% among all patients undergoing elective surgery [10] and may be as high as 10% among patients undergoing curative-intent surgery for the treatment of cancer [11]. Surgeon approaches to opioid prescription after elective surgery have therefore taken on urgent public health ramifications, and new efforts are needed to reduce the morbidity associated with post-operative opioid use and misuse.

Enhanced recovery after surgery (ERAS) is a multimodal approach to perioperative care that focuses on stress reduction, achievement of adequate pain control, return of bowel function, and early ambulation [12–14]. Implementation of ERAS for patients undergoing gynecologic surgery at our institution successfully reduced median inpatient opioid consumption by 72% among women undergoing open gynecologic surgery, while achieving similar results for key patient reported outcomes [15]. It remains an open question whether the reduction in inpatient opioid usage achieved with ERAS can be successfully translated into a safe, evidence-based reduction in post-discharge opioid prescribing.

Notably, post-operative opioid usage in the hospital is correlated with post-discharge opioid usage and patients who achieve opioid-free pain control prior to discharge often use little if any opioid pain medication at home [16,17]. The successful implementation of restrictive opioid prescribing after gynecologic surgery has been described, and it appears this can be done with no adverse effect on complications, refill requests, or pain scores after surgery [18]. At our institution, we are developing an evidence-based protocol to safely reduce the amount of opioids prescribed at hospital discharge following gynecologic surgery. It is not known whether there exist demographic or clinical factors associated with the achievement of opioid-free pain control prior to discharge in this patient population. Identification of patient characteristics associated with the absence of opioid usage prior to discharge would improve efforts to develop a personalized approach to restrictive opioid prescribing. We therefore examined associations between clinical and demographic variables and opioid use on the day before hospital discharge following open gynecologic surgery within the ERAS program at our institution.

2. Methods

All patients undergoing elective open gynecologic surgery in the ERAS program at MD Anderson Cancer Center [12] between November 1, 2014 and September 30, 2018 were included in this study if they were discharged between post-operative day (POD) 2 and 7. Patients discharged after POD7 comprised <1% of all patients who underwent surgery during the study period and otherwise met inclusion criteria, and many patients in this group were extreme outliers with length of stay longer than 2 weeks. Since nearly all patients will eventually achieve opioid-free pain control after surgery, the exclusion of patients with extremely prolonged inpatient stays would tend to increase the sensitivity of the study for detecting true relationships between clinical or demographic characteristics and pre-discharge opioid use. Patients were excluded if they had undergone a total pelvic exenteration or were a chronic opioid user prior to surgery (defined as having a current opioid prescription documented at the time of the pre-operative visit).

Clinical and demographic data were collected from the medical record and included age at the time of surgery, body mass index (BMI, calculated as weight (kg)/[height (m)]^2), marital status, race, ethnicity, smoking status, prior chemotherapy exposure, prior radiotherapy exposure, history of prior laparotomy, history of prior laparoscopy, Charlson Comorbidity Index (CCI) [19], American Society of Anesthesiologists (ASA) classification of physical health [20], primary disease site, and indication for surgery. Ovarian, fallopian tube, and primary peritoneal cancer were combined for the purpose of analysis. Other disease sites were cervix, uterine (non-sarcoma), and uterine sarcoma. For participants with ovarian, fallopian tube, or primary peritoneal cancer, a surgical complexity score [21] was assigned. The current malignancy was not included in the calculation of the CCI to more accurately reflect other non-cancer comorbidities. Perioperative data were also collected including surgical time, estimated blood loss (EBL), intraoperative complications (EBL >2000 mL or injury to major blood vessel, nerve, or organ), and length of stay in days (LOS). Information on opioid usage during post-operative hospitalization was also collected. The absence of opioid usage on the day before discharge was defined as no opioid usage during the calendar day immediately prior to the day of hospital discharge (morphine equivalent daily dosage [MEDD] = 0 mg). MEDD was calculated using a standard opioid equivalent dose conversion table, with total opioid dose on the calendar day before hospital discharge serving as the basis for calculation. For example, oxycodone has a morphine equivalent conversion factor of 1.5x. This would mean that a total usage of 15 mg oxycodone on the day prior to discharge would be converted to a MEDD of 22.5 mg (15 mg × 1.5 = 22.5 mg).

Descriptive statistics were used to analyze associations between clinical and demographic characteristics and the absence of opioid usage on the day before discharge. Categorical variables were compared between the cohorts using a Fisher exact test or chi-squared test, as appropriate, with $P < .05$ considered statistically significant. Continuous variables were compared using a Wilcoxon rank-sum test. Multivariable logistic regression was used to evaluate independent associations between variables of interest and the absence of opioid usage on the day before discharge. Variables were included in the multivariable model if a statistically significant univariate associated was observed at a threshold of $P < .1$. Statistical analyses were performed using R 3.5.1 for Mac OS X [22]. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson Cancer Center as part of an institutionally approved quality improvement study (QI-6033) [23]. The retrospective analysis of these data was approved by the institutional review board (PA18–1176).

3. Results

A total of 1009 patients underwent non-emergent open gynecologic surgery in the ERAS program at MD Anderson Cancer Center between November 1, 2014 and September 30, 2018 and were discharged between post-operative day POD2 and POD7. After exclusion of patients undergoing total pelvic exenteration procedures (N = 7) and those patients with chronic pre-operative opioid use (N = 31), a total of 971 patients were included in the final analysis cohort (Fig. 1). In this cohort, the median MEDD on the day before discharge was 7.5 mg (range 0–290 mg), which is equivalent to a single 5 mg tablet of oxycodone. Overall, on the day before discharge 445 patients (45.8%) used no opioids (MEDD = 0 mg) and 526 patients (54.2%) used at least one dose of opioid pain medication (MEDD >0 mg). A key principle of ERAS is the use of opioid-sparing pain control methods, including in the pre-operative period. In this cohort compliance with pre-operative medications was high including 95% receiving acetaminophen, 85% receiving celecoxib, 83% receiving tramadol, and 77% receiving pregabalin. We did not identify any statistically significant association between opioid usage groups and the receipt of individual opioid-sparing pre-medications (all $P > .05$). In addition, >98% of patients in this cohort had some form of local anesthetic infiltrated into the incision during surgery with only 3.4% of the entire cohort receiving a liposomal

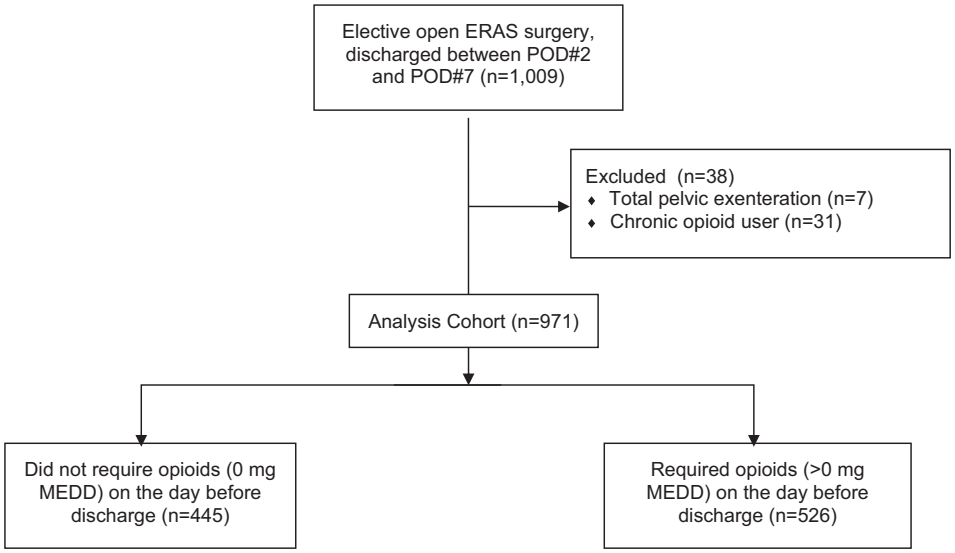

Fig. 1. Overview of analysis schema. ERAS, enhanced recovery after surgery; POD, post-operative day; MEDD, morphine equivalent daily dosage.

formulation. There was no difference between opioid usage groups with regard to local anesthetic infiltration (P = .94).

Clinical and demographic characteristics of this cohort are summarized in Table 1 by opioid usage category. The median age at the time of surgery of patients who did not use opioids on day prior to discharge (62 years; range 18–87 years) was higher than for those who were using opioids at the time of discharge (56 years; range 20–86; P < .001). There were statistically significant differences in CCI between opioid usage groups (P < .001). Among patients who did not use opioids on day prior to discharge, a higher proportion had a CCI of 3 or greater (34.8% vs. 21.5%) and a lower proportion had a CCI of zero (15.7% vs. 28.5%). Statistically significant differences were also observed between opioid usage groups with respect to marital status (P = .004), race (P = .04), and smoking status (P = .002). Patients who did not use opioids on day prior to discharge were less likely to be single (11.0% vs. 17.7%), be of white race (64.0% vs. 71.9%), or be a current (2.7% vs. 7.2%) or former (20.9% vs. 23.8%) smoker. There were no statistically significant differences between opioid usage groups with regard to ethnicity, ASA classification, BMI, history of prior laparotomy, history of prior laparoscopy, prior chemotherapy, or prior radiotherapy.

Peri-operative characteristics of this cohort are summarized in Table 2 by opioid usage category. Length of post-operative stay, indication for surgery, primary disease site, surgical time, EBL, and the presence of intraoperative complication were not associated with the use of opioids on day prior to discharge (all P > .05). Among patients undergoing surgery for ovarian, fallopian tube, or primary peritoneal carcinoma the distribution of low, intermediate, or high surgical complexity scores did not differ between the opioid usage groups (P = .86). A multivariable logistic regression model was built using the absence of opioid usage on the day prior to discharge as the outcome variable. Age at the time of surgery, marital status, smoking status, CCI, and race were included in the multivariable model based on statistically significant univariate associations (P < .1) with the outcome of interest (Table 3). After adjustment for co-variates, older age at the time of surgery (adjusted OR 1.04; 95% CI 1.02–1.06; P < .001), current smoker status (adjusted OR 0.42; 95% CI 0.20–0.81; P = .01), and white or Caucasian race (adjusted OR 0.59; 95% CI 0.38–0.91; P = .02) remained significantly associated with no use of opioids on day prior to discharge.

4. Discussion

Our study found that nearly half (45.8%) of patients who underwent open gynecologic surgery as part of an ERAS program did not require

Table 1
Sociodemographic, lifestyle, and clinical characteristics by opioid usage group.

	Did not require opioids (0 mg MEDD) on the day before discharge (n = 445)	Required opioids (>0 mg MEDD) on the day before discharge (n = 526)	P
Age (y)	62 (18–87)	56 (20–86)	<.001
BMI (kg/m^2)			.46
<25	148 (33.3)	166 (31.6)	
25–34.9	253 (56.9)	295 (56.1)	
35 or greater	44 (9.9)	65 (12.4)	
Ethnicity[a]			.86
Not Hispanic or Latina	360 (80.9)	424 (80.6)	
Hispanic or Latina	73 (16.4)	82 (15.6)	
Not reported	12 (2.7)	20 (3.8)	
Race[a]			.04
White or Caucasian	285 (64.0)	378 (71.9)	
Black or African American	60 (13.5)	56 (10.6)	
Asian	29 (6.5)	20 (3.8)	
Other	57 (12.8)	56 (10.6)	
Not reported	14 (3.1)	16 (3.0)	
Marital status[a]			.004
Single	49 (11.0)	93 (17.7)	
Married, significant other	297 (66.7)	339 (64.4)	
Separated, divorced, widowed	98 (22.0)	87 (16.5)	
Not reported	1 (0.2)	7 (1.3)	
Smoking status			.002
Never smoker	340 (76.4)	363 (69.0)	
Former smoker	93 (20.9)	125 (23.8)	
Current smoker	12 (2.7)	38 (7.2)	
Charlson Comorbidity Index			<.001
0	70 (15.7)	150 (28.5)	
1–2	220 (49.4)	263 (50.0)	
3 or greater	155 (34.8)	113 (21.5)	
ASA[a]			.58
I–II	38 (8.5)	51 (9.7)	
III–IV	400 (89.9)	469 (89.2)	
Not reported	7 (1.6)	6 (1.1)	
Prior chemotherapy	194 (43.6)	207 (39.4)	.19
Prior radiotherapy	13 (2.9)	10 (1.9)	.40

MEDD, morphine equivalent daily dosage; BMI, body mass index; ASA, American Society of Anesthesiologists. Data are median (minimum–maximum) or n (%) unless otherwise specified.

[a] Statistical tests were performed after excluding "Not reported" category.

Table 2
Peri-operative characteristics by opioid usage group.

	Did not require opioids (0 mg MEDD) on the day before discharge (n = 445)	Required opioids (>0 mg MEDD) on the day before discharge (n = 526)	P
Prior laparotomy	262 (58.9)	286 (54.4)	.17
Prior laparoscopy	181 (40.7)	233 (44.3)	.24
Surgical indication[a]			.10
Benign	78 (7.8)	112 (11.0)	
Cervical cancer	9 (0.9)	25 (2.5)	
Ovarian, fallopian tube, primary peritoneal cancer	254 (26.0)	265 (27.0)	
Uterine cancer (nonsarcoma)	61 (6.1)	73 (7.3)	
Uterine sarcoma	17 (1.7)	17 (1.7)	
Other	37 (3.7)	47 (4.7)	
Tumor type			.39
Malignant/UMP – primary	304 (68.3)	354 (67.3)	
Malignant/UMP – recurrent	59 (13.3)	59 (11.2)	
Benign	71 (16.0)	103 (19.6)	
Other	11 (2.5)	10 (1.9)	
EBL (mL)	250 (5–3000)	250 (5–4750)	.54
Operative time (min)	213 (46–568)	216 (33–721)	.31
Intra-operative complication	24 (5.4)	30 (5.7)	.89
Length of stay (days)			.63
2	170 (38.2)	219 (41.6)	
3	139 (31.2)	152 (28.9)	
4	74 (16.6)	73 (13.9)	
5	29 (6.5)	35 (6.7)	
6	18 (4.0)	29 (5.5)	
7	15 (3.4)	18 (3.4)	

EBL, estimated blood loss; UMP, unknown malignant potential. Data are median (minimum–maximum) or n (%) unless otherwise specified.
[a] Patients may have had more than one indication for surgery.

any opioid pain medication on the day before to discharge. Previous work by Hill et al. demonstrated that pre-discharge opioid usage after general surgery procedures is correlated with opioid pain medication needs at home [16]. Specifically, the authors found that the mean number of 5 mg oxycodone equivalent tablets taken at home was 1.5 if no opioids were used on the day before discharge and 21.2 if ≥30 MEDD was used on the day before discharge [16]. Although not yet specifically examined in a gynecologic surgery population, this correlation between pre- and post-discharge opioid consumption is intuitive and could allow opioid prescribing to be better tailored to patient needs. Our data suggest that a substantial fraction of patients undergoing open gynecologic surgery may be eligible for reduced opioid prescribing, based on minimal or no opioid usage prior to discharge. By adapting previously published evidence-based opioid prescribing protocols to gynecologic surgery [16,17], it may be feasible to substantially reduce post-operative opioid prescribing in a manner that is tailored to opioid usage prior to hospital discharge.

Table 3
Logistic regression model for rapid achievement of opioid-free pain control.

	Adjusted OR	95% CI	P
Age	1.04	1.02–1.06	<.001
Smoking status (reference: never smoker)			
Former smoker	0.74	0.53–1.03	.08
Current smoker	0.42	0.20–0.81	.01
Marital status (reference: single)			
Married, significant other	1.25	0.82–1.92	.31
Separated, divorced, widowed	1.37	0.83–2.27	.22
Charlson Comorbidity Index (reference: 0)			
1–2	0.97	0.60–1.58	.92
3 or greater	1.05	0.55–2.02	.88
Race (reference: Black or African American)			
White or Caucasian	0.59	0.38–0.91	.02
Asian	1.45	0.71–3.03	.31
Other	1.04	0.60–1.81	.89

OR, odds ratio; CI, confidence interval.

Until July 1, 2018 when our department implemented a reduced opioid prescribing protocol it had been our standard practice to prescribe thirty 5 mg oxycodone tablets (MED 225 mg) at the time of discharge to all patients who underwent open gynecologic surgery. This amount of opioid pain medication was broadly consistent with national trends in opioid prescribing after gynecologic surgery [5]. ERAS principles encourage the use of non-opioid, multi-modal analgesia as a means of reducing opioid needs. In our ERAS protocol on the morning of surgery, all patients undergoing open surgery receive pre-medication with tramadol ER, pregabalin, celecoxib, and acetaminophen [12]. While in the hospital, oxycodone is the standard opioid pain medication. At hospital discharge, in addition to opioid pain medication, it is our practice to also prescribe 800 mg ibuprofen three times daily with meals and 1 g acetaminophen every 6 h at the time of discharge to all post-operative patients without an allergy or other contraindication to these medications. The use of ibuprofen and acetaminophen after discharge bolsters any effort to reduce opioid prescribing by providing non-opioid options for post-discharge pain control.

Prior work by Mark et al. demonstrated that opioid prescribing after open gynecologic surgery can safely be reduced to 60–90 mg MED (12 tablets hydrocodone/acetaminophen 5/325 mg or oxycodone/acetaminophen 5/325 mg) for most patients without a detectable increase in post-operative pain scores, refill requests, or complications [18]. It seems possible that additional efforts to stratify patients by inpatient opioid usage, including the special category of patients who use no opioids on the day before discharge, could allow for further reductions in opioid prescribing. As an example of what might be achieved by linking opioid prescribing to inpatient opioid usage, we propose an approach that calibrates opioid prescriptions to usage on the day before discharge (Table 4). Such a protocol would have the potential to substantially reduce excess opioid prescriptions. Among the 445 patients in this analysis cohort who used no opioid pain medication on the day before discharge, our standard practice would be to prescribe thirty 5 mg oxycodone tablets (MED 225 mg) per patient or a total of 13,350 oxycodone tablets. If these 445 patients were each prescribed five 5 mg oxycodone tablets (MED 37.5 mg) we would have instead prescribed 2225 oxycodone tablets over the study period, or approximately 20% of the amount that was actually prescribed. For the entire study cohort, this hypothetical protocol for reduced opioid prescribing would have resulted in a >50% reduction in prescribed opioids.

Efforts to reduce opioid prescribing after surgery must carefully avoid creating unintentional patient harms associated with unrelieved post-discharge pain. It may eventually become possible to reliably identify a subset of patients who require no opioids after hospital discharge and who can therefore be safely prescribed only non-opioid pain medications. A data-driven, step-wise approach to refinement of post-discharge opioid prescribing will maximize patient safety and satisfaction and may eventually allow for extreme reductions in opioid prescribing for some patients. However until such practices have been studied further, it will continue to be appropriate to provide some amount of opioid pain medication to all patients being discharged after open gynecologic surgery.

At our institution we are in the process of evaluating an evidence-based protocol for reduced opioid prescribing based on pre-discharge opioid needs, as part of a quality improvement initiative in which post-discharge outcomes such as opioid consumption, refill requests, and re-admission are closely tracked to ensure patient safety. The real harms of opioid use and misuse after surgery make it incumbent upon surgeons to seek methods of better matching opioid prescriptions to actual pain control needs after hospital discharge. Maximization of non-opioid pain modalities and the calibration of opioid prescribing to pre-discharge usage are two approaches to achieving this important goal, and established ERAS programs provide the best framework for doing so.

Table 4
Proposed protocol for reduced post-operative opioid prescribing.

	Opioid usage on the day before discharge		
	0 mg MEDD (N = 445)	0 mg > MEDD ≤ 30 mg (N = 357)	>30 mg MEDD (N = 169)
Current prescribing (5 mg oxycodone tabs)		#30	
Current oxycodone tablets prescribed	13,350	10,710	5070
Proposed prescribing (5 mg oxycodone tabs)	#5	#15	#30
Proposed oxycodone tablets prescribed	2225	5355	5070

MEDD, morphine equivalent daily dosage.

Although previous studies have examined pre-discharge opioid usage among general surgery patients [16], this work adds important new information to our understanding of opioid usage after open gynecologic surgery. The strengths of our study also include a large sample size that included patients undergoing surgery for a variety of benign and malignant indications.

Our ERAS implementation has been in place for several years [12,14] and these data therefore reflect opioid usage under conditions where multi-modal analgesia is in routine use [15]. These conclusions may not therefore be broadly applicable to all practice environments, especially those where ERAS programs do not yet exist. Other limitations of this study include the retrospective design and the lack of information on actual opioid usage following hospital discharge. Similarly, although in general patients discharged from our service following open gynecologic surgery are prescribed ibuprofen and acetaminophen we do not have data on the usage of these non-opioid pain medications at home after surgery. Lastly, this study only addressed patients undergoing open gynecologic surgery and patients undergoing minimally invasive surgery were not included since the large majority are discharged on the day of surgery at our institution.

It is interesting to note that no peri-operative variables were significantly associated with the absence of opioid use on the day prior to discharge, but rather the patient characteristics that mattered most in this regard tended to be demographic (e.g. race, age at the time of surgery) or related to co-existing tobacco use. Opioid usage and co-existing tobacco use suggests that co-occurring substance usage disorders may play a role in influencing opioid use after surgery, and future studies will be needed to examine whether pre-operative smoking cessation efforts can modify opioid usage patterns after surgery. The association of white/Caucasian race with a higher rate of opioid usage prior to discharge may be due to unmeasured confounding social or economic variables that are not captured by the current study. In addition, our results may also reflect a molecular etiology, as some data suggest that polymorphisms in genes such as the mu-opioid receptor may influence post-operative opioid needs [24] which could in turn lead to population differences in opioid usage based on the frequency of relevant polymorphisms among various racial groups.

For patients with ovarian, fallopian tube, or primary peritoneal carcinoma even surgical complexity score, a metric associated with post-operative morbidity [21], was not associated with an absence of opioid use on the day prior to discharge. These data suggest that opioid usage after surgery has less to do with a particular procedure or surgical indication and is instead closely tied to less mutable aspects of patient background and lifestyle. As a result, even patients undergoing long, complex surgeries or those who have intra-operative complications may be eligible for reduced opioid prescribing based on their individual opioid usage prior to discharge.

Although opioid needs after hospital discharge are correlated with pre-discharge opioid usage [16], further work will be needed to examine whether efforts to reduce inpatient opioid intake can have a causative effect on the amount of opioid pain medication needed after discharge. Identification of a causative link between inpatient and outpatient opioid needs would indicate that the inpatient hospital stay is a crucial time period for influencing opioid pain medication needs after discharge. Such an observation would further emphasize the importance of multi-modal analgesia within an ERAS framework prior to hospital discharge, as a means of achieving longitudinal reductions in opioid usage throughout the post-operative recovery period.

Conflict of interest

The authors report no conflict of interest.

Author contributions

RTH, AS-M, LAM, and PTR conceived the study and wrote the first draft of the manuscript. RTH, AS-M, MDI, KCC, APLS, SV, and TSS collected and analyzed data. LAM, JDL, and PTR jointly supervised the study and provided oversight during the manuscript editing process. All authors discussed the results and contributed to the final manuscript.

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