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Reducing postoperative opioids after minimally invasive hysterectomy with enhanced recovery

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Abstract

Introduction

We evaluated the efficacy of various strategies utilized for the control of postoperative pain after minimally invasive hysterectomy. The primary enhanced recovery after surgery (ERAS) protocol of interest utilized premedication (acetaminophen, celecoxib and pregabalin), then intraoperative subcutaneous liposomal bupivacaine followed by scheduled oral acetaminophen and ibuprofen postoperatively. Patients also had tramadol and oxycodone as needed for moderate or severe breakthrough pain, respectively.

Materials and Methods

We conducted a retrospective cohort study that included all patients who underwent minimally invasive hysterectomy (total laparoscopic hysterectomy and laparoscopic-assisted vaginal hysterectomy) for both benign and oncologic indications over a two-year period. We then compared six protocols; three were ERAS protocols and three were traditional pain control methods. The control group was comprised of the traditional pain control group without intraoperative placement of local analgesia. Patient medical records were evaluated for demographics, surgical characteristics, opioid type and dose, pain scores, length of stay and complications. Opioids were converted to oral morphine dose equivalents.

Results

954 patients were included within the six protocols. Median opioid usage was the lowest in the ERAS group with premedication and highest in the control group (22.5mg versus 55.0mg, $p<0.001$). Patients in the ERAS group with premedication, when compared to control, were three times more likely to decline opioids, ($p<0.001$) without any concomitant increase in pain scores.

Discussion

ERAS protocol with premedication was associated with significant reductions in postoperative opioid use and median pain scores when compared to traditional methods.

Keywords

Enhanced Recovery after Surgery, ERAS, Multimodal, Opioids, Pain Control, Substance Abuse

Introduction

Enhanced recovery after surgery (ERAS) programs have been shown to reduce hospital stay and decrease cost, opioid use and postoperative complications without any impact on patient pain control and satisfaction scores.[1-7] ERAS programs vary in their specific respective regimens. Generally they include premedication, early ambulation, early urinary catheter removal, early feeding, and multimodal approaches to pain control to minimize opioid use.[1-7] Recently, a

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randomized control trial utilizing a combination of liposomal bupivacaine injected in the subcutaneous space with scheduled acetaminophen, and ibuprofen with opioids available for breakthrough pain reduced day of surgery opioids by almost 50 percent[4], when compared to traditional methods of pain control. Our subsequent study also found a 54% reduction in opioids along with a 14% reduction in pain scores.[5] Liposomal bupivacaine is a lipid encapsulated formulation of bupivacaine that extends the therapeutic benefit to several days[8] and is indicated for injection into the operative site for postsurgical pain.[8]

West Virginia is a high-risk area with 35.2% obesity[9] and is one of the highest drug overdose areas in the country at 41.5 per 100,000 and rising.[10] Anecdotally, the prevalence of opioid abuse and addiction in the area complicates all aspects of postoperative pain control. This highlights the importance of developing new methods of pain control that utilize a multimodal approach to reduce the need for potent opioids in this unique population.

Over the past two years, providers at Cabell Huntington Hospital implemented various approaches for postoperative pain control. The implementation and modifications were provider driven and implemented equally among each provider's patients. Each provider utilized the same protocol for all of their patients, instead of choosing different protocols for each patient based on preconceived pain tolerance. Some providers elected to continue with traditional pain control methods, while others utilized the traditional postoperative pain control with the addition of the On-Q® bupivacaine pump or subcutaneous liposomal bupivacaine. The On-Q® system utilizes percutaneous catheters that infiltrate the abdominal and pelvic cavities with bupivacaine over a two to three day period. Others utilized ERAS orders with the addition of liposomal bupivacaine.

Few studies examine the efficacy of multimodal pain control in benign gynecologic cases. Even fewer examine this in populations with a high prevalence of addiction. No existing studies analyze the use of the local anesthetics, liposomal bupivacaine or On-Q® while comparing their efficacy with traditional postoperative orders and ERAS. We hypothesized that a specific ERAS approach that includes premedication would be superior to traditional control methods in controlling postoperative pain and reducing opioid use. In addition to premedication, the hypothesized protocol includes a subcutaneous trocar-site liposomal bupivacaine injection, scheduled acetaminophen with tramadol and/or oxycodone as needed for breakthrough pain. We compared this approach to five other existing protocols among women undergoing minimally invasive hysterectomy. Our previously reported study was a relatively small study with only 100 subjects divided into two groups, multimodal and traditional methods.[5] This study has 954 subjects and builds on those findings by adding premedication, evaluation of liposomal bupivacaine and On-Q® with traditional pain control methods, and analysis of the potential benefit among patients with benign pathology.

Materials and Methods

This is a retrospective cohort study on women undergoing minimally invasive hysterectomy categorized into six existing postoperative pain management protocols. The protocol of interest was an enhanced recovery protocol including premedication, subcutaneous liposomal bupivacaine, scheduled acetaminophen, and tramadol and/or oxycodone as needed for

breakthrough pain (ERAS-1). The protocols are outlined in Table 1. ERAS-2 and 3 are similar, however they differ from ERAS-1 in that ERAS-2 and 3 do not include premedication. ERAS-2 and 3 differ from each other in that ERAS-3 utilizes scheduled tramadol rather than as needed tramadol utilized in ERAS-2. ERAS-3 is the ERAS protocol we previously reported[5]. Three other protocols were considered traditional. Traditional pain control methods utilize ibuprofen and acetaminophen/oxycodone for breakthrough pain, with IV morphine or hydromorphone for severe pain. These protocols all utilized the same postoperative medication and only differed in the local that was utilized, liposomal bupivacaine, On-Q® or none. The group that utilized traditional postoperative pain medications without the use of liposomal bupivacaine or On-Q® served as the control group (SOC).

Patients were included if they underwent minimally invasive hysterectomy at Cabell Huntington Hospital, a tertiary care center, between September 1, 2016 and August 31, 2018 for benign or oncologic indications. This includes both simple and radical hysterectomy with or without bilateral salpingo-oophorectomy. Minimally invasive hysterectomy for the purposes of this paper include: robotic-assisted total laparoscopic hysterectomy, total laparoscopic hysterectomy, and laparoscopic-assisted vaginal hysterectomy. Patients were excluded if they had a known intraoperative complication, such as gastrointestinal injury or genitourinary injury, or a complication that required reoperation within twenty four hours. Furthermore, patients were excluded if an additional abdominal incision was needed for specimen removal. These exclusions were necessary to minimize confounding from pain due to additional incisions, prolonged catheterization, or bowel repair. Patients were also excluded if they were discharged on the day of surgery, due to the inability to track postoperative pain and opioid use. The Institutional Review Board approved the study protocol and found it exempt from full review based on the low risk to the research subjects. The authors have no financial disclosures. We have no financial relationship with Pacira Pharmaceuticals, Inc., the manufacturer of Exparel® liposomal bupivacaine. Pacira Pharmaceuticals, Inc. had no role on the study design of this project or in the analysis of the data.

Patient medical records were evaluated for the following data points: surgical characteristics, demographics, type and dose of opioid administered during hospitalization, and postoperative pain scores. Operative time was defined as the time from incision to skin closure as recorded by the circulating nurse. Pain scores were documented by the floor nurses every 4 hours as part of their routine postoperative care using a Likert whole number scale from 0 to 10 with 0 being no pain and 10 being severe pain. Our institution defined adequate pain control as 3 or less. Inadequate pain control is considered 5 or more. All patients received the standard prophylactic anti-emetic treatment which was a scopolamine patch. The need for breakthrough antiemetic for nausea and vomiting was also collected.

Preoperative indication was defined as the primary indication for the surgery. These indications were then grouped into indications for oncology, chronic pelvic pain, abnormal uterine bleeding, and pelvic organ prolapse. Oncologic indication was defined as cervical dysplasia or cancer, adnexal mass or ovarian cancer, endometrial hyperplasia or cancer, or prophylaxis.

Opioid use recording began once the patient left the operating suite. Opioids given in the PACU was defined as the first postoperative hour, regardless of actual physical location (e.g. recovery

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room, medical surgical unit). Opioids given after PACU was defined as opioids given between postoperative hours 2 and 24. Total opioids was defined as opioids given in the first 24 hours. Standard opioid dose calculators were utilized to convert all opioid class medications to oral morphine equivalents.[11,12] Conversion from the given opioid to oral morphine used the following ratios: IV morphine 1:3, oxycodone 1:1.5, hydromorphone 1:20, meperidine 1:0.1, hydrocodone 1:1, fentanyl 1:0.3, and tramadol 0:0.1.

For the purposes of this study, opioids given preoperatively and intraoperatively are not included in the dose calculation. Primary outcomes were morphine total equivalents administered during their postoperative course. Secondary outcomes include median pain scores, nausea and vomiting. For equally distributed data with more than two groups we utilized the analysis of variance (ANOVA) or analysis of covariance (ANCOVA). For non-parametric data with more than two groups we utilized the Independent-Kruskal-Wallis tests. Mann-Whitney U tests was used on non-parametric data when there were only two groups. Fisher Exact test was used on all categorical data. All analyses were performed using SPSS 25.

Results

954 subjects were identified for inclusion within the six protocols described in Table 1. Demographics of each groups are shown in Table 2. Mean age ranged between 44 and 55 years with youngest group as control group and oldest as the ERAS-2 group (44 years versus 55 years, $p<0.001$). Mean BMIs were in the obesity range for each group with the highest in the ERAS-1 and ERAS-3 groups and the lowest in the control group (36.5 kg/m^2 versus 32.1 kg/m^2, $p<0.001$). ERAS groups had less healthy patients with higher incidences of hypertension, pulmonary disease and diabetes. Tobacco use was similar between the groups. A higher proportion of the hysterectomies performed in the ERAS groups were robotic-assisted laparoscopic hysterectomies. ERAS groups had higher proportion of hysterectomies performed for oncologic indications whereas the traditional pain control groups had a higher proportion of hysterectomies performed for chronic pelvic pain.

As outlined in Table 3 and Figure 1, patients in the ERAS-1 group used the least amount of opioids in the PACU at 0.0mg versus 10.0mg in the control group ($p=0.004$). After the PACU, patients in the ERAS-1 group used 63% less opioids than the control group (13.8mg versus 37.5mg, $p<0.001$). Overall opioid use was the lowest in the ERAS-1 group at 59% less than the control at 22.5mg versus 55.0mg, ($p<0.001$). Patients in the ERAS-1 group were three times more likely, when compared to control, to decline all opioids after the PACU (OR 3.13, CI 1.36-7.10, $p=0.006$). Likewise, patients in the ERAS-1 group were three times more likely, when compared to control, to decline all opioids (OR 3.62, CI 1.83-7.18, $p<0.001$). When compared to control, ERAS-1 patients were five times more likely to use less than 10mg of opioid (OR 4.93, CI 2.83-8.59, $p<0.001$). A higher proportion of the control group used greater than 50mg and 100mg at 23% ($p<0.001$) and 9% ($p=0.003$) respectively, when compared to the other groups. Median pain scores were lowest in the ERAS-2 group at 2.5 and highest in the control group at 3.5 ($p=0.01$). ERAS-1 group, when compared to the control, had a higher proportion of patients obtaining a pain score of 3 or less, (64% versus 49%, $p=0.01$) and 4 or less (87% versus 74%, $p=0.002$). Conversely, the control group, when compared to the ERAS-1 group, had a higher proportion of patients reporting poorly controlled pain with scores of 5 or higher (23% versus

10%, p=0.001) and 6 or higher (9% versus 5%, p=0.019). Patients in the ERAS-1 group reported the least nausea at 21% versus 50%, (p<0.001).

For patients undergoing a robotic-assisted hysterectomy, overall opioid use was lowest in the ERAS-1 group at 22.5mg versus 58.0mg in the control group (p<0.001). For patients undergoing a TLH or LAVH, overall opioid use was likewise lowest in the ERAS-1 group at 27.5mg versus 47.5mg in the control (p=0.045).

Outlined in Table 4 and Figure 2, 413 patients had a hysterectomy for an oncologic indication. Patients used similar amount of opioids in the PACU, regardless of grouping. After the PACU, patients in the ERAS-1 group used 60% less opioids than the control group (10.0mg versus 24.8mg, p<0.001). Overall opioid use was the lowest in the ERAS-2 group at 44% less than the control (22.5mg versus 36.0mg, p<0.001). Patients in the ERAS-1 group had a higher proportion of patients who declined all opioids at 11% versus 0% (p=0.006). Median pain scores were similar amongst the groups. Patients in the ERAS-1 group reported the least nausea at 17% versus 25% in the control (p<0.001).

Outlined in Table 5 and Figure 3, 318 patients had a hysterectomy for chronic pelvic pain. Patients used similar amount of opioids in the PACU, regardless of grouping. After the PACU, patients in the ERAS-1 group used 60% less opioids than the control group (15.0mg versus 37.5mg, p<0.001). Overall opioid use was the lowest in the ERAS-1 group at 52% less than the control at 26.3mg versus 55.0mg (p<0.001). Patients in the ERAS-1 group were six times more likely, when compared to control, to decline all opioids after the PACU (OR 6.08, 2.16-17.1, p<0.001). Likewise, patients in the ERAS-1 group were six times more likely, when compared to control, to decline all opioids (OR 6.06, 1.92-19.07, p=0.02). When compared to control, ERAS-1 patients were ten times more likely to use less than 10mg of opioid (OR 9.74, 4.00-23.73, p<0.001). Median pain scores were similar amongst the groups. Patients in the ERAS-2 and ERAS-3 groups reported the least nausea at 31% versus 54% in the control and 59% in the SOC-OQ (p<0.001).

Discussion

Our data show that the ERAS-1 protocol was associated with a dramatic reduction in the overall opioid use and performed the best in our patient population, regardless of preoperative indication. This protocol includes the use of premedication consisting of acetaminophen, celecoxib, and pregabalin followed by liposomal bupivacaine with scheduled acetaminophen, ibuprofen and simethicone with as needed tramadol for breakthrough pain and oxycodone for severe breakthrough pain. Similar results have been shown with oncologic patients.[2-7] This is the first study to demonstrate 59% overall reduction in opioid use when compared to control, in a population that expects to experience minimal to no pain with surgery and often demands high potency opioids. Furthermore, this study is among the first to evaluate pain control for benign conditions as 57 percent of cases were for benign indications.

The use of On-Q® without any changes to postoperative medications did not appear to be associated with any reduction in postoperative opioids regardless of the preoperative indication. The utilization of subcutaneous liposomal bupivacaine was associated with a 23% reduction in

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overall opioid use in patients undergoing a hysterectomy for any indication. However, there was no observed difference between those undergoing a hysterectomy for oncologic indications or chronic pelvic pain.

ERAS-3, which did not use premedication, was associated with a 9% reduction in overall opioid use, which was lower than we previously reported.[5] This may be related to a higher n, 190 in our current study versus 50 in the previous publication. There was no observed reduction in overall opioid use in patients undergoing a hysterectomy for chronic pelvic pain or oncologic indication. We did observe a similar reduction in pain scores as previously reported.[5]

ERAS-1 and ERAS-2 were very similar in structure with both utilizing liposomal bupivacaine with scheduled acetaminophen, ibuprofen and simethicone with as needed tramadol for breakthrough pain and oxycodone for severe breakthrough pain. ERAS-1 added premedication consisting of PO acetaminophen, celecoxib, and pregabalin. Both ERAS-1 and ERAS-2 showed significant decreases in overall opioid use of 59 and 55 percent, respectively. ERAS-1 when compared to ERAS-2 was, however, associated with a higher proportion of patients declining all opioids after PACU (25% versus 16%, $p<0.001$), and declining all postoperative opioids (16% versus 8%, $p<0.001$). ERAS-1 and ERAS-2 performed similar to each other for patients undergoing hysterectomy for oncologic indication with both performing better than the control. The patients who appear to benefit the most from the premedication are those undergoing a hysterectomy for chronic pelvic pain. We observed a modest decrease of 32% without the premedication (ERAS-2), when compared to control. However, the addition of the premedication (ERAS-1) was associated with a 52% reduction in overall opioid use. ERAS-1, when compared to ERAS-2, was associated with a higher proportion of patients declining all opioids after PACU (31% versus 14%, $p<0.001$), and declining all postoperative opioids (25% versus 9%, $p<0.001$).

Our data show that opioid use for postoperative pain can be reduced substantially by using premedication, a multimodal approach postoperatively and liposomal bupivacaine. We observed relatively small or no differences, when compared to the control, when liposomal bupivacaine or the On-Q® were used with traditional postoperative medications. We observed the largest reductions in opioid use amongst the patients in the enhanced recovery groups which utilized liposomal bupivacaine exclusively. This study was not designed to compare On-Q® with liposomal bupivacaine. It is unclear if similar reductions would be identified if the enhanced recovery protocols utilized On-Q® instead of liposomal bupivacaine. Furthermore, it is unclear how the enhanced recovery protocols would perform, if no local anesthetic was utilized.

Strengths of our project include that our study also explores a unique population that is obese with a high smoking percentage at 32-41%, and lives in an area with a high prevalence of opioid use. Anecdotally, the high prevalence of opioid use complicates postoperative pain management as anecdotally we observed that patients expect to experience little to no pain. This is among the larger of the studies examining enhanced recovery in minimally invasive hysterectomy with an n of 954. This is among the first studies to examine pain control in patients who underwent a hysterectomy for chronic pelvic pain.

Our study has several limitations. First, as a retrospective study, patients were not randomized to any of the groups. Certain providers implemented this protocol in all their patients and others exclusively used traditional approaches. This does impose a bias in selection and surgical characteristics, which leads to the aberrations observed in the intrinsic validity characteristics. Patients in the control group were younger, healthier, more likely to undergo hysterectomy for benign indications, and were less likely to undergo a robotic-assisted laparoscopic hysterectomy. To account for this potential confounding, ANCOVA was utilized to create corrected models shown in Table 6. These corrected models show similar means when compared to the uncorrected model. Also shown in Table 6, model 7 shows the corrected means for each group, when corrected for age, pathology, estimated blood loss, preoperative indication, total operative time, comorbidities and type of hysterectomy. The corrected model shows a statistically significant 55% reduction in overall opioid use. As noted in the results section, patients who were in the control group were more likely to undergo a hysterectomy for chronic pelvic pain. Model 6 specifically addresses this by adjusting for preoperative indication. When adjusted for preoperative indication, we observed a 57% reduction in opioid use (28.7mg versus 66.3mg, $p<0.001$). Therefore, despite the differences between the groups, it does not appear that these differences significantly altered or cofounded our results.

Second, our population is vastly Caucasian, with insufficient minorities to draw any meaningful statistical conclusions regarding minorities. Therefore, this study is not generalizable to minority populations.

Third, patients who underwent surgery earlier in the day would logically have a longer postoperative day 0 and thus use more opioids, however this discrepancy would have a limited impact as an additional 4 hours of postoperative time would not account for the significant differences seen between the groups. Furthermore, operative start time would be evenly distributed between the groups as all providers have their own block time in the morning for their cases.

Fourth, our study was not designed to evaluate cost-effectiveness of using liposomal bupivacaine. Despite the higher initial cost of liposomal bupivacaine compared to no local anesthetic,[6,7] pharmacy costs have been shown to be overall equivocal[6] and overall hospital costs reduced by ten percent.[7]

Fifth, a patient's personal history of drug use was not included as this information is often inconsistent and unreliable. Urine drug screens are not routinely collected preoperatively, therefore this information was not included. Therefore, our data may not be reproducible in patients with a known history of substance dependence. This would be a potential area for future research.

In conclusion, ERAS-1 is an acceptable alternative to traditional methods of pain control, regardless of preoperative indication. This protocol was associated with the highest opioid use reduction at 59%. Patients with chronic pelvic pain appeared to benefit the most and those who received this protocol were six times more likely to decline all opioids and ten times more likely to use less than 10mg of opioid. This study shows the promise of multimodal protocols in

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reducing opioid need postoperatively. Further prospective randomized control trials are warranted.

Table 1. Groups Included for Analysis

Group	Preoperative	Intraoperative Local	Postoperative
ERAS-1 n=110	1g PO acetaminophen 200mg PO celecoxib 75mg PO pregabalin Routine anti-emetic prophylaxis	266mg (20mL) subcutaneous liposomal bupivacaine	• 500mg PO acetaminophen q4 hours scheduled • 800mg PO ibuprofen q8 hours scheduled • 50mg PO tramadol q4 hours as needed for breakthrough pain • 5mg PO oxycodone q6 hours as needed for severe breakthrough pain • 80mg PO simethicone three times daily • Abdominal binder
ERAS-2 N=84	Routine anti-emetic prophylaxis	266mg (20mL) subcutaneous liposomal bupivacaine	• 500mg PO acetaminophen q4 hours scheduled • 800mg PO ibuprofen q8 hours scheduled • 50mg PO tramadol q4 hours as needed for breakthrough pain • 5mg PO oxycodone q6 hours as needed for severe breakthrough pain • 80mg PO simethicone three times daily • Abdominal binder
ERAS-3 n=190	Routine anti-emetic prophylaxis	266mg (20mL) subcutaneous liposomal bupivacaine	• 500mg PO acetaminophen q4 hours scheduled • 800mg PO ibuprofen q8 hours scheduled • **50mg PO tramadol q4 hours scheduled** • 5mg PO oxycodone q6 hours as needed for severe breakthrough pain • 80mg PO simethicone three times daily • Abdominal binder
SOC-LB n=140	Routine anti-emetic prophylaxis	**266mg (20mL) subcutaneous liposomal bupivacaine**	• 325/5 acetaminophen/oxycodone q4 hours as needed for mild pain • 325/10 acetaminophen/oxycodone q4 hours as needed for severe pain • IV Morphine or hydromorphone for severe pain • 800mg PO ibuprofen every 8 hours scheduled
SOC-OQ n=249	Routine anti-emetic prophylaxis	**On-Q®**	• 325/5 acetaminophen/oxycodone q4 hours as needed for mild pain • 325/10 acetaminophen/oxycodone q4 hours as needed for severe pain • IV Morphine or hydromorphone for severe pain • 800mg PO ibuprofen every 8 hours scheduled
SOC (Control) n=181	Routine anti-emetic prophylaxis	**None**	• 325/5 acetaminophen/oxycodone q4 hours as needed for mild pain • 325/10 acetaminophen/oxycodone q4 hours as needed for severe pain • IV Morphine or hydromorphone for severe pain • 800mg PO ibuprofen every 8 hours scheduled

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Table 2. Demographics by Group (n=954)

Characteristic	ERAS-1 (n=110)	ERAS-2 (n=84)	ERAS-3 (n=190)	SOC-LB (n=140)	SOC-OQ (n=249)	Control (n=181)	p
Age (years)	51 (49 - 54)	55 (52 - 58)	54 (52-55)	53 (51 - 55)	46 (45 - 48)	44 (43-45)	<0.001‡
BMI (kg/m^2)	36.4 (34.5-38.4)	34.5 (32.6-36.4)	36.4 (34.9-38.0)	32.9 (31.4-34.4)	32.6 (31.5-33.7)	32.1 (33.1-33.2)	<0.001‡
Medical Characteristics							
Hypertension	51 (46)	38 (45)	106 (56)	71 (51)	82 (33)	65 (36)	<0.001§
Pulmonary Disease							<0.001§
Asthma	15 (14)	6 (7)	17 (9)	17 (12)	38 (15)	22 (12)	
COPD	17 (16)	2 (2)	11 (6)	13 (9)	10 (4)	4 (2)	
Diabetes							<0.001§
Type 1	0 (0)	1 (1)	2 (1)	1 (1)	2 (1)	0 (0)	
Type 2	28 (26)	14 (17)	49 (26)	27 (19)	27 (11)	12 (7)	
Tobacco							0.415§
Former	18 (16)	15 (18)	34 (18)	20 (14)	42 (17)	20 (11)	
Current	27 (25)	12 (14)	38 (20)	37 (26)	62 (25)	47 (26)	
Surgical Characteristics							
Duration (min)	69 (62-76)	76 (69-83)	69 (64-74)	74 (68-80)	120 (114-125)	126(119-133)	<0.001§
EBL (mL)	58 (52-65)	49 (40-58)	52 (46-57)	58 (51-66)	79 (72-85)	92 (80-103)	<0.001§
Adhesion lysis	19 (17)	19 (23)	28 (15)	19 (14)	54 (22)	16 (181)	0.182§
Type							<0.001§
TLH	4 (4)	0 (0)	1 (1)	0 (0)	18 (7)	20 (11)	
RaTLH	97 (88)	77 (92)	187 (98)	130 (93)	205 (82)	114 (63)	
LAVH	9 (8)	8 (8)	2 (1)	10 (7)	26 (10)	47 (26)	
Preoperative Indication							<0.001§
Oncologic	66 (60)	52 (61)	128 (67)	89 (64)	62 (25)	16 (8)	
Chronic pelvic pain	32 (29)	22 (26)	31 (16)	36 (26)	145 (58)	115 (64)	
Abnormal bleeding	10 (9)	8 (10)	29 (15)	13 (9)	37 (15)	31 (17)	
Pelvic organ prolapse	2 (2)	2 (2)	2 (1)	2 (1)	5 (2)	19 (11)	
Final Path Malignant	37 (34)	26 (31)	72 (38)	52 (37)	26 (10)	0 (0)	<0.001§

data are mean (95% Confidence Interval) or n (percent)
‡ANOVA
§Fisher-Exact
TLH – Total Laparoscopic Hysterectomy with or without oophorectomy
RaTLH – Robotic Assisted Total Laparoscopic Hysterectomy with or without oophorectomy
LAVH – Laparoscopic Assisted Vaginal hysterectomy with or without oophorectomy

Table 3. Primary Outcomes Group (n=954)

Characteristic	ERAS-1 (n=110)	ERAS-2 (n=84)	ERAS-3 (n=190)	SOC-LB (n=140)	SOC-OQ (n=249)	Control (n=181)	p
Opioid use (mg PO Morphine)							
PACU	0.0 (0.0– 15.0)	8.0 (0.0 -23.0)	15.0 (0 - 30)	15.0 (0 - 23)	8.0 (0 - 23)	10.0 (0 - 25)	0.004‡
(% change, p)*	-100 (0.420)	-20 (0.876)	+50 (0.015)	+50 (0.133)	-20 (0.889)		
After PACU	13.8 (4.4-23.1)	15.0 (5.0-25.0)	35.0 (25.0-45.0)	28.0 (14.4-42.6)	37.5 (9.1-65.9)	37.5 (10.0-65.0)	<0.001‡
(% change, p)*	-63 (<0.001)	-60 (<0.001)	-7 (<0.001)	-25 (<0.001)	0 (0.960)		
Total	22.5 (4.7-40.3)	25.0 (5.0-45.0)	50.0 (30.0-70.0)	42.5 (22.0-63.0)	51.0 (22.3-79.8)	55.0 (21.1-88.9)	<0.001‡
(% change, p)*	-59 (<0.001)	-55 (<0.001)	-9 (0.025)	-23 (0.001)	-7 (0.928)		
Zero opioid after PACU	27 (25)	13 (16)	0 (0)	12 (9)	24 (10)	15 (8)	<0.001§
Zero opioid use	17 (16)	7 (8)	0 (0)	6 (4)	16 (6)	10 (6)	<0.001§
Opioid use <10mg	51 (46)	38 (45)	8 (4)	31 (22)	46 (19)	27 (15)	<0.001§
Opioid use >50mg	3 (3)	3 (4)	14 (7)	11 (8)	44 (18)	42 (23)	<0.001§
Opioid use >100mg	0 (0)	1 (1)	1 (1)	2 (1)	14 (6)	16 (9)	0.003§
Pain							
Median Pain Scores	3.0 (2.0-4.0)	2.5 (1.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.5 (2.4-4.6)	0.010‡
3 or less	70 (64)	60 (71)	112 (59)	87 (62)	138 (55)	89 (49)	0.010§
4 or less	96 (87)	78 (93)	157 (83)	115 (82)	193 (78)	134 (74)	0.002§
5 or more	11 (10)	5 (6)	26 (14)	23 (16)	52 (21)	42 (23)	0.001§
6 or more	5 (5)	1 (1)	7 (4)	7 (5)	23 (9)	17 (9)	0.019§
7 or more	2 (2)	1 (1)	2 (1)	1 (1)	9 (4)	5 (3)	0.318§
Nausea	23 (21)	20 (24)	52 (27)	34 (25)	132 (53)	91 (50)	<0.001§

data are median (interquartile range) or n (percent)
‡Independent-Kruskal-Wallis Test
§Fisher-Exact
*percent change compared to control (Mann-Whitney U test)

Table 4. Primary Outcomes by Group Oncologic Indication (n=413)
Oncological Indication includes: endometrial hyperplasia/malignancy, cervical dysplasia/malignancy, adnexal mass/malignancy, prophylaxis

Characteristic	ERAS-1 (n=66)	ERAS-2 (n=52)	ERAS-3 (n=128)	SOC-LB (n=89)	SOC-OQ (n=62)	Control (n=16)	p
Opioid use (mg PO Morphine)							
PACU	0.0 (0 – 15.0)	6.0 (0.0 -21.0)	20.0 (5.0-35.0)	15.0 (0 – 30.0)	8.0 (0 – 3.0)	3.0 (0 – 18.0)	0.107‡
(% change, p)*	-100 (0.890)	+100 (0.975)	+567 (0.225)	+400 (0.313)	+167 (0.861)		
After PACU	10.0 (1.3-18.8)	15.0 (5.0-25.0)	35.0 (27.8-42.2)	26.0 (12.9-39.1)	30.8 (10.4-51.1)	24.8 (0-56.9)	<0.001‡
(% change, p)*	-60 (0.015)	-40 (0.025)	+41 (0.539)	+5 (0.206)	+24 (0.741)		
Total	22.5 (8.3-36.8)	20.0 (0-40.0)	50.0 (31.3-68.8)	42.0 (22.1-61.9)	37.5 (0-76.3)	36.0 (0.00-74.3)	<0.001‡
(% change, p)*	-38 (0.033)	-44 (0.061)	+39 (0.955)	+17 (0.490)	+4 (0.849)		
Zero opioid after PACU	15 (23)	10 (19)	0 (0)	9 (10)	10 (16)	1 (6)	<0.001§
Zero opioid use	7 (11)	5 (10)	0 (0)	5 (6)	7 (11)	0 (0)	0.006§
Opioid use <10mg	34 (52)	24 (47)	5 (4)	22 (25)	15 (24)	4 (25)	<0.001§
Opioid use >50mg	0 (0)	2 (4)	7 (6)	7 (8)	12 (19)	3 (19)	<0.001§
Opioid use >100mg	0 (0)	1 (2)	0 (0)	2 (2)	1 (2)	1 (6)	0.230§
Pain							
Median Pain Scores	3.0 (1.7-4.3)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (1.8-4.3)	3.0 (1.8-4.3)	0.113‡
3 or less	42 (64)	41 (79)	73 (57)	61 (69)	40 (65)	9 (56)	0.113§
4 or less	61 (92)	51 (100)	103 (81)	77 (87)	50 (81)	15 (94)	0.005§
5 or more	4 (6)	0 (0)	20 (16)	12 (14)	11 (18)	1 (6)	0.017§
6 or more	2 (3)	0 (0)	6 (5)	3 (3)	4 (7)	0 (0)	0.485§
7 or more	1 (2)	0 (0)	2 (2)	0 (0)	3 (5)	0 (0)	0.200§
Nausea	11 (17)	11 (21)	33 (26)	19 (21)	32 (52)	4 (25)	<0.001§

data are median (interquartile range) or n (percent)
‡Independent-Kruskal-Wallis Test
§Fisher-Exact
*percent change compared to control (Mann-Whitney U test)

Table 5. Primary Outcomes by Group Chronic Pelvic Pain (n=381)

Characteristic	ERAS-1 (n=32)	ERAS-2 (n=22)	ERAS-3 (n=31)	SOC-LB (n=36)	SOC-OQ (n=145)	Control (n=115)	p
Opioid use (mg PO Morphine)							
PACU	0.0 (0.0 – 15.0)	12.5 (0.0 -27.5)	20.0 (0.0-40.0)	15.0 (0.0 – 30.0)	6.0 (0.0 – 21.0)	12.0 (0.0 – 27.0)	0.178‡
(% change, p)*	-100 (0.454)	+4 (0.968)	+67 (0.153)	+25 (0.630)	-50 (0.349)		
After PACU	15.0 (0-31.3)	22.5 (7.2-37.8)	35.0 (25.0-45.0)	32.5 (15.0-50.0))	43.5 (17.3-69.8)	37.5 (11.3-63.8)	<0.001‡
(% change, p)*	-60 (<0.001)	-40 (0.003)	-7 (0.055)	-13 (0.065)	+16 (0.233)		
Total	26.3 (4.4-48.1)	37.3 (5.4-49.2)	55.0 (39.3-70.8)	59.3 (37.3-81.4)	59.0 (31.3-86.8)	55.0 (19.8-90.3)	0.001‡
(% change, p)*	-52 (<0.001)	-32 (0.001)	0 (0.568)	+8 (0.213)	+7 (0.432)		
Zero opioid after PACU	10 (31)	3 (14)	0 (0)	2 (6)	11 (8)	9 (8)	0.001§
Zero opioid use	8 (25)	2 (9)	0 (0)	0 (0)	8 (6)	6 (5)	<0.001§
Opioid use <10mg	19 (59)	14 (64)	1 (3)	5 (14)	22 (15)	15 (13)	<0.001§
Opioid use >50mg	3 (9)	1 (5)	5 (16)	4 (11)	27 (19)	68 (18)	0.119§
Opioid use >100mg	0 (0)	0 (0)	1 (3)	0 (0)	11 (8)	10 (9)	0.128§
Pain							
Median Pain Scores	3.0 (1.8-4.2)	3.00 (1.6-4.4)	3.0 (2.0-4.0)	3.5 (2.6-4.5)	3.0 (1.8-4.3)	3.0 (2.3-3.8)	0.839‡
3 or less	20 (63)	9 (41)	15 (48)	18 (50)	71 (49)	57 (50)	0.839§
4 or less	24 (75)	17 (77)	26 (84)	27 (75)	108 (75)	87 (76)	0.936§
5 or more	6 (19)	4 (18)	3 (10)	8 (22)	35 (24)	27 (24)	0.597§
6 or more	3 (9)	1 (5)	0 (0)	4 (11)	17 (12)	12 (10)	0.435§
7 or more	1 (3)	1 (5)	0 (0)	1 (3)	5 (3)	2 (2)	0.859§
Nausea	11 (34)	7 (32)	10 (32)	11 (31)	85 (59)	62 (54)	0.001§

data are median (interquartile range) or n (percent)
‡Independent-Kruskal-Wallis Test
§Fisher-Exact
*percent change compared to control (Mann-Whitney U test)

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Table 6. Unadjusted and Adjusted Total Opioid Mean (mg PO Morphine) By Group (n=954)

Model	ERAS-1	ERAS-2	ERAS-3	SOC-LB	SOC-OQ	Control	p
Model 1	28.8 (20.4-37.2)	32.5 (22.8-42.1)	56.4 (50.0-62.8)	49.2 (41.8-56.7)	65.9 (60.3-71.5)	66.4 (59.8-72.9)	<0.001*
Model 2	30.2 (22.0-38.4)	36.6 (27.1-46.1)	59.4 (53.1-65.7)	51.9 (44.6-59.2)	63.2 (57.7-68.8)	62.0 (55.5-68.5)	<0.001*
Model 3	28.1 (19.5-36.7)	32.0 (22.2-41.7)	55.7 (49.0-62.3)	48.7 (41.1-56.3)	66.6 (60.7-72.4)	67.2 (60.3-74.2)	<0.001*
Model 4	28.4 (19.9-36.8)	32.4 (22.7-42.0)	55.9 (49.5-62.4)	49.4 (41.9-56.9)	66.1 (60.5-71.7)	66.7 (60.1-73.3)	<0.001*
Model 5	28.4 (19.9-36.8)	33.0 (23.4-42.7)	57.4 (50.9-63.9)	49.5 (42.1-57.0)	65.2 (59.5-70.8)	66.1 (59.5-72.7)	<0.001*
Model 6	28.7 (20.3-37.2)	32.4 (22.8-42.1)	56.4 (50.0-62.8)	49.1 (41.6-56.6)	66.1 (60.5-71.7)	66.3 (59.7-72.9)	<0.001*
Model 7	28.9 (20.4-37.3)	35.6 (26.0-45.2)	57.9 (51.3-64.5)	41.1 (43.7-58.6)	64.4 (58.7-70.2)	63.7 (56.8-70.7)	<0.001*

Data are mean, (95% CI)
*ANCOVA
Model 1: Unadjusted
Model 2: Adjusted for Age
Model 3: Adjusted for Operative Time
Model 4: Adjusted for BMI
Model 5: Adjusted for Comorbidities (Hypertension, Pulmonary Disease, and Diabetes)
Model 6: Adjusted for Preoperative Indication (Oncologic, Abnormal Uterine Bleeding, Chronic Pelvic Pain, Pelvic Organ Prolapse)
Model 7: Adjusted for age, pathology (malignancy vs. benign), estimated blood loss, total operative time, comorbidities, preoperative indication, and type of hysterectomy (RaTLH, TLH, LAVH)

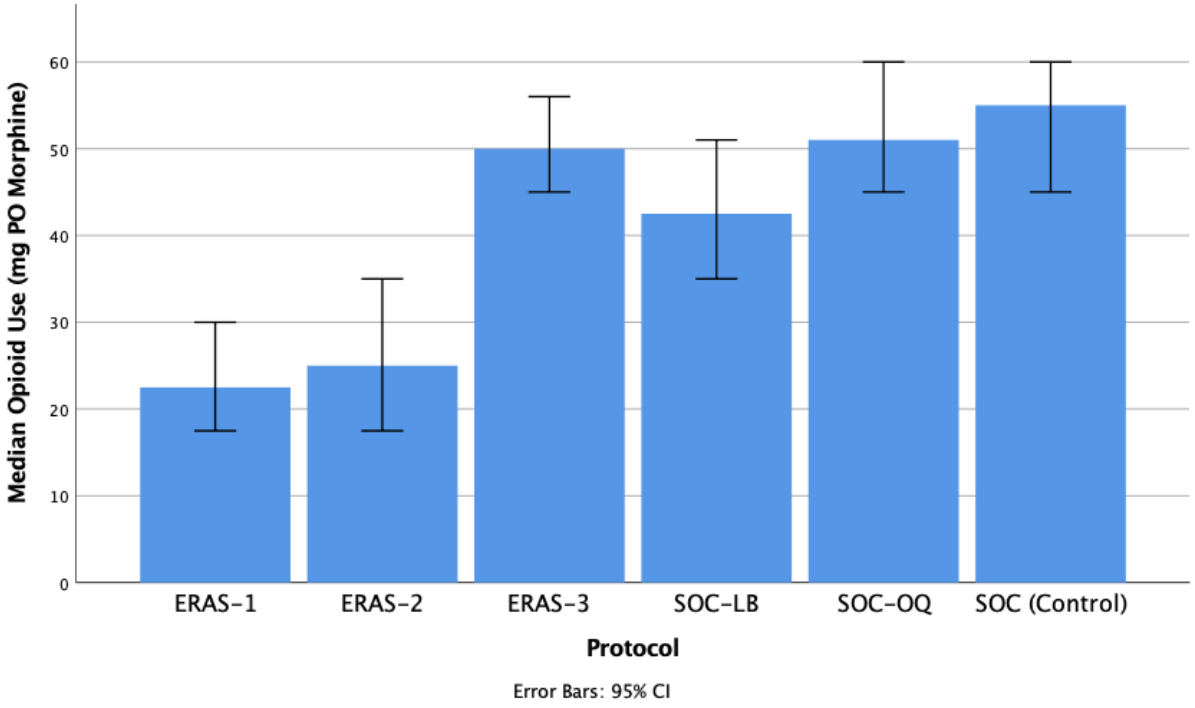

Figure 1. Median Opioid Use by Protocol. Median opioid use by group patients who underwent a hysterectomy for any indication (n=954) in mg PO Morphine.

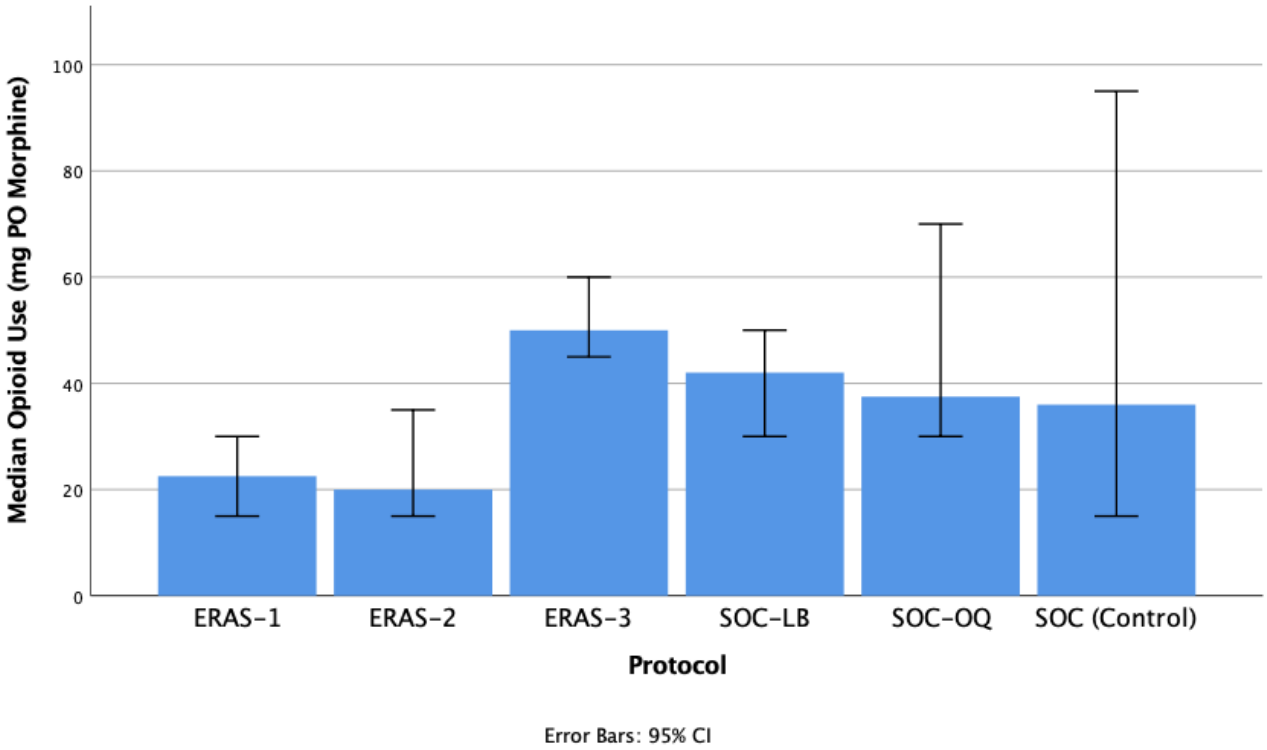

Figure 2. Median Opioid Use by Protocol by those with Oncologic Indication. Median opioid use by group in patients who underwent a hysterectomy for oncologic indication (n=413) in mg PO Morphine.

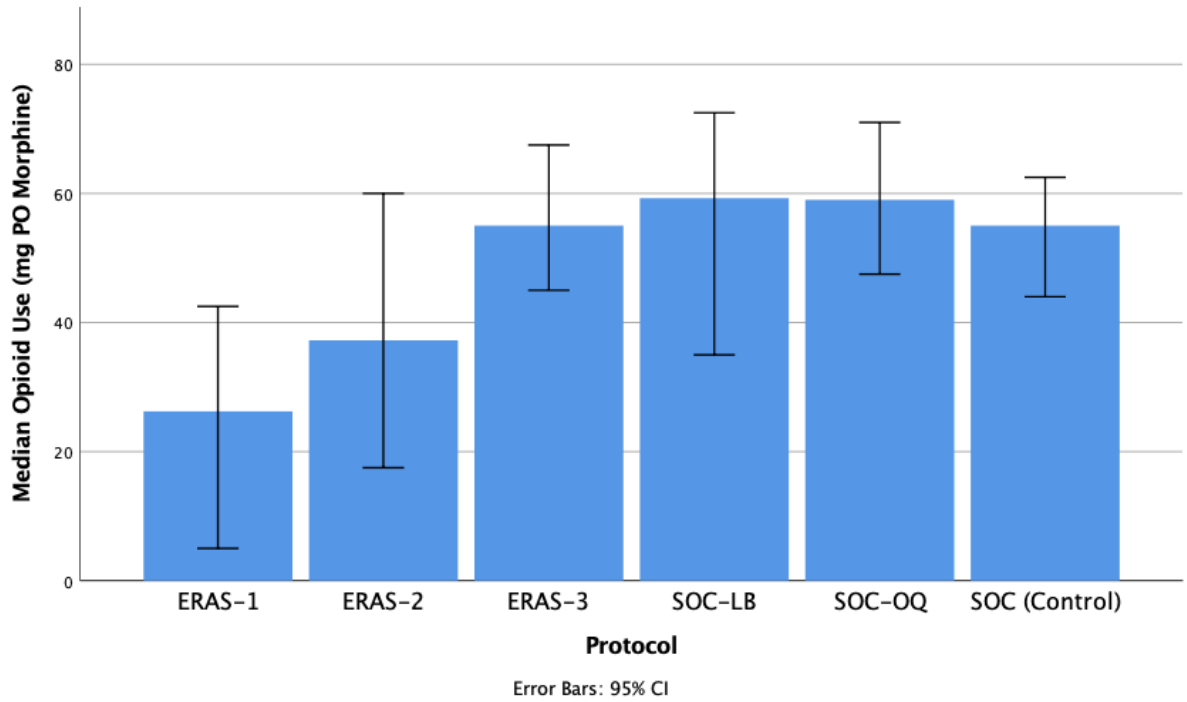

Figure 3. Median Opioid Use by Protocol by those with Chronic Pelvic Pain. Median opioid use by group in patients who underwent a hysterectomy for oncologic indication (n=381) in mg PO Morphine.

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