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Intraoperative Factors Associated with More Postoperative Opioid Use after Laparoscopic Hysterectomy

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ABSTRACT

BACKGROUND AND OBJECTIVES: To identify intraoperative factors during laparoscopic hysterectomy associated with postoperative opioid use and increased pain scores during the acute postoperative period.

METHODS: This is a prospective survey-based cohort study at two teaching hospitals in the Boston metropolitan area. A total of 125 patients undergoing laparoscopic hysterectomy were enrolled. Surveys were administered by telephone at one-week postoperatively and in-person at their two-week postoperative visit to elicit opioid consumption converted to morphine milligram equivalents (MMEs) and pain scores.

RESULTS: The median total opioid consumption was 37.5 MME (range 0–960 MMEs). Intraoperative factors associated with increased total MME consumption were lower uterine weight and resection of endometriosis at the time of surgery. Patients with uteri less than 250 grams used twice as much opioid compared to participants with uteri greater than 250 grams (median of 49.8 MME (interquartile range [IQR] 7.5–120.5) vs. 22.5 MME (IQR 7.5–61.0). The median opioid consumption by patients with resection or ablation of endometriosis was three times that of those who did not undergo surgical treatment of endometriosis (97.0 MME (IQR 53.1–281.3) vs. 30.0 MMEs (IQR 7.5–81.3 MME)). Maximum pain scores and reported pain score at one and two-week interviews were also significantly higher in patients with these characteristics.

CONCLUSION: Several easily identified intraoperative factors may be correlated with opioid requirements during the acute postoperative period. This can allow surgeons to set expectations and dispense patient-specific opioid prescriptions. Individualizing prescriptions may lower the amount of excess circulating opioids and help combat the opioid epidemic.

Key Words: Hysterectomy, Laparoscopy, Opioid, Pain, Postoperative.

INTRODUCTION

Opioid misuse is one of the most pressing health concerns facing the American public.[1,2] The number of women who died from prescription opioid overdose quadrupled between 1999 and 2010.[3] Prior studies have noted a strong correlation between therapeutic exposure to opioids and the magnitude of abuse.[4,5] As women's health specialists, obstetricians and gynecologists are uniquely poised to assist in combating this important issue through proper stewardship of opioid prescriptions.

Hysterectomy is one of the most commonly performed surgeries in women.[6] In the last decade, there has been an increase in the number of hysterectomies done using minimally invasive approaches due to decreased infection, lower postoperative pain, and faster recovery.[7,8] It is important to achieve adequate pain control without overprescribing opioids. Postoperative opioid prescriptions can lead to chronic abuse even among opioid-naive patients.[5,9,10] Women may be susceptible to opioid dependence in a shorter period of time and at lower doses.[3]

Prior studies have described postoperative prescribing patterns, average use after minimally invasive hysterectomy,

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and factors associated with increased opioid requirement during the acute postoperative phase.[11–15] The primary aim of this study is to identify intraoperative factors that predict the total amount of opioid utilized during the first two weeks postoperatively. The secondary aim is to identify intraoperative factors associated with increased pain scores at one and two weeks after surgery.

METHODOLOGY

This is a prospective cohort study of patients at two Boston-area community teaching hospitals undergoing minimally invasive hysterectomies through the minimally invasive gynecologic surgery (MIGS) departments. This study was approved by the Institutional Review Boards at both hospitals.

Participants were recruited during their new patient visit or by mail starting March 1, 2017 at hospital 1 and April 1, 2017 at hospital 2. Enrollment concluded on December 31, 2018 at both sites. All consecutive patients planning to have a laparoscopic hysterectomy for benign indications were asked to participate in this study. Exclusion criteria included pre-operative diagnosis of malignancy, concurrent additional surgical procedures (i.e. abdominoplasty, urogynecologic procedures), or if mini-laparotomy was planned for specimen removal. Patients with significant pre-operative opioid requirements for management of chronic pain were included in the study. Per the surgeons' discretion and typical practice, some patients were seen in a hospital-affiliated outpatient pain clinic for pre-operative counseling and postoperative pain management planning. Among patients on chronic opioids prior to surgery, only opioids ingested in addition to their chronic regimen were used to calculate their postoperative opioid use.

Six participating surgeons were instructed to make no changes in their pre-operative pain management counseling or their opioid prescribing practices. Pre-operatively, all patients were counseled in-person and given instructions to use scheduled acetaminophen and ibuprofen for the first 72 hours after surgery, with opioid use reserved for breakthrough pain. After counseling, patients received an opioid prescription. Demographic characteristics, pre-operative pain medication use, medical, and surgical histories were collected via a pre-operative survey that participants completed after providing informed consent. Participants also completed surveys designed to assess pre-operative characteristics such as pain catastrophizing and depression screening that may be related to postoperative opioid use. Pre-operative factors that predict postoperative opioid use in patients undergoing laparoscopic hysterectomy have been previously published using this dataset.[15]

All procedures were conducted by one of the MIGS surgeons with a resident or a fellow assist. More than 90% of the cases were planned as outpatient procedures. After surgery, members of the surgical team collected details about the indication for surgery, the type of surgery performed, intraoperative findings, surgical details, opioid prescription provided, in-hospital pain medication use, and pathology results.

Participants were surveyed at approximately one week and two weeks after their procedure. Using a script, study investigators asked participants about their pain scores and pain medication use since hospital discharge. Patients were asked to subjectively rate their current pain and maximum pain in the last 24 hours on an 11-point Numeric Rating Scale from 0 to 10 with 0 being no pain and 10 being the worst pain imaginable. The initial encounter was via phone between postoperative days 4 and 7. Approximately 88% of patients were reached on postoperative day 6 or 7. At their two-week postoperative in-person visit, participants completed a survey reporting their pain scores and opioid medication use since surgery.

The primary objective of this study was to identify pre-operative and intraoperative factors associated with increased opioids use by participants during the acute postoperative period. Acute postoperative opioid use was defined as all opioids ingested by patients between discharge from the postanesthesia care unit (PACU) and their scheduled two-week postoperative visit. For patients requiring postoperative hospitalization, acute opioid use was calculated using opioids taken on the hospital floor as well as opioids used at home after hospital discharge during the first two weeks. All opioid use either reported by participants or extracted from the electronic medical record were converted into morphine milligram equivalents (MMEs) using Center for Disease Control (CDC) guidelines.[16] The secondary objective was to identify intraoperative factors that correlate with patients' subjective pain scores during the acute postoperative period.

All variables were analyzed to determine normality and nonparametric analysis was executed based on the results of the Shapiro Wilks test. To test if intraoperative factors were associated with total opioid use, Spearman's ρ correlation was calculated for discrete and continuous variables and Mann-Whitney test was calculated for categorical variables. P-values less than .05 were considered signi-

ficant. Data was analyzed using IBM SPSS for Windows, Version 24.

RESULTS

Patient Characteristics

One hundred and twenty-five patients completed the study. Of the 133 patients eligible to enroll: four declined, two decided to withdraw, and one was lost to follow-up. One patient was excluded after an intraoperative bowel injury requiring mini-laparotomy for repair.

Patient demographic characteristics are outlined in **Table 1**. This study was composed of primarily parous (90%), Caucasian women (84%) with an average age of 46.5

Table 1.
Patient Characteristics

Characteristics	Patients (n = 125)
Age, Years	46.5 ± 6.7 (30 – 76)
Ethnicity	
White	105 (84%)
Asian/Pacific Islander	7 (5.6%)
Hispanic	7 (5.6%)
Black	4 (3.2%)
Multiracial	2 (1.6%)
Body Mass Index	28.9 ± 6.7 (18.4 – 58)
Parous	91 (72.8%)
Past Surgical History	
Prior abdominal surgery 84 (67.2%)	
Prior laparoscopic surgery	49 (39.2%)
Prior laparotomy	54 (43.2%)
Pre-operative Pain Medication	
Any pain medication (including opioid)	53 (42.4%)
Daily Opioid	5 (4%)
Opioid as needed	5 (4%)
Past Medical History	
Chronic pelvic pain	28 (22.4%)
Endometriosis	26 (22.4%)
Chronic back pain	11 (8.8%)
Fibromyalgia	7 (5.6%)

Data: Mean ± SD or n (percentage).

Table 2.
Surgical Characteristics

Surgical Details	Patients (n = 125)
Surgical Approach	
Total laparoscopic hysterectomy	122 (97.6%)
Laparoscopic supracervical hysterectomy	3 (2.4%)
Additional Surgical Procedures	
Bilateral/Unilateral salpingectomy	100 (80%)
Bilateral/Unilateral salpingo-oophorectomy	28 (22.4%)
Ovarian cystectomy	3 (2.4%)
Lysis of adhesions	30 (24%)
Resection/Ablation of endometriosis	12 (9.6%)
Cystoscopy	53 (42.4%)
Morcellation of uterine specimen	56 (44.8%)
Intraoperative Characteristics	
Local anesthesia with trocar placement	80 (64%)
Length of procedure, minutes	94.3 ± 54.2 (33–344)
Estimated blood loss, mL	48.4 ± 87.2 (0–800)
Uterine specimen weight, g	321 ± 505.0 (21–1500)
Pathology results	
Fibroids	102 (81.6%)
Endometriosis	20 (16%)
Adenomyosis	39 (31.2%)
Endometrial or endocervical polyp	6 (4.8%)
Dermoid	2 (1.6%)
Simple cystadenoma	3 (2.4%)
Mucinous cystadenoma	1 (0.8%)
Endometrial intraepithelial neoplasia	2 (1.6%)
Cervical intraepithelial neoplasia	2 (1.6%)
Carcinoid tumor within a dermoid cyst	1 (0.8%)
Leiomyosarcoma	1 (0.8%)
No abnormal pathology	9 (7.2%)
Intraoperative complications	
Cystotomy	1 (0.8%)
Transfusion due to severe preop anemia	1 (0.8%)

Table 2. Continued

Surgical Details	Patients (n = 125)
Postoperative	
Admission to hospital	16 (12.5%)
Vaginal cuff dehiscence	1 (0.8%)

Note: Data: Mean± SD (range, Median (IQR) or n (percentage). Some patients had more than one diagnosis on pathology. One pathology report failed to report uterine weight (124 patients with reported uterine weight).

(range 30–76). Majority of patients had prior abdominal surgery (67.2%). Almost half of the participants reported using some pain medication prior to their surgery (42.4%), and five patients reported taking daily opioid for chronic pain (range 5–160 MME, which is equivalent to 00.7–21.3 pills of oxycodone 5 mg). Chronic opioid users were included in the study to reflect the general population undergoing laparoscopic hysterectomy more accurately. Many patients reported a history of chronic pain conditions such as endometriosis (22.4%), chronic pelvic pain (22.4%), chronic back pain (8.8%), and fibromyalgia (5.6%).

Operative characteristics are found in **Table 2**. Most participants had a total laparoscopic hysterectomy (122/125, 97.6%). The mean uterine weight was 321 grams (range 21–1500 grams). Common pathologic diagnoses included fibroids (81.6%), adenomyosis (31.2%), and endometriosis (16%).

Opioid Use during the Acute Postoperative Period

The median opioid prescription provided by the surgeons was 150 MME (range 0–720). This is equivalent to 20 pills of oxycodone 5 mg or 30 pills of hydrocodone 5 mg. The median opioid use by patients during the acute postoperative period was only 37.5 MME (range of 0–960 MME), which is equivalent to approximately 5 pills of oxycodone 5 mg or 7 pills of hydrocodone 5 mg. Of the 121 patients who filled their opioid prescription, 109 patients reported having leftover medication. The median number of leftover pills was 16, which is equivalent to a median of 120 MME (range 0–200 MME) of unused opioid.

Intraoperative Factors Associated with Opioid Use

Intraoperative factors associated with significantly increased total opioid use during the acute postoperative period were uterine weight less than 250 grams and resection or ablation of endometriosis during the procedure (**Table 3**). A total of 12 patients underwent resection or ablation of endometriosis at time of their hysterectomy, 11 of those patients had a uterus weighing less than 250g. Small uterine weight is associated with resection or ablation of endometriosis at time of hysterectomy (P = .01). Participants with uteri less than 250 grams used twice as many opioids compared to participants with uteri greater than 250 grams (median of 49.8 MME (interquartile range [IQR] 7.5–120.5) vs. 22.5 MME (IQR 7.5–61.0), p = .028) (**Table 4**). The median opioid used by participants with resection or ablation of endometriosis was three times that of those who did not have resection of endometriosis (97.0 MME (IQR 53.1–281.3) vs. 30.0 MMEs (IQR 7.5–81.3 MME), p = .014). Local anesthetic was used before placement of trocars in 80 procedures (64%) based on surgeon preference and was associated with significantly lower opioid use (median opioid use 30 MME (IQR 7.5–70) vs. 52.5 MME (IQR 17.5–127), p = .033). Pathologic factors, such as fibroids or adenomyosis, were not associated with changes in

Table 3.
Intraoperative Factors and Their Association with Postoperative Opioid Use

	Factors Associated with Increased Opioid Use	Factors with No Significant Relationship to Opioid Use
Anatomical Factors	Uterus weighing < 250 grams[a]	Endometriosis on pathology
	Resection or ablation of endometriosis[b]	Fibroids on pathology Adenomyosis on pathology
Operative Technique	No use of local anesthetic at the trocar site[c]	Operative Time Estimated blood loss
		Tissue extraction
		Lysis of adhesions

Note: Spearman's correlation for discrete and continuous variables. Mann-Whitney test was calculated for categorical variables.
[a]P = .028, [b]P = .014, [c]P = .033.

Table 4.
Median Total Morphine Milligrams Equivalent Use During the Acute Postoperative Period

Intraoperative Factors	Median MME (IQR)	P-Value
Uterine weight		
Small uteri (< 250 g)	49.8 (7.5 – 120.5)	p = 0.028
Large uteri (≥ 250 g)	22.5 (7.5 – 61.0)	
Local anesthesia with trocar placement		
Yes	30.0 (7.5 – 70.0)	p = 0.033
No	52.5 (17.5 – 127.0)	
Resection or ablation of endometriosis		
Yes	97.0 (53.1 – 281.3)	p = 0.014
No	30.0 (7.5 – 81.3)	
Endometriosis on pathology		
Yes	51.3 (1.9 – 113.6)	P = 0.540
No	32.0 (7.5 – 82.5)	
Fibroids on pathology		
Yes	34.8 (7.5 – 80.6)	P = 0.737
No	46.0 (0 – 157)	
Adenomyosis on pathology		
Yes	22.5 (7.5 – 90.0)	P = 0.270
No	45.0 (7.5 – 97.0)	
Morcellation		
Yes	33.8 (7.5 – 69.4)	p = 0.177
No	40.0 (7.5 – 127)	
Lysis of adhesions		
Yes	47.8 (0.0 – 101.3)	P = 0.787
No	32.0 (7.5 – 82.5)	
Uterine weight*		P = 0.044
Estimated blood loss		p = 0.868
Length of surgery*		p = 0.774
Body mass index		p = 0.461

Abbreviations: MME, morphine milligrams equivalent; IQR, interquartile range.
Mann Whitney U Test for dichotomous variables, Spearman's ρ for continuous variables. *Indicates inverse relationship.

opioid use during this period. Operative factors such as contained specimen extraction, lysis of adhesions, estimated blood loss and length of surgery were also not associated with total opioid use during the acute postoperative period.

Length of Postoperative Opioid Requirement

About 25 patients (20%), did not take any opioid medication after discharge from the PACU. Only two patients were still taking opioid medication at their two-week postoperative visit. For the 100 participants who took opioids, the mean number of days participants ingested opioid pain medication was 3.3 days (standard deviation [SD] 3.2), median 3.0 days (IQR 1–5). Intraoperative factors associated with increased number of days patients took opioid medication were uterine weight less than 250 grams and resection of endometriosis. The median number of days participants with uteri < 250 grams took opioid medication was three days (IQR 1–6) compared with two days (IQR 1–4) in patients with uteri > 250 grams.

Although 20 patients had endometriosis identified on the pathology report, only 12 patients had resection or ablation of endometriosis at the time of their hysterectomy dictated as a separate procedure in their operative report. Patients who had resection or ablation of endometriosis at the time of their hysterectomy reported taking opioid medications longer than women who did not have resection or ablation of endometriosis. The median number of days patients who had resection or ablation of endometriosis at the time of their hysterectomy took opioids was four days (IQR 2.3–7) compared with a median of 2.5 days (IQR 1–4) by patients who did not have endometriosis ablated or excised at the time of their hysterectomy.

Subjective Pain Scores

At the one-week postoperative telephone interview, patients were asked about both their maximum pain score since surgery and their current pain score. The mean maximum pain score since surgery reported by patients was 6.5 (SD 2.5, Range 0–10). Maximum pain scores since surgery were significantly higher in patients with smaller uteri (< 250 grams), uteri that did not require morcellation for extraction, concurrent resection or ablation of endometriosis, and lack of local anesthesia at the time of trocar placement. These same factors were also associated with significantly higher current pain scores at the time of the one-week phone interview. At the two-week in-person interview, patients were asked about their maximum pain score in the last 24 hours and their current pain score. The use of local anesthetic before trocar placement no longer had a significant impact on current or maximum pain score in the last 24 hours. The average patient satisfaction with pain control was 9.1 (SD 1.9) on a 11-point scale (0 unsatisfied and 10, totally satisfied) at both the one and two-week postoperative contact.

Table 5.
Correlation Between Total Morphine Milligrams Equivalent and Subjective Pain Scores and Satisfaction with Pain Control

	Current Pain Score 1 Week	Maximum Pain Score Since Surgery	Satisfaction with Pain Control at 1 Week	Current Pain Score at 2 Weeks	Maximum Pain Score in the last 24 hours at 2 Weeks	Satisfaction with Pain Control at 2 Weeks
Correlation Coefficient (df)	0.503 (122) *	0.554 (122)*	−0.423 (122)*	0.407 (122)*	0.498 (122)*	−0.39 (122)*

Note: Spearman's ρ correlation coefficient.
*All correlations significant at $P < .01$.

A Spearman's rank correlation was run to determine the relationship between total MME used during the acute postoperative period and subjective pain scores and satisfaction with pain control (**Table 5**). Patients who used more opioid medications in the acute postoperative period reported higher pain scores and maximum pain scores at both one and two-week postoperative surveys. Patients who used more opioid medications also reported lower satisfaction with pain control compared to patient who used fewer opioid medications in the acute postoperative period.

DISCUSSION

Intraoperative factors associated with significantly higher opioid consumption during the acute postoperative period were smaller uteri (< 250 grams) and resection or ablation of endometriosis. These same factors were associated with higher pain scores and longer duration of opioid consumption. Most patients who had concurrent laparoscopic hysterectomy and excision or ablation of endometriosis had small uteri. We suspect that the presence and treatment of endometriosis contributes more to postoperative opioid use than having a small uterus.

Pain is a multifactorial phenomenon with psychological, anatomical, behavioral, and genetic components.[17,18] Most of the factors known to be associated with increased opioid use during the acute postoperative period are factors that can be identified during the pre-operative evaluation such as younger age, anxiety, pain specific anxiety, pre-operative pain with pre-operative opioid use, pain catastrophizing, depression, and a history of endometriosis.[12,15,19–21]

This study identifies intraoperative factors that are associated with postoperative opioid consumption. As-Sanie et al. previously described an inverse relationship between uterine weight and total MMEs consumed during the first two postoperative weeks.[12] We similarly found the same relationship; however, the majority of patients with smaller uteri underwent resection or ablation of endometriosis at time of their surgery and the relationship between small uteri and postoperative pain use remains to be assessed further. Perhaps the underlying motivation for surgery in women with smaller uteri may be chronic pain, such as endometriosis which is also associated with smaller uteri and an increase in postoperative pain medication use, instead of fibroids which cause bulk or bleeding symptoms.

Wong et al. previously reported that a pre-operative history of endometriosis was predictive of postoperative opioid consumption in women undergoing laparoscopic hysterectomy.[15] Our analysis found that resection of endometriosis, but not presence of endometriosis on pathology was associated with significantly increased opioid consumption as well as pain scores. Perhaps the location of endometriosis implants impacts postoperative pain. In other words, endometriosis on the uterus or fallopian tubes may be reported on pathology report, but it is the resection of endometriosis from locations like the uterosacral ligaments or pelvic sidewalls that is associated with increased pain. The etiology of endometriosis pain has been hypothesized to be nociceptive, neuropathic, or a combination of the two.[17] Psychological and physical stress also increases the perception of pain.[17,18] All these factors can be stimulated in the acute postoperative period and may lead to increased pain and opioid use. Further research detailing the location of endometriosis found on pathology and location of endometriosis resection may help clarify this finding.

Study participants were prescribed a median of 150 MMEs, but only used a median of 37.5 MME (equivalent of 5 pills of oxycodone 5 mg or 7 pills of hydrocodone 5 mg), over a median of three days. This is consistent with other studies that have demonstrated that patients

undergoing minimally invasive hysterectomies are routinely overprescribed opioids for pain management.[5,12,13,22] The findings of this study support and affirm the Michigan Opioid Prescribing Engagement Network recommendation of prescribing 112.5 MME (15 tablets of 5 mg oxycodone) for opioid naive patients undergoing a laparoscopic hysterectomy.[15,19] In fact, for the average patient, this may still be too much. The median and mean days of opioid use by our study participants were both approximately three days. By one week, 92% of patients were no longer requiring opioids for pain control. Thus, the CDC recommendation for providing no more than a seven-day supply of opioid medication is reasonable and sufficient for the majority of patients.[19]

The strengths of this study are that it is a prospective study with close patient follow-up after surgery to accurately reflect actual opioid use, pain scores, and satisfaction with pain control. A major strength of this study is the inclusion of patients with chronic pain issues. This patient population is often excluded from studies evaluating postoperative pain and analgesic consumption. Combatting the opioid epidemic requires that the postoperative pain requirements of this population are understood and met.

There are also some important limitations. Since this was an observational study, the correlations identified may not be causal. The findings may not be generalizable to all gynecologic surgeons or even to all MIGS surgeons. This was also a fairly homogenous population and their pain management plan may not be applicable to a more diverse population. Opioid use in the outpatient setting was completely self-reported and recall bias is always a concern. The time interval between surgery and the first contact was intentionally short to limit the impact of recall bias. In addition, we did not evaluate compliance with the suggested nonopioid regimen of scheduled acetaminophen and ibuprofen for the first 72 hours after surgery.

CONCLUSION

Due to the recognition of the danger of the opioid epidemic by gynecologic surgeons, there has been a recent increase in research on the perioperative opioid prescription patterns and perioperative opioid use by patients undergoing gynecological procedures. The goal of this growing body of literature is to identify factors associated with perioperative opioid consumption so that patient specific perioperative pain medication plans can be formulated to avoid the pitfalls of over prescription of opioids. This study suggests that there are several intraoperative factors that are associated with postoperative opioid requirements that can be used to help tailor an individualized pain management plan. Further research is needed to validate this data in a larger, more diverse patient population.

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