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Reducing postoperative opioids after minimally invasive gynecologic surgery with multimodal pain control

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Abstract

Introduction

We evaluated the efficacy of a multimodal pain regimen that approaches pain control by utilizing different mechanisms of action. This novel protocol utilizes liposomal bupivacaine, acetaminophen, tramadol and oxycodone as needed in reducing the overall opioid use by patients after undergoing robotic assisted total laparoscopic hysterectomy in an obese population that is heavily afflicted by the opioid epidemic.

Materials and Methods

We conducted a retrospective study wherein a sample of 100 (50 multimodal group and 50 controls) was taken from 433 eligible cases conducted over a 1 year period. 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

Overall opioid use in the multimodal group decreased by 54% (75.1mg versus 35.5mg, $p<0.0001$). Patients in the multimodal group reported 14% ($p<0.01$) less pain.

Discussion

A multimodal approach to pain control is an acceptable alternative to traditional methods of pain control, regardless of BMI, for those with benign or malignant disease. It decreases opioid use by 44 to 62 percent with no concomitant increase in pain scores and may decrease pain by 9 to 24 percent.

Keywords

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

Introduction

Nationally, multiple studies demonstrate that Enhanced Recovery After Surgery (ERAS) programs reduce hospital stay, decrease cost, opioid use and postoperative complications without any impact on patient pain control and satisfaction scores.[1-6] While specific ERAS programs vary in their specific respective regimens, they generally include early ambulation, early urinary catheter removal, early feeding, and multimodal approaches to pain control to minimize opioid use.[1-6] Indeed a recent randomized control trial utilizing a combination of liposomal bupivacaine injected in the subcutaneous space with scheduled acetaminophen, and ibuprofen with opioids available for breakthrough reduced postoperative day 0 opioid by almost 50% and day 1 use by 25%,[4] when compared to traditional methods of pain control. Liposomal

bupivacaine is a lipid encapsulated formulation of bupivacaine that extends the therapeutic benefit to several days[7] and is indicated for injection into the operative site for postsurgical pain.[7]

Additionally, national efforts to reduce the use of prescription opioids[8,9] drive new approaches to pain control. Although the treatment of acute postoperative pain rarely leads to opioid addiction,[10] diversion of medications remains a concern.[10] Studies suggest that 55% of those that abuse prescription drugs obtained these from relatives or friends with many receiving the medications directly from a physician[11] and with 51% starting while undergoing treatment of acute pain.[12] Therefore, it seems prudent to reduce postoperative opioid use.

West Virginia happens to be a high-risk area with 35.2% obesity[13] and one of the highest drug overdose areas in the country at 41.5 per 100,000 and rising.[14] Anecdotally, the prevalence of opioid abuse and addiction in the area makes it uniquely difficult to control postoperative pain. This highlights the importance of developing new methods of pain control that utilizes a multimodal approach to reduce the need for potent opioids in this unique population.

Few studies examine the efficacy of multimodal pain control in benign gynecologic cases. None examine this in populations with a high prevalence of addiction, or evaluate the efficacy of liposomal bupivacaine in patients who are largely obese, with many being morbidly obese. We hypothesize that a multimodal approach that includes liposomal bupivacaine injection, scheduled acetaminophen and tramadol with oxycodone as needed for breakthrough pain can be used effectively to control pain while reducing the overall opioid use postoperatively from robotic-assisted total laparoscopic hysterectomy when compared to traditional pain control methods.

Materials and Methods

Patients were included if they underwent a robotic assisted total laparoscopic hysterectomy by Marshall University physicians at Cabell Huntington Hospital, a tertiary care center, between March 1, 2016 and February 28, 2017 for benign or oncologic indications (including both simple and radical hysterectomy) with or without bilateral salpingo-oophorectomy. There were no excluded patients. 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. Furthermore, Marshall University and its affiliated hospital Cabell Huntington Hospital have no financial relationship with Pacira Pharmaceuticals, Inc.

Eligible cases were grouped into multimodal pain management or traditional pain management. A Mann-Whitney test showed to have 80% power with an alpha of 0.05 to detect reduction of 40% in opioid use and 20% reduction in pain we needed 41 and 29 patients, respectively per group. Using a random number generator, we randomly selected 50 cases from patients who had their postoperative pain managed with a multimodal approach and 50 cases with the traditional approach. A sampling method, instead of including all eligible cases, was chosen to better represent our population and reduce potential confounding. While including all cases would

increase power, our power analysis shows that our sample size is sufficient for the purposes of this pilot study.

Those in the multimodal pain control group received 133mg (10mL) of liposomal bupivacaine injected prior to incision, then 133mg (10mL) after skin closure, for a total of 266mg (20mL) or 1 vial. In addition, patients received an abdominal binder, 500mg acetaminophen and 50mg tramadol scheduled every 4 hours, oxycodone 5mg as needed for breakthrough, and intravenous pain medications if oral medications failed to control pain adequately. Those in the traditional pain control group did not receive any local anesthetic injection. All the patients in the traditional pain group received the On-Q® pain system, hydromorphone or morphine given IV as needed every 2 hours or through patient centered anesthesia (PCA) as decided by their physician's preference. Once tolerating oral medication, they were switched to 800mg ibuprofen every 8 hours or 10mg ketorolac every 6 hours and acetaminophen-oxycodone 5/325 or 10/325 as needed every 6 hours.

Patient medical records were evaluated for the following data points: surgical characteristics, demographics, type and dose of opioid administered during hospitalization, postoperative pain scores, postoperative complications, and length of stay (LOS). 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 the following scale: 0 = no pain, 1 = mild, 2 = moderate, 3=severe pain. All patients received the prophylactic anti-emetic treatment standard at our institution (included scopolamine patch). The need for breakthrough antiemetic for nausea and vomiting was also collected. All participants were given a unique identifier with the master code kept on a secure password protected computer. All data were collected on a password-protected computer in a locked room and deidentified prior to analysis.

Standard opioid dose calculators were utilized to convert all opioid class medications to oral morphine equivalents.[15,16] Conversion from the given opioid to oral morphine used the follow 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 were not included in the dose calculation. Postoperative drug administration started at the time the patient left the operative suite as documented by the circulating nurse. Primary outcomes were morphine total equivalents administered during their postoperative course as well as mean pain scores on postoperative days 0 and 1. Secondary outcomes include length of stay, nausea and vomiting. T-tests, Wilcoxon rank-sum tests, and Chi-squared tests were used to detect differences between the multimodal treatment group and the traditional control group. We further assessed the difference in total narcotic use between the multimodal and control groups using multiple quantile regression and simultaneously adjusted for significant differences in demographics, comorbidities, and surgical characteristics between our two study groups. All analyses were performed using Stata 14.0 (College Station, TX).

Results

429 cases were identified for inclusion, 220 in the traditional group and 209 in the multimodal group. 50 cases were randomly selected from each group, using a random number generator, for a total inclusion of 100 subjects. Demographics and surgical characteristics of each group are outlined on table 1. Overall BMI was 35.8 with a range of 19-63 and standard deviation of 9.8. Patients in the multimodal group were older 56.5 versus 49.5 years ($p<0.05$). BMI, smoking, insurance status, and medical comorbidities were similar in each group. Types of hysterectomy were evenly distributed amongst the groups. The multimodal group did have decreased EBL 54.4mL versus 79.1mL ($p<0.05$) and less surgery time 72.7 versus 110.5 ($p<0.05$). A second analysis was done to ensure that a shorter operative time did not significantly impact the results of this study. Length of stay did not vary between the groups. 1 patient left on the day of surgery, 91 left on postoperative day 1 and 8 left on postoperative day 2. 14 of the patients in the traditional therapy group had PCAs; none of the patients in the multimodal group received a PCA. No complications were identified. None of the patients admitted to a history of drug use. There was no difference in breakthrough nausea as defined by the administration of postoperative an anti-emetic.

Table 1. Demographic and Surgical Characteristics by Group (n=100)

Characteristic	Control	Multimodal	P
Demographic			
Age(y)	50 [49.5 (45.4-53.6)]	50 [56.5 (52.3-60.5)]	p<0.05*
BMI	50 [35.3 (32.6-38.1)]	50 [36.3 (33.5-39.2)]	p=0.61*
Smoking			p=0.15
Never	28 (56)	37 (74)	
Former	10 (20)	7 (14)	
Current	12 (24)	6 (12)	
Insurance			p=0.57‡
Medicaid	12 (24)	16 (32)	
Private Insurance	26 (52)	21 (42)	
Medicare	12 (24)	13 (26)	
Comorbidities			
Hypertension	26 (52)	31 (62)	p=0.31‡
Coronary Artery Disease	3 (6)	3 (6)	p=1.00‡
Pulmonary Disease	10 (20)	8 (16)	p=0.63‡
Diabetes Mellitus			p=0.63‡
Type 1	1 (2)	2 (4)	
Type 2	10 (20)	9 (18)	
Insulin dependent	6 (12)	3 (6)	
Non-Gynecologic Malignancy	4 (8)	2 (4)	p=0.67‡
Surgical Characteristics			
Type of Hysterectomy			p=0.10‡
RaTLH	6 (12)	3 (6)	
RaTLH/BSO	32 (64)	24 (48)	
RaTLH/BSO/LND	12 (24)	22 (44)	
Rad RaTLH/BSO/LND	0 (0)	1 (2)	
Final Pathology			p<0.05‡
Benign	35 (70)	25 (50)	
Malignant	15 (30)	25 (50)	
EBL (mL)	50 [79.1 (64.4-93.8)]	50 [54.4 (46.1-62.7)]	p<0.05§
Surgery Time (min)	50 [110.5 (97.8-123.2)]	50 [72.7 (64.0-81.2)]	p<0.05§

Data are n [mean (95% CI)] or n (%)
* *t* test
‡ Chi-squared test
§ Wilcoxon rank-sum test
TLH = Robotic assisted total laparoscopic hysterectomy
TLH/BSO = Robotic assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy
TLH/BSO/LND = Robotic assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection
Rad TLH/BSO/LND = Radical robotic assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection

As outlined in table 2 patients in the multimodal group used 42% less narcotics on day 0 (22.0mg versus 42.9mg, p<0.0001), 32% less narcotics on day 1 (13.5mg versus 32.2mg, p<0.0001) and overall 53% less (35.5mg versus 75.1mg, p<0.0001). Overall pain score was 14% lower (p<0.01). We further examined total narcotic use in our two study groups using quantile regression and found similar reductions in narcotic use in the multimodal group while simultaneously adjusting for age, pathology (benign vs. malignant), estimated blood loss, and total operative time (Table 3).

Table 2. Outcomes by Group (n=100)

Characteristic	Control	Multimodal	Decrease(%) (p)
Narcotic Use (mg PO Morphine)			
Day 0	50 [42.9 (32.6-53.1)]	50 [22.0 (17.6-26.4)]	42 (p<0.0001)*
Day 1	50 [32.2 (25.1-39.3)]	50 [13.5 (10.5-16.4)]	32 (p<0.0001)*
Total	50 [75.1 (61.6-88.6)]	50 [35.5 (29.8-41.2)]	53 (p<0.0001)*
Pain Score			
Day 0	50 [1.99 (1.82-2.16)]	50 [1.82 (1.67-1.96)]	9 (p<0.05)*
Day 1	50 [1.98 (1.80-2.17)]	50 [1.60 (1.37-1.83)]	19 (p<0.05)*
Overall	50 [1.99 (1.83-2.14)]	50 [1.71 (1.55-1.86)]	14 (p<0.01)*
Breakthrough Antiemetic Given			p=0.60 ‡
No	43 (86)	40 (80)	
Yes	7 (14)	10 (20)	
Age			

Data are n [mean (95% CI)] or n (%)
* Wilcoxon rank-sum test
‡ Chi-squared test

Table 3. Unadjusted and Adjusted Quantile Regression Coefficients of Total Narcotic Use by Multimodal vs. Control Groups

Model 1	Model 2	Model 3	Model 4
-42,5*	-41.2*	-42.5*	-42.3*
(-59.0 to -26.0)	(-58.0 to -24.4)	(-58.9 to -26.0)	(-61.4 to -25.5)

Data are coefficient, (95% CI)
*(p<0.001)
Model 1: Unadjusted
Model 2: Adjusted for Age
Model 3: Adjusted for Operative Time
Model 4: Adjusted for age, pathology (malignancy vs. benign), estimated blood loss and total operative time

70 subjects qualified as obese (BMI>30) with 31 being morbidly obese (BMI>40), shown on tables 4 and 5. Obese patients in the multimodal group used 41% less narcotics on day 0 (22.7mg versus 38.4mg, p<0.01), 55% less narcotics on day 1 (15.1mg versus 33.7mg, p<0.001) and overall 47% less (37.8mg versus 72.1mg, p<0.001). Although the overall pain score was 9% lower in the multimodal group, it was not statistically different. Morbidly obese patients in the multimodal group used 49% less opioids; however, it did not reach statistical significance. On day 1 the multimodal group used 60% less narcotics (14.4mg versus 35.7mg, p<0.05) and overall 54% less (34.8mg versus 75.7mg, p<0.01). Increased pain was reported on postoperative day 0, however, on postoperative day 1 overall pain scores were lower, none of which reached statistical significance.

Table 4. Outcomes by Group – Obese (n=70)

Characteristic	Control	Multimodal	Decrease(%) (p)
Narcotic Use (mg PO Morphine)			
Day 0	32 [38.4 (29.2-47.6)]	38 [22.7 (17.8-27.5)]	41 (p<0.01)*
Day 1	32 [33.7 (23.9-43.5)]	38 [15.1 (11.7-18.5)]	55 (p<0.001)*
Total	32 [72.1(56.7-87.5)]	38 [37.8 (31.2-44.3)]	47 (p<0.001)*
Pain Score			
Day 0	32 [2.01 (1.82-2.21)]	38 [1.90 (1.75-2.05)]	9 (p<0.05)*
Day 1	32 [1.91 (1.66-2.16)]	38 [1.69 (1.42-1.95)]	12 (p=0.21)*
Overall	32 [1.96 (1.77-2.16)]	38 [1.79 (1.61-1.97)]	9 (p=0.28)*
Breakthrough Antiemetic Given			p=1.00 ‡
No	17 (53)	20 (53)	
Yes	15 (47)	18 (47)	

Data are n [mean (95% CI)] or n (%)
* Wilcoxon rank-sum test
‡ Chi-squared test

Table 5. Outcomes by Group – Morbid Obesity (n=31)

Characteristic	Control	Multimodal	Decrease(%) (p)
Narcotic Use (mg PO Morphine)			
Day 0	13 [40.0 (20.1-59.8)]	18 [20.4 (14.0-26.8)]	49 (p=0.10)*
Day 1	13 [35.7 (19.2-52.1)]	18 [14.4 (9.5-19.3)]	60 (p<0.05)*
Total	13 [75.7(43.4-107.8)]	18 [34.8 (25.7-43.9)]	54 (p<0.01)*
Pain Score			
Day 0	13 [1.86 (1.46-2.26)]	18 [2.01 (1.92-2.10)]	+7 (p=0.76)*
Day 1	13 [1.94 (1.54-2.34)]	18 [1.67 (1.27-2.06)]	14 (p=0.49)*
Overall	13 [1.90 (1.53-2.27)]	18 [1.84 (1.68-2.06)]	3 (p=0.40)*
Breakthrough Antiemetic Given			p=0.28 ‡
No	9 (69)	9 (50)	
Yes	4 (31)	9 (50)	

Data are n [mean (95% CI)] or n (%)
* Wilcoxon rank-sum test

‡ Chi-squared test

60 subjects had benign disease and 40 had a malignancy on their final pathology report, shown on tables 6 and 7. Patients with benign disease in the multimodal group used 45% less narcotics on day 0 (24.2mg versus 30.3mg, p<0.05), 43% less narcotics on day 1 (16.7mg versus 29.5mg, p<0.05) and overall 44% less (41.0mg versus 73.5mg, p<0.01). Those with malignancy in the multimodal group used 51% less narcotics (19.8 versus 40.3, p<0.01), on day 1 the multimodal group used 74% less narcotics (10.2mg versus 38.6mg, p<0.001) and overall 62% less (30.0mg versus 78.9mg, p<0.001). Pain scores were 15% lower on day 0 (p<0.01), 32% lower on day 1 (p<0.01) and 24% lower overall (p<0.01).

Table 6. Outcomes by Group – Benign (n=60)

Characteristic	Control	Multimodal	Decrease(%) (p)
Narcotic Use (mg PO Morphine)			
Day 0	35 [44.0 (30.3-57.5)]	25 [24.2 (17.5-30.9)]	45 (p<0.05)*
Day 1	35 [29.5 (21.2-37.8)]	25 [16.7 (12.0-21.5)]	43 (p<0.05)*
Total	35 [73.5 (56.1-90.9)]	25 [41.0 (32.1-49.9)]	44 (p<0.01)*
Pain Score			
Day 0	35 [1.97 (1.75-2.19)]	25 [1.89 (1.67-2.11)]	4 (p=0.37)*
Day 1	35 [1.91 (1.65-2.17)]	25 [1.75 (1.41-2.08)]	3 (p=0.73)*
Overall	35 [1.94 (1.73-2.15)]	25 [1.82 (1.57-2.06)]	6 (p=0.41)*
Breakthrough Antiemetic Given			p=0.59‡
No	23 (66)	14 (56)	
Yes	12 (34)	11 (44)	

Data are n [mean (95% CI)] or n (%)
* Wilcoxon rank-sum test
‡ Chi-squared test

Table 7. Outcomes by Group – Malignant (n=40)

Characteristic	Control	Multimodal	Decrease(%) (p)
Narcotic Use (mg PO Morphine)			
Day 0	15 [40.3 (25.6-54.9)]	25 [19.8 (13.8-25.8)]	51 (p<0.01)*
Day 1	15 [38.6 (24.0-53.3)]	25 [10.2 (6.8-13.6)]	74 (p<0.001)*
Total	15 [78.9 (56.3-101.5)]	25 [30.0 (22.9-37.1)]	62 (p<0.001)*
Pain Score			
Day 0	15 [2.04 (1.80-2.29)]	25 [1.74 (1.54-1.95)]	15 (p<0.01)*
Day 1	15 [2.17 (1.96-2.38)]	25 [1.46 (1.11-1.80)]	32 (p<0.01)*
Overall	15 [2.10 (1.91-2.29)]	25 [1.6 (1.40-1.80)]	24 (p<0.01)*
Breakthrough Antiemetic Given			p=0.52‡
No	8 (53)	16 (64)	
Yes	7 (47)	9 (36)	

Data are n [mean (95% CI)] or n (%)
* Wilcoxon rank-sum test
‡ Chi-squared test

Discussion

Our data show that the use of liposomal bupivacaine with scheduled acetaminophen and scheduled tramadol and oxycodone as needed was associated with a dramatic reduction in the overall opioid use. Similar results have been shown with oncologic patients.[2-6] This, however, is the first study to demonstrate 53% 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. Our study is the first to have a sample with 70% and 31% obesity and morbid obesity rates, respectively. The multimodal approach was associated with a 47% reduction in opioid use in obese patients. Our protocol was associated with 54% reduction in opioid use among the morbidly obese. This protocol was associated with 44% reduction in opioid use in patients with benign disease. Our data show a reduction of 62% reduction in opioid use for those with malignancy, which is greater than the approximate 50% reported in the literature.[2-6] Our study did not show any difference in the amount of breakthrough antiemetic needed and none of the patients in either group had postoperative complications. Length of stay did not differ among the groups as 91% of our patients went home on the day after surgery.

Our data show that opioid need for postoperative pain can be reduced substantially by using a multimodal approach and the use of liposomal bupivacaine. This study was not designed to compare On-Q® with liposomal bupivacaine. Rather this study compares a multimodal protocol that utilizes liposomal bupivacaine with traditional methods that utilize On-Q® pain system. However, other data in the general surgery literature that directly compared On-Q® with liposomal bupivacaine found liposomal bupivacaine was superior.[17]

Our study was not designed to evaluate cost-effectiveness of using liposomal bupivacaine. Our pharmacy charge for liposomal bupivacaine and On-Q® are essentially equal. Despite the higher initial cost of liposomal bupivacaine compared to no local anesthetic,[5,6] pharmacy costs have been shown to be overall equal[5] and overall hospital costs reduced by ten percent.[6]

Our project has many strengths: a unique population that is obese (mean BMI of class II obesity), high smoking (26-40 percent), and a geographic area that is highly addicted to opioids. While the intrinsic validity characteristics demonstrate the lack of randomization, a preponderance of the patient-specific characteristics that increase surgical difficulty (obesity, type of surgery and medical comorbidities) were similar between the treatment groups. An unadjusted quantile regression (table 3) shows an associated reduction of 42.5mg ($p<0.001$) in the amount of opioid used by those in the multimodal group. When adjusted for age, the multimodal group is associated with 41.2mg reduction ($p<0.001$). When adjusted for operative time total narcotic use was associated with a decrease of 42.5mg ($p<0.001$). A model that adjusts for pathology (malignant vs. benign), EBL, total operative time, and age still shows an associated reduction in opioid use of 43.4mg ($p<0.001$). Therefore, our model shows that this multimodal protocol was associated with significant reductions in opioid use regardless of age, pathology, BMI, EBL and total operative time.

As it was a retrospective study, patients were not randomized to either the control group or the multimodal group. 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. However, this alone would not explain the large decrease in narcotics. This contributed to the multimodal group being older (56.5 years versus 49.5) and higher proportion of malignant cases (50 versus 30 percent). Our multimodal group also had shorter operative time (72.7 minutes versus 110.5) with a 31% reduction of estimated blood loss. 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.

In summary, even though our demographics and surgical characteristics were not as evenly distributed as a prospective randomized control trial would have been, there is no statistical evidence that this made a difference and certainly would not explain the dramatic results. Our study included a relatively small sample (n=100) however this is consistent with the studies currently done in this area of research.[2-6] 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.

Liposomal bupivacaine with an abdominal binder, acetaminophen, along with as needed or scheduled tramadol and oxycodone as needed is an acceptable alternative to traditional methods of pain control, regardless of BMI, for those with benign or malignant disease and decreases opioid use by 44 to 62 percent with no concomitant increase in pain scores and may decrease pain by 9 to 24 percent. This study shows the promise of multimodal protocols in reducing opioid need postoperatively. Further prospective randomized control trials are warranted.

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