



## Post-operative Nausea and Analgesia Following Total Mastectomy is Improved After Implementation of an Enhanced Recovery Protocol

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### ABSTRACT

**Background.** Enhanced Recovery Protocols (ERPs) provide a multimodal approach to perioperative care, with the aims of improving patient outcomes while decreasing perioperative antiemetic and narcotic requirements. With high rates of post-operative nausea or vomiting (PONV) following total mastectomy (TM), we hypothesized that our institutional designed ERP would reduce PONV while improving pain control and decrease opioid use.

**Methods.** An ERP was implemented at a single institution for patients undergoing TM with or without implant-based reconstruction. Patients from the first two months of implementation (ERP group,  $N = 72$ ) were compared with a retrospective usual-care cohort from a three-month period before implementation (UC group,  $N = 83$ ). Outcomes included PONV incidence, measured with antiemetic use; patient-reported pain scores; perioperative opioid consumption, measured by oral morphine equivalents (OME); and length of stay (LOS).

**Results.** The characteristics of the two groups were similar. PONV incidence and perioperative opioid consumption were lower in the ERP than the UC group (21% vs. 40%,

$p 0.011$  and mean 44.1 OME vs. 104.3 OME,  $p < 0.001$ ), respectively. These differences in opioid consumption were observed in the operating room and post-anesthesia care unit (PACU); opioid consumption on the floor was similar between the two groups. Patient-reported pain scores were lower in the ERP than the UC group (mean highest pain score 6.4 vs. 7.4,  $p 0.003$ ). PACU and hospital LOS were similar between the two groups.

**Conclusion.** ERP implementation was successful in decreasing PONV following TM with and without reconstruction, while simultaneously decreasing overall opioid consumption without compromising patient comfort.

Enhanced Recovery Protocols (ERPs) utilize a multimodal, multidisciplinary approach to the care of the surgical patient. This approach enables clinical caregivers to design a coordinated protocol, where the components work synergistically to optimize the shared goals of improved patient recovery. While the term *fast-track surgery* has sometimes been used, the key aim is the quality, rather than the speed, of recovery.<sup>1</sup>

ERPs developed by various surgical subspecialties are aimed at improving patient outcomes, specifically by decreasing post-operative pain via a multimodality approach to analgesia that also reduces perioperative opioid consumption, postoperative nausea and vomiting (PONV), postoperative pain and hospital length of stay. The subspecialties include but are not limited to colorectal,<sup>2–6</sup> other intra-abdominal,<sup>7–10</sup> pelvic,<sup>11,12</sup> and

orthopedic<sup>13,14</sup> surgery. ERPs have also been developed for mastectomy patients undergoing autologous reconstruction.<sup>15</sup> However, ERPs have not been well studied in mastectomy patients who are not undergoing autologous reconstruction. This may be particularly important, especially with regard to PONV, which has been reported to be as high as 80% after mastectomy.<sup>16–18</sup>

As part of a system wide effort to reduce narcotic administration and decrease contributions to the opioid epidemic, while using an evidence-based approach with preceding ERPs in other specialties and procedures, we developed an institution specific ERP for patients undergoing total mastectomy, either without reconstruction or with implant-based reconstruction. The protocol was built upon review of other standardized protocols for breast surgery including the published University of California, San Francisco model in 2018.<sup>19</sup> The goals were to decrease postoperative pain, perioperative opioid consumption and hospital length of stay. We hypothesize that the ERP would additionally decrease PONV and report our experience with implementation of the protocol and its associated improvements in patient recovery.

## METHODS

The ERP for total mastectomy patients was initiated at a tertiary referral, academic institution on August 20, 2018. With approval from the Quality Improvement Review Committee, we performed a single-institution chart review of all patients who underwent total mastectomy with implant-based reconstruction or without any reconstruction. Data for the reference group of patients in the usual care (UC) arm were retrospectively collected in the time period before breast ERP initiation, from June to August 2018. Data from the comparison group of patients cared for with the ERP were prospectively collected during the time-period of September to October 2018. We excluded the first several ERP patients from August 20 through August 31, 2018, to eliminate any inconsistencies or deviations in ERP implementation during the early part of transition from UC to ERP based care.

All patients cared for at a single institution by a group of dedicated breast surgeons with coordinated care from dedicated reconstructive surgeons undergoing a mastectomy for a diagnosis of breast cancer or risk reduction surgery were included in the analysis. The cohort also included a small number of transgender patients undergoing a mastectomy as part of their gender affirmation surgery. Patients undergoing concurrent bilateral salpingo-oophorectomy were included. Exclusion criteria included

concurrent total hysterectomy with bilateral salpingo-oophorectomy, tissue-based reconstruction, or any other major surgical procedure under general anesthesia.

The UC group consisted of patients who underwent the procedure prior to initiation of the ERP. There was no existing, standardized pre-operative counseling packet. The choice for intraoperative anesthetic was at the discretion of the anesthesiologist. Intraoperative blocks were not standard part of care for the breast or reconstructive surgeon and the mainstay for post-operative pain control was opioid-based medication both in the hospital and upon discharge.

In contrast, the ERP was designed by a multidisciplinary team, after review of the literature and institutional experience with ERP for other surgical procedures. The protocol consisted of three phases: preoperative, intraoperative, and postoperative. Each phase included medication and counseling components (Fig. 1).

The preoperative phase began in the surgical clinic. Patients received education about the ERP, as well as smoking-cessation and nutrition counseling, to help set stage for the patient and frame the recovery process. They were advised to walk daily for at least 30 min for prehabilitation. Patients were instructed to avoid prolonged fasting; solid food was allowed up to 8 h before surgery, and clear liquids were allowed up to 3 h before surgery. Preoperative medications in the holding area included oral acetaminophen 1000 mg, oral gabapentin 400 mg, and oral perphenazine 8 mg.

Intraoperative anesthetic management included general anesthesia with propofol-based total intravenous anesthesia, intravenous dexamethasone 4–5 mg after induction, intravenous ondansetron 4 mg during emergence, and minimal use of opioids. Intravenous boluses of ketamine or dexmedetomidine were administered as needed, at the discretion of the anesthesia provider. Following removal of the breasts, the breast surgeon performed a Pecs I and Pecs II block, and a serratus anterior block,<sup>20–22</sup> using a total of 30 ml of bupivacaine 0.5% with epinephrine 1:200,000. For bilateral cases, the bupivacaine was diluted with an additional 30 ml of saline for a total volume of 60 ml evenly divided between both sides. Intravenous ketorolac 15 mg was administered at the end of the case. Patients were kept euvolemic and normothermic perioperatively.

Postoperatively, patients received multimodal analgesia. This included intravenous acetaminophen 1000 mg Q6H for two doses, before transitioning to oral acetaminophen 1000 mg Q6H; intravenous ketorolac 15 mg Q6H for four doses, before transitioning to oral ibuprofen 600 mg Q6H; oral oxycodone 5–10 mg Q4H PRN pain; and intravenous hydromorphone 0.5 mg Q2H PRN breakthrough pain. Patients could request an alternative oral opioid if they did not wish to take oxycodone, usually due to previous side

Office Visit	Pre-op	Intra-op	Post-op
<ul style="list-style-type: none"> <li>• Nutrition counseling</li> <li>• 30-minute daily walks</li> <li>• Smoking cessation</li> </ul>	<ul style="list-style-type: none"> <li>• Fasting               <ul style="list-style-type: none"> <li>• Solids up to 8 hours prior to surgery</li> <li>• Liquids up to 3 hours prior to surgery</li> </ul> </li> <li>• Medications:               <ul style="list-style-type: none"> <li>• Acetaminophen 1000 mg PO</li> <li>• Gabapentin 400 mg PO</li> <li>• Perphenazine 8 mg PO</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Anesthesia               <ul style="list-style-type: none"> <li>• Propofol based total IV anesthesia</li> <li>• Dexamethasone 5mg IV after induction</li> <li>• Ketamine Q1 hour boluses</li> <li>• Dexmedetomidine IV boluses PRN</li> <li>• Avoid N2O and opioids</li> <li>• Ondansetron 4mg IV during emergence</li> </ul> </li> <li>• PECS II and serratus anterior block by surgeon intraoperatively               <ul style="list-style-type: none"> <li>• Bupivacaine 0.5% with epinephrine 1:200,000, 30mLs</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Early ambulation</li> <li>• Regular diet POD #0</li> <li>• Medications               <ul style="list-style-type: none"> <li>• Acetaminophen 1000mg IV Q6 x 2 doses then transition to 100mg PO Q6</li> <li>• Ketorolac 15mg IV Q6 x 4 doses then transition to ibuprofen 600mg PO Q6</li> <li>• Qxycodone 5mg PO Q4 PRN</li> <li>• Hydromorphone 0.5mg IV Q2 PRN</li> </ul> </li> </ul>

**FIG. 1** University of Pittsburgh breast program enhanced recovery program protocol

effects. Patients were encouraged to ambulate on post-operative day (POD) 0, and they were immediately provided with a solid diet. Patients met discharge criteria if they tolerated a solid diet, were independent with mobility and ambulation, had adequate pain control with oral analgesics, and did not have any signs of early complications. Patients were given a discharge goal of POD 1, but could be discharged on POD 0 if they were motivated and met discharge criteria. Patients were kept in-hospital beyond POD 1 if there were any clinical concerns, if additional time was needed to arrange for social services, or if additional time was needed for continued inpatient pain or nausea control.

The electronic health record was reviewed for patient demographic and clinical characteristics, medication administration, numerical rating scale (NRS) pain scores, and length of stay. Outcomes included PONV, postoperative pain, perioperative opioid use, and length of stay.

PONV was defined as the use of any antiemetic, including ondansetron, prochlorperazine, and metoclopramide, in either the post-anesthetic care unit (PACU) or on the hospital floor. Postoperative pain was measured using the NRS pain score, which was on a scale from zero (no pain) to ten (worst pain imaginable). Each patient's highest NRS pain score and average NRS pain scores were recorded, both in the PACU and on the hospital floor. Perioperative opioid consumption was calculated by converting opioid use into oral morphine equivalents. The calculations were done based on the institutional opioid equivalence table. Patients with a past history of opioid abuse or dependence were excluded from the analysis of perioperative opioid consumption.

Variables between the UC and ERP groups were compared using the student's *t* test or  $\chi^2$  test for continuous and categorical variables, respectively. All measures of statistical significance were measured at an alpha level of 0.05. All statistical analysis was performed using Stata version 15 (College Station, TX).

## RESULTS

A total of 83 UC patients and 72 ERP patients were included in the analysis. Demographic and clinical characteristics of the two groups were similar (Table 1).

Overall anti-emetic administration, as a surrogate for PONV, was lower in the ERP group compared to the UC group, 21% vs. 40% ( $p = 0.011$ ). This trend was statistically significant in the hospital floor setting but not in the PACU (Table 2).

The mean patient-reported NRS pain scores were lower in the ERP group compared to the UC group, both in the PACU (2.6 vs. 4.1,  $p < 0.001$ ) and in the hospital floor setting (3.3 vs. 4.5,  $p < 0.001$ ). The mean highest-reported pain score was also lower in the ERP group compared to the UC group, 6.4 vs. 7.4 ( $p = 0.003$ ) (Table 3).

Overall perioperative opioid consumption was lower in the ERP group compared to the UC group, 44.1 OME vs. 104.3 OME,  $p < 0.001$ . When stratified into perioperative phases, the ERP group had lower opioid consumption than the UC group in the intraoperative setting (14.9 OME vs. 50.4 OME,  $p < 0.001$ ) and PACU (8.7 OME vs. 21.8 OME,  $p < 0.001$ ). The hospital floor opioid consumption was similar between the two groups (23.1 OME in the ERP group vs. 32.4 OME in the UC group,  $p = 0.18$ ) (Table 4).

**TABLE 1** Patient demographic and clinical characteristics

	UC (N = 83)	ERP (N = 72)	p value
Age, mean (SD)	52.6 (12.5)	54.3 (16.3)	0.460
Gender			0.179
Female	78 (94%)	63 (88%)	
Male	2 (2%)	1 (1%)	
Transgender	3 (4%)	8 (11%)	
Race			0.053
White	75 (90%)	70 (97%)	
Black	8 (10%)	1 (1%)	
Other	0 (0%)	1 (1%)	
ASA Class			0.770
1	2 (2%)	2 (3%)	
2	52 (63%)	41 (57%)	
3	29 (35%)	29 (40%)	
BMI $\geq$ 30	32 (39%)	24 (33%)	0.500
CKD III and up	8 (10%)	7 (10%)	0.986
Smoking history	26 (31%)	15 (21%)	0.140
Opioid abuse/dependence	4 (5%)	2 (3%)	0.511
PONV history	15 (18%)	15 (21%)	0.664
Neoadjuvant therapy			0.472
None	62 (75%)	59 (82%)	
Chemotherapy	18 (22%)	12 (17%)	
Endocrine therapy	3 (4%)	1 (1%)	
Bilateral surgery	48 (58%)	36 (50%)	0.329
Axillary surgery			0.425
None	14 (17%)	14 (19%)	
SLNB	55 (66%)	51 (71%)	
ALND	14 (17%)	7 (10%)	
Reconstruction	41 (49%)	25 (35%)	0.065
Concurrent BSO	1 (1%)	1 (1%)	0.919

UC usual care, ERP enhanced recovery protocol, SD standard deviation, ASA American society of anesthesiologists, BMI body mass index, CKD chronic kidney disease, PONV postoperative nausea or vomiting, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, BSO bilateral salpingo-oophorectomy

**TABLE 2** Postoperative nausea or vomiting

	UC (N = 83)	ERP (N = 72)	p value
Any post-op	33 (40%)	15 (21%)	0.011
PACU	11 (13%)	7 (10%)	0.494
Floor	30 (37%)	10 (16%)	0.005

UC usual care, ERP enhanced recovery protocol, PACU post-anesthesia care unit

The mean PACU length of stay for the patients was similar in the two groups (154 min in the ERP group and 165 min in the UC group,  $p = 0.205$ ). The majority of patients were discharged on POD 1 in both groups: 90% of the ERP patients and 88% of the UC patients (Table 5). For those patients who had a delayed discharge beyond POD 1, the reasons for delayed discharge are listed in Table 6.

## DISCUSSION

This study confirmed the hypothesis that patients in the ERP group had a lower incidence of PONV, likely secondary to several strategies including multi-modal non-narcotic pre-operative pain control, use of pre-operative and intraoperative anti-emetics, and a deliberate preference for non-opioid medications during the intraoperative phase and avoidance of volatile anesthetics. The pattern of decreased PONV that is more striking in the hospital floor setting but not in the PACU is consistent with findings from implementation of an ERP for total mastectomy patients at the University of California, San Francisco.<sup>19</sup> We postulate that this trend could be related to the relatively low baseline incidence of PONV in the PACU compared to the floor, even in the UC group.

This finding is of importance because the incidence of PONV following mastectomy is reported to be as high as 80% and is likely related to the use of volatile anesthetics. As health systems shift focus to value based care, successful reduction in PONV will also result in improved patient satisfaction.<sup>16,23,24</sup> Additionally, cost-effectiveness analyses have demonstrated benefits to PONV prophylaxis compared to therapy, when including both the direct and indirect costs.<sup>23,25</sup> Some interventions shown to reduce PONV include intraoperative antiemetic use and limited intraoperative opioid use.<sup>16-18</sup> Our study describes the implementation of an ERP for patients undergoing total mastectomy, either without reconstruction or with implant-based reconstruction, at a single institution. The aim of decreasing procedure-associated PONV while concurrently decreasing overall opioid consumption was achieved by design with the ERP, without compromising patient comfort. There was no difference in hospital length of stay pre- or post-ERP implementation.

These systematic efforts are important as decreasing perioperative opioid consumption has become a critical component in the fight against the opioid epidemic. New persistent opioid use is a common iatrogenic complication in cancer patients undergoing curative-intent surgery, including breast cancer surgery.<sup>26</sup> Multimodal analgesic strategies, such as those used in this ERP, can decrease perioperative opioid consumption without compromising patient comfort in the recovery period. These strategies can

**TABLE 3** Postoperative numerical rating scale pain scores

	UC (N = 83) Mean (SD)	ERP (N = 72) Mean (SD)	p value
PACU mean	4.1 (2.3)	2.6 (2.1)	< 0.001
Floor mean	4.5 (1.9)	3.3 (2.1)	< 0.001
Highest	7.4 (1.9)	6.4 (2.4)	0.003

UC usual care, ERP enhanced recovery protocol, SD standard deviation, PACU post-anesthesia care unit

**TABLE 4** Perioperative opioid consumption, oral morphine equivalents

	UC (N = 79*)	ERP (N = 70*)	p value
Overall total, mean (SD)	104.3 (51.3)	44.1 (55.9)	< 0.001
Intraoperative	50.4 (24.6)	14.9 (13.6)	< 0.001
Postoperative total	53.8 (44.1)	29.2 (50.8)	0.002
PACU	21.8 (21.8)	8.7 (11.1)	< 0.001
Floor	32.4 (29.7)	23.1 (47.0)	0.18

UC usual care, ERP enhanced recovery protocol, SD standard deviation, PACU post-anesthesia care unit

\*Patients with a history of opioid abuse/dependence were excluded from this analysis

**TABLE 5** Length of stay

	UC (N = 83)	ERP (N = 72)	p
PACU (minutes), mean (SD)	165 (57.5)	154 (53.1)	0.205
Discharge day			0.643
POD 1 or earlier	73 (88%)	65 (90%)	
POD 2 or later	10 (12%)	7 (10%)	

UC usual care, ERP enhanced recovery protocol, PACU post-anesthesia care unit, SD standard deviation, POD postoperative day

**TABLE 6** Reasons for delayed discharge

	UC (N = 10/83)	ERP (N = 7/72)
Clinical	3 (30%)	4 (57%)
Social	2 (20%)	0 (0%)
Pain control	6 (60%)	3 (50%)
Nausea	1 (10%)	1 (17%)

Percentages may add to greater than 100% because some patients had multiple reasons for delayed discharge

UC usual care, ERP enhanced recovery protocol

be used in conjunction with increased prescriber awareness of actual perioperative opioid requirements, that in turn will lead to a decrease in narcotic over-prescription.<sup>27</sup>

It is interesting to note that there were no statistically significant differences in total OME use for the ERP group compared to the UC group in the hospital floor setting, despite a statistically significant lower patient reported NRS pain score. A potential explanation is the on-demand nature by which opioid medications are administered in the hospital floor setting. Despite parameters that are set for type of medication to be given based upon a patient reported NRS pain score, the retrospective design of this study does not allow for precise identification of the root cause of this finding.

There were no observed difference in length of stay between the UC or ERP groups, either in the PACU or in the overall hospitalization because the majority of patients at baseline were discharged on POD 1. Other modern studies describing ERP for breast cancer surgery with autologous reconstruction have shown either similar findings or do not measure LOS due to the short baseline timeframe.<sup>25,28,29</sup>

Limitations to our study include the single-institution setting and associated small cohort size. The patients were not formally randomized to treatment groups. Though the two groups were well-balanced with regard to baseline demographic and clinical characteristics, there may have been influence on outcomes related to unmeasurable confounders, such as institutional awareness of patient recovery after the ERP implementation. Furthermore, post-discharge opioid and anti-emetic consumption was not measured.

Our results are consistent with other recently reported studies describing multimodal ERP for breast cancer surgery.<sup>25,28,29</sup> However, one of the unique characteristics of this study is the observation that not only can post-operative analgesia be achieved with a decreased opioid requirement, it in turn results in a decrease in PONV, a significant problem in breast surgery.<sup>18</sup> To our knowledge, there is only one other study from UCSF that has reported this observation.<sup>19</sup>

With the increasing prevalence of ERP for breast cancer surgery, collaborative adjustments to these protocols can further improve the recovery of breast cancer patients. With our expanded experience with this ERP protocol, some of the improvements that have since been implemented include providing the regional anesthetic block prior to surgery start instead of intraoperatively. It is

expected that these refinements will continue to improve the patient experience with breast surgery, as we aim to eliminate PONV while providing appropriate pain control for an extended period of time in the post-operative setting.

**ACKNOWLEDGMENT** We appreciate the efforts of Adrian Tudose with data collection.

**DISCLOSURES** There are no conflict of interest.

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