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Enhanced recovery after surgery (ERAS) protocol reduces perioperative narcotic requirement and length of stay in patients undergoing mastectomy with implant-based reconstruction

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ABSTRACT

Introduction: Enhanced Recovery after Surgery (ERAS) protocols have contributed to shortened hospital stays and reduced narcotic use after common surgical procedures. Though ERAS protocols exist for breast surgery, they have not been studied for implant-based reconstruction after mastectomy.

Methods: Twenty-three consecutive patients undergoing mastectomy with implant-based reconstruction were treated with perioperative gabapentin, acetaminophen, and NSAIDs. Data regarding clinical course and medication requirement were compared to a historical control cohort ($n = 23$) receiving usual care after mastectomy. Opioid analgesics were converted to oral morphine equivalents (OMEs) for comparison between groups.

Results: Patients treated with the ERAS protocol required significantly fewer narcotics as measured in OMEs over postoperative days 0–2. Patient reported pain scores were equivalent between groups, as were postoperative complication rates of nausea, hematoma, and infection. Additionally, ERAS patients had significantly shorter mean length of hospital stay (1.3 vs. 2.5 days, $p = 0.037$).

Conclusions: Patients receiving perioperative gabapentin, acetaminophen, and NSAIDs under an ERAS protocol required significantly fewer narcotics and shorter length of stay. This protocol may merit consideration for use at other centers.

Introduction

Enhanced Recovery after Surgery (ERAS) protocols have revolutionized the care of surgical patients, contributing to shortened hospital stays and reduced narcotic use amidst a national opioid crisis.[1] An ERAS pathway includes a standard perioperative pain medication regimen combined with strategies to enhance postoperative recovery to allow a rapid return to function and reduced hospital stay. Two medications with similar mechanism of action – gabapentin and pregabalin–have been used consistently in ERAS protocols to improve pain control and reduce narcotic requirement in the perioperative period.[2,3]

Pain control without the secondary effects of narcotic analgesia has been shown to expedite patients' return to functionality across a number of surgical subspecialties, including breast surgery. Two recently published prospective studies have demonstrated the efficacy of ERAS protocols in reducing postoperative narcotic requirement and length of stay (LOS) in patients undergoing breast-conserving treatment as well as mastectomy with microvascular autologous tissue reconstruction.[4,5] However, there are no existing studies of ERAS protocols in women undergoing mastectomy with immediate subpectoral implant-based reconstruction. Implant reconstruction is commonly accompanied by acute and chronic chest wall pain,[6–8] making it an optimal target for narcotic-sparing analgesia. Therefore, we conducted a prospective, single-armed pilot study to examine the feasibility and efficacy of a multimodal, opioid-sparing ERAS protocol in women undergoing mastectomy with implant-based reconstruction.

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Methods

Study design

This study was reviewed and determined to be a Quality Improvement Project by the University of Pennsylvania's Institutional Review Board. All participating patients provided written informed consent prior to surgery. Between April and December of 2017, twenty patients were identified in a breast surgery clinic who were planning to undergo mastectomy with subpectoral implant-based reconstruction at our institution. Clinical and demographic information including age, sex, race, comorbid conditions, and indication for surgery was collected. This patient cohort was treated with an initial ERAS protocol (hereafter referred to as ERAS1) detailed as follows:

Patients took 300 mg (mg) of gabapentin by mouth at bedtime the night before surgery (ERAS1). On the day of surgery, enrolled patients received 800 mg of gabapentin and 975 mg of acetaminophen by mouth with a sip of water in the preoperative area shortly before their surgery. Intraoperative anesthetic care was not standardized and was deferred to the individual anesthesia providers. Postoperative pain management included standing gabapentin (600 mg BID), ibuprofen (600 mg TID), and acetaminophen (650 mg QID), with 5–10 mg of oxycodone administered on an as needed basis. Dosages and intervals of medications were adapted from similar protocols used at our institution in Colorectal and Bariatric Surgery, as well as review of existing literature for ERAS protocols in lumpectomy or tissue-based reconstruction.

After preliminary data suggested high rates of postoperative nausea and vomiting in the ERAS1 cohort, a second cohort of 23 women planning mastectomy with implant reconstruction was enrolled between July 2018 and February 2019 and treated with a second ERAS protocol (hereafter referred to as ERAS2). This protocol was identical to ERAS1 except that the preoperative loading dose of gabapentin was gradually increased from 100 mg, 200 mg and 300 mg at bedtime over 3 nights before surgery. In addition, standing intravenous ondansetron (4 mg every 8 h) was included for the first 24 h after surgery in patients without a prolonged QTc interval. The ERAS1 and ERAS2 cohorts were compared with a retrospective control cohort who underwent mastectomy with tissue expander reconstruction between January 2016 and December 2017, and received routine care postoperatively. We excluded patients without complete documentation of medication administration or comprehensive nursing reports with pain scores.

Data collection

The perioperative medication administration records of all patients were reviewed by a single researcher to ensure standardization of coding. Data relating to type and quantity of intraoperative medication administration were collated from anesthesia records. The medication administration record (MAR) of each patient was also queried to analyze the amount of analgesic and non-analgesic medications received by each patient in the postoperative period. These data were subsequently stratified by postoperative day (POD) for all groups, with POD1 was defined as the 24-h period starting from midnight on the day of surgery. All narcotics use, including those received via PCA, in the postoperative period was converted into Oral Morphine Equivalents (OMEs), also known as morphine milligram equivalents (MMEs), using the Center for Disease Control's guidelines.[9] A comprehensive review of all nursing and discharge reports was performed for each patient and postoperative complications including bleeding, infection, nausea/vomiting and urinary retention logged within these reports were recorded.

Statistical analysis

Statistical analyses were performed using SPSS software (IBM Corporation). Demographic and clinical variables including age at surgery, race, body mass index (BMI), comorbidities, reasons for mastectomy, as well as postsurgical complications including nausea requiring anti-emetics, infection, hematoma, and the need for urethral catheterization due to urinary retention were analyzed using Chi-Square (χ^2) analyses. Paired *t*-tests and Fisher's exact tests were employed to analyze differences in intra-operative as well as postoperative medication use between the two groups. All *p* values were considered significant if below a threshold of 0.05.

Results

Patient characteristics

The clinical and treatment characteristics of our study patients in each study group are summarized in Table 1. Patients within each treatment cohort were primarily white (85%), in their mid-forties, with normal BMI (61%), and without significant comorbidities (95%). There were no significant differences in any of these characteristics between cohorts. Furthermore, the vast majority of patients in all cohorts underwent bilateral mastectomies for treatment of malignancy (and contralateral prophylactic mastectomy), rather than bilateral mastectomies for prophylaxis or risk reduction. Length of surgery and estimated blood loss during surgery were similar in both groups (data not shown). In total, there were two attending surgeons and fifteen attending anesthesiologists that treated patients included in the study.

Intraoperative medications

Table 2 summarizes the intraoperative medication administration data collated from anesthesia records. While the overall trends in intraoperative medication administration are quite similar among the three groups, there are salient differences in the anti-emetics, opioids, and non-opioid analgesics administered. Specifically, patients in the ERAS2 cohort received less ondansetron intraoperatively than those in the control cohort ($p = 0.027$). With regard to opioid analgesia, ERAS2 patients received less hydromorphone on average, than did those treated with the non-ERAS protocol ($p < 0.0001$). Compared to the ERAS1 cohort, patients in the ERAS2 cohort received more ketorolac and less hydromorphone intraoperatively ($p = 0.019$ and $p < 0.0001$, respectively).

Postoperative medications

Table 3 enumerates the postoperative medications received by all patients enrolled in the study. There are many significant differences related to the types and amounts of narcotic and non-narcotic medications received by patients in the postoperative period. Patients treated on either ERAS protocol required significantly fewer opioid analgesics quantified by OMEs than those treated with standard care. Those treated on the ERAS2 protocol received significantly less narcotics than those on the ERAS1 protocol, with $p < 0.05$ for all postoperative days. Not surprisingly, those treated with either ERAS protocol received more acetaminophen, ibuprofen, and gabapentin as compared to the historical control group. Additionally, those on the ERAS2 protocol received more ondansetron than those in the ERAS1 or control groups.

Complications and length of stay

Table 4 denotes the incidence of postoperative complications,

Table 1
Patient demographics.

	Overall	Non-ERAS	ERAS v1	ERAS v2	*P*-Value		
					P1	P2	P3
N (%)	66	23	20	23			
Mean age at procedure [y ± SD]	46.2 ± 10.3	46.2 ± 10.8	44.5 ± 10.4	47.7 ± 9.8	0.588	0.624	0.305
Race							
White	56 (85)	20 (87)	17 (85)	19 (83)	0.336	>0.999	0.363
Hispanic	1 (1.5)	1 (4.3)	0	0			
Other	7 (11)	2 (8.7)	1 (5)	4 (17)			
Data Missing	2 (3.0)	0	2 (10)	0			
BMI							
Underweight (<18.5)	4 (6.1)	1 (4.3)	2 (10)	1 (4.3)	0.862	0.280	0.270
Normal (18.5–24.9)	40 (61)	16 (69.6)	13 (65)	11 (48)			
Overweight (25–29.9)	17 (26)	4 (17.4)	3 (15)	10 (43)			
Obese (>30)	4 (6.1)	2 (8.7)	1 (5)	1 (4.3)			
Data Missing	1 (1.5)	0	1 (5)	0			
Surgical Intent							
Prophylactic/risk reduction	4 (6.1)	4 (17.4)	0	0	0.111	0.109	>0.999
Cancer Treatment	62 (94)	19 (82.6)	20 (100)	23 (100)			
Comorbidities							
None	63 (95)	23 (100)	17 (85)	23 (100)	0.092	>0.999	0.092
Diabetes	2 (3)	0	2 (10)	0			
Myocardial Infarction	1 (1.5)	0	1 (5)	0			

P1 = Non-ERAS and ERAS v1.
P2 = Non-ERAS and ERAS v2.
P3 = ERAS v1 and ERAS v2.

Table 2
Intraoperative medications.

N (%)	Overall	Non-ERAS		ERAS v1		ERAS v2		*P*-Value		
		n	Average ± SD	n	Average ± SD	n	Average ± SD	*P1*	*P2*	*P3*
	66	23		20		23				
Pre-Operative Medications										
Acetaminophen (mg)	32 (48)	0 (0)	–	18 (90)	975 ± 0	14 (61)	975 ± 0	–	–	–
Gabapentin (mg)	29 (44)	0 (0)	–	17 (85)	800 ± 0	12 (52)	800 ± 0	–	–	–
Lidocaine (mL)	2 (3)	0 (0)	–	1 (5)	0.5 ± 0	1 (4)	4 ± 0	–	–	–
Midazolam (mg)	2 (3)	0 (0)	–	2 (10)	6.0 ± 5.7	0	–	–	–	–
Intra-Operative Medications										
Antiemetics										
Dexamethasone (mg)	54 (82)	18 (78.3)	5.6 ± 2.4	17 (85)	6.0 ± 2.8	19 (83)	5.5 ± 2.4	0.623	0.888	0.532
Midazolam (mg)	41 (62)	15 (65.2)	3.5 ± 3.8	11 (55)	2.2 ± 1.2	15 (65)	2.4 ± 0.9	0.313	0.184	0.537
Ondansetron (mg)	60 (91)	19 (82.6)	5.1 ± 2.3	18 (90)	4.4 ± 1.3	23 (100)	4 ± 0	0.322	0.027	0.147
Scopolamine (mg)	7 (11)	3 (13)	1.5 ± 0	3 (15)	1.8 ± 0.4	1 (4)	1.5 ± 0	0.371	–	–
Inhaled Anesthetics										
None	11 (17)	4 (17.4)		2 (10)		5 (22)		0.423	0.107	0.410
Desflurane alone	26 (39)	13 (56.5)		8 (40)		5 (22)				
Sevoflurane alone	19 (29)	3 (13)		6 (30)		10 (43)				
Desflurane + Sevoflurane	7 (11)	3 (13)		4 (20)		0				
IV Anesthetics										
Ketamine (mg)	4 (6.1)	1 (4.3)	50 ± 0	1 (5)	30.0 ± 0	2 (9)	33 ± 9.9	–	–	–
Propofol (mg)	65 (98)	23 (100)	570.8 ± 564.6	19 (95)	637.5 ± 931.8	23 (100)	519.1 ± 605.2	0.776	0.766	0.620
Opioids										
Fentanyl (mcg)	58 (88)	21 (91.3)	214.3 ± 108.6	20 (100)	182.5 ± 105.4	17 (74)	185.3 ± 72.4	0.348	0.292	0.919
Hydromorphone (*mg)	52 (79)	17 (73.9)	2.1 ± 1.1	16 (80)	1.72 ± 0.5	19 (83)	1.0 ± 0.4	0.178	<0.0001	<0.0001
Remifentanil (mcg)	11 (17)	5 (21.7)	1566.0 ± 1121.1	1 (5)	2832.0 ± 0	5 (22)	2367.8 ± 1559.7	–	<0.0001	0.191
Other medications										
Ketorolac (mg)	25 (38)	5 (21.7)	30.0 ± 0.0	6 (30)	36.7 ± 16.3	14 (61)	27.9 ± 5.4	0.389	0.069	0.019
Lidocaine (mg)	61 (92)	20 (87)	66.5 ± 21.1	18 (90)	71.8 ± 25.6	23 (100)	97.1 ± 78.3	0.491	0.077	0.175

P1 = Non-ERAS and ERAS v1.
P2 = Non-ERAS and ERAS v2.
P3 = ERAS v1 and ERAS v2.

including nausea/vomiting, hematoma development, wound infection, and urinary retention requiring straight catheterization among the three study groups. Postoperative nausea was a common development among patients treated with the ERAS1 protocol, affecting 70% of patients in that cohort over the two days following mastectomy as compared to 30.4% in the control group ($p = 0.010$). Patients treated with the ERAS2 protocol had similar incidence of postoperative nausea as compared to the control group (17% vs. 30.4%, $p = 0.300$). Rates of hematoma, surgical site infection, and urinary retention were not significantly different among the three groups.

Length of stay data is also reported in Table 4. Mean LOS varied widely in the control cohort (2.5 ± 2.61 days). Statistically significant reductions in LOS were achieved in the patient cohort treated

Table 3
Postoperative medications.

	Non-ERAS		ERAS v1		ERAS v2		*P*-Value		
							P1	*P2*	*P3*
Oral Morphine Equivalents(mg)									
POD 0	29.47 ± 27.40		28.31 ± 27.52		15.16 ± 11.75		0.908	0.026	0.043
POD 1	62.86 ± 46.32		36.56 ± 32.01		11.84 ± 15.57		0.044	<0.001	0.002
POD 2	42.39 ± 22.64		23.0 ± 12.48		8.75 ± 11.04		0.017	<0.001	<0.001
Acetaminophen (mg)	**N (%)**	**Avg ± SD**	**N (%)**	**Avg ± SD**	**N (%)**	**Avg ± SD**			
POD 0	7 (30.3)	742.9 ± 309.1	17 (85)	725 ± 142.5	22 (96)	1559.6 ± 655.4	0.231	0.023	0.019
POD 1	15 (65.2)	953.3 ± 498.5	19 (95)	1556.6 ± 755.1	23 (100)	2128.8 ± 774.4	0.017	0.004	0.096
POD 2	11 (47.8)	1270.5 ± 1001.2	14 (70)	696.4 ± 173.7	5 (22)	2360 ± 1103.2	0.142	<0.001	0.01
Ibuprofen (mg)									
POD 0	0	–	19 (95)	1211.11 ± 226.1	21 (91)	500 ± 241.4	<0.001	<0.001	0.021
POD 1	2 (8.7)	800.0 ± 565.7	18 (90)	1622.2 ± 449.3	22 (97)	1521.2 ± 282.8	<0.001	0.003	>0.999
POD 2	2 (8.7)	700.0 ± 141.4	13 (65)	692.3 ± 225.3	4 (17)	532.3 ± 848.5	<0.001	0.393	0.01
Ketorolac (mg)									
POD 0	0	–	2 (10)	37.5 ± 31.8	13 (57)	21.9 ± 13.2	0.12	<0.001	0.12
POD 1	5 (21.7)	48.0 ± 12.6	1 (5)	30 ± 0	17 (74)	24.7 ± 11.8	0.114	<0.001	<0.001
POD 2	3 (13)	35.0 ± 0.0	0	–	1 (4)	30 ± 0	0.094	0.611	>0.999
Gabapentin (mg)									
POD 0	1 (4.3)	300 ± 0	17 (85)	521.4 ± 112.2	23 (100)	774.3 ± 140.6	<0.001	<0.001	>0.999
POD 1	1 (4.3)	300 ± 0	19 (95)	1090.5 ± 433.3	21 (91)	1040 ± 274.6	<0.001	<0.001	0.182
POD 2	2 (8.7)	450.0 ± 212.1	15 (75)	640.0 ± 154.9	5 (22)	900 ± 300	<0.001	0.222	0.004
Ondansetron (mg)									
POD 0	3 (13)	4.0 ± 0	6 (30)	4.0 ± 0	23 (100)	9.3 ± 3.3	0.173	0.001	0.007
POD 1	4 (17.4)	6.0 ± 2.3	6 (30)	4.0 ± 0	5 (22)	6.4 ± 2.2	0.329	0.711	0.723
POD 2	0	–	1 (5)	4.0 ± 0	1 (4)	4.0 ± 0	0.278	0.465	>0.999
Promethazine (mg)									
POD 0	0	–	5 (25)	8.8 ± 3.4	0	–	0.011	–	0.04
POD 1	2 (8.7)	9.4 ± 4.4	3 (15)	9.4 ± 4.4	0	–	0.52	–	0.23
POD 2	0	–	0	–	0	–	–	–	–

P1 = Non-ERAS and ERAS v1.
P2 = Non-ERAS and ERAS v2.
P3 = ERAS v1 and ERAS v2.

Table 4
Postoperative course and complications.

N (%)	Overall	Non-ERAS	ERAS v1	ERAS v2	*P*-Value		
					P1	P2	P3
	66	23	20	23			
Experienced nausea during:							
POD 0-2	25 (38)	7 (30.4)	14 (70)	4 (17)	0.010	0.300	<0.001
POD 0	18 (27)	3 (13)	11 (55)	4 (17)	0.003	0.687	0.013
POD 1	11 (17)	4 (17.4)	7 (35)	0	0.187	0.109	0.002
Average Pain Score							
POD 0	4.23 ± 2.82	4.30 ± 3.13	4.21 ± 2.06	4.17 ± 3.10	0.913	0.888	0.961
POD 1	5.16 ± 2.19	5.56 ± 2.19	4.61 ± 1.87	5.19 ± 2.43	0.137	0.59	0.391
POD 2	5.78 ± 2.30	5.58 ± 2.34	5.32 ± 2.11	5.29 ± 2.41	0.706	0.681	0.966
Infection	1 (1.5)	1 (4.3)	0	0	–	–	–
Hematoma	3 (4.5)	2 (8.7)	1 (5)	0	–	–	–
Straight Catheterization	1 (1.5)	1 (4.3)	0	0	–	–	–
Average length of stay (days)		2.5 ± 2.61	1.7 ± 0.37	1.3 ± 0.57	0.182	0.037	0.011

P1 = Non-ERAS and ERAS v1.
P2 = Non-ERAS and ERAS v2.
P3 = ERAS v1 and ERAS v2.

with the ERAS2 protocol, as compared to both the ERAS1 cohort and the control cohort ($p = 0.011$ and 0.037, respectively).

Discussion

In this prospective trial, we found that an ERAS protocol involving perioperative administration of gabapentin combined with standing postoperative ibuprofen, acetaminophen, gabapentin, and ondansetron reduced postoperative narcotic requirement and LOS in women undergoing mastectomy with immediate tissue expander reconstruction. There were no significant differences in postoperative pain scores among the ERAS cohort as compared to a historical control cohort. While an initial ERAS1 cohort displayed increased rates of postoperative nausea and vomiting, a modified ERAS2 protocol including standing ondansetron and a gradually increased loading dose of gabapentin showed no significant differences in any postoperative complication rates as compared to the control cohort. We included the initially negative data from the ERAS1 cohort in our study to reflect the iterative process inherent in Quality Improvement work, which ultimately helped create the more effective ERAS2 protocol. This is the first such trial of ERAS protocols in patients undergoing immediate implant-based breast reconstruction after mastectomy. This work builds upon prior studies that have established the

benefit of similar ERAS protocols across a number of surgical subspecialties.

Within the field of breast surgery, there is a relative paucity of data on ERAS protocols, and only two prior prospective studies have examined their use. A landmark 2015 trial performed at the Mayo Clinic studied a gabapentin-based ERAS protocol in 100 women undergoing mastectomy with autologous microvascular breast reconstruction, demonstrating decreased LOS and total inpatient opioid requirement among women treated with a multidisciplinary ERAS protocol as compared to standard care.[4] Subsequently, Rojas et al. from Maimonides Medical Center found that postoperative narcotic prescription requirement was completely eliminated in women undergoing lumpectomy and treated with an ERAS protocol.[5]

Gabapentin-based ERAS protocols–similar to those detailed in our study and the aforementioned breast trials–have shown efficacy across a number of surgical specialties. First approved as an antiepileptic medication, gabapentin is an analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) with profound anticonvulsant, anti-nociceptive, and anxiolytic effects.[10,11] It is an integral component of successful ERAS protocols in colorectal,[12–14] orthopedic,[2,14] gynecologic,[15] vascular,[16] hepatobiliary,[17,18] bariatric,[19] and esophageal[20] surgeries.

Our study is reflective of a broad national trend toward opioid-sparing analgesic regimens. Such regimens are beneficial at the individual patient level in speeding return to function without the secondary effects of narcotics, but also represent a critical public health need in this era of a national opioid epidemic. A recent CDC report underscored the scope of the epidemic, noting that nearly 400,000 individuals died from opioid overdoses between 1999 and 2017.[21] Many of these victims' initial exposure to opioids came in the form of narcotic analgesics prescribed by physicians.[22,23] With deaths from opioid overdoses increasing each year,[21] the imperative for narcotic-sparing postoperative analgesic regimens grows concomitantly, and we therefore believe our study is an important contribution to this trend.

Nonetheless, there are significant limitations to this study. While prospective in nature, the study was not randomized, and relied upon the use of a historical control cohort for comparison. As such, it is possible that initial differences in our patient populations or changes in practice between the two periods could account for some of the changes. Intraoperative analgesia management in patients in our control and ERAS cohorts was also somewhat heterogeneous, which may have influenced our findings. The somewhat large range of certain intraoperative and postoperative medications among the various patient cohorts likely reflects the variance in baseline pain tolerance and opioid metabolism among the general population, including those non-opioid naïve patients. Finally, this pilot study had a relatively small sample size and future studies will need to examine this ERAS protocol in a larger cohort of women undergoing mastectomy with implant-based reconstruction.

Despite its limitations, this study conclusively demonstrates significant benefits to a gabapentin-based ERAS protocol for implant-based reconstruction after mastectomy. Patients treated with an ERAS regimen required significantly fewer narcotics in the postoperative period and had shorter LOS with no differences in pain scores or postoperative complication rates. Our results demonstrate that the inclusion of standing antiemetics and parenteral/oral NSAIDs is integral in managing postoperative nausea and pain. The long-term effects of such protocols on the narcotic requirement during the post-hospital recovery process and their influence on the incidence of postmastectomy pain syndrome is unclear and will be the subject of future studies. With further study in larger patient cohorts, this protocol may merit consideration for use at other centers and may contribute to the ongoing public health efforts to limit postoperative narcotic prescriptions amidst a national opioid crisis.

Disclosures

There are no conflicts of interest for any of the authors. Informed consent was obtained from all individual participants included in the study. The study was approved by the University of Pennsylvania Institutional Review Board.

Declaration of competing interest

All authors on the submitted manuscript "Enhanced recovery after surgery (ERAS) protocol reduces perioperative narcotic requirement and length of stay in patients undergoing mastectomy with implant-based reconstruction" report that they have no conflicts of interest or relevant financial disclosures.

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