Preoperative Multimodal Analgesia Decreases Postanesthesia Care Unit Narcotic Use and Pain Scores in Outpatient Breast Surgery

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PATIENT SAFETY

Background: The opioid epidemic demands changes in perioperative pain management. Of the 33,000 deaths attributable to opioid overdose in 2015, half received prescription opioids. Multimodal analgesia is a practice-altering evolution that reduces reliance on opioid medications. Ambulatory breast surgery is an ideal opportunity to implement these strategies.

Methods: A retrospective review of 560 patients undergoing outpatient breast procedures was conducted. Patients received (1) no preoperative analgesia ($n = 333$); (2) intraoperative intravenous acetaminophen ($n = 78$); (3) preoperative oral acetaminophen and gabapentin ($n = 95$); or (4) preoperative oral acetaminophen, gabapentin and celecoxib ($n = 54$). Outcomes included postanesthesia care unit narcotic use, pain scores, postanesthesia care unit length of stay, rescue antiemetic use, and 30-day complications.

Results: Both oral multimodal analgesia regimens significantly reduced postanesthesia care unit narcotic use (oral acetaminophen and gabapentin, 14.3 ± 1.7; oral gabapentin, acetaminophen, and celecoxib, 11.9 ± 2.2; versus no drug, 19.2 ± 1.1 mg oral morphine equivalents; $p = 0.0006$), initial pain scores (oral acetaminophen and gabapentin, 3.9 ± 0.4; oral gabapentin, acetaminophen, and celecoxib, 3.4 ± 0.7; versus no drug, 5.3 ± 0.3 on a 1 to 10 scale, $p = 0.0002$) and maximum pain scores (oral acetaminophen and gabapentin, 4.3 ± 0.4; oral gabapentin, acetaminophen, and celecoxib, 3.6 ± 0.7; versus no drug, 5.9 ± 0.3 on a 1 to 10 scale; $p < 0.0001$). Both oral regimens were better than no medications or intravenous acetaminophen alone in multivariate models after controlling for age, body mass index, American Society of Anesthesiologists class, length of surgery, prior narcotic prescription availability, and intraoperative local anesthetic. Postanesthesia care unit length of stay, antiemetic use, and 30-day complications were not different.

Conclusions: Preoperative oral multimodal analgesia reduces narcotic use and pain scores in outpatient breast plastic surgery. These regimens are inexpensive, improve pain control, and contribute to narcotic-sparing clinical practice in the setting of a national opioid epidemic. (*Plast. Reconstr. Surg.* 142: 443e, 2018.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

The opioid epidemic demands changes in the way that clinicians practice and approach pain control.[1] Of the 33,000 deaths caused by opioid overdose in 2015, half were attributable to prescription opioids,[2] highlighting the role of physicians in the growing problem. The most common

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reason for opioid prescriptions is for acute postoperative pain.[3] Opioid-based pain regimens put patients at significantly higher risk of long-term use after the perioperative period, creating a situation for dependence.[4] Moreover, unused prescriptions and diversion of opioids contribute to the presence of available narcotic medications in the community,[5] providing the potential for abuse.[6]

In addition to the risk of long-term use or recreational abuse, opioid-based pain regimens increase postoperative complications, including respiratory depression, deep venous thrombosis and pulmonary embolism, postoperative infections, decreased gastrointestinal motility, postoperative nausea and vomiting, and increased length of stay and increased health care costs.[7–9] Multimodal analgesia is a strategy that aims to reduce reliance on opioids, and involves the use of two or more drugs that have different mechanisms of action to provide adequate analgesia.[10] These regimens are procedure-specific, and use varying combinations of locoregional anesthetics, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2–specific inhibitors, steroids, *N*-methyl-D-aspartate antagonists, alpha-2-agonists, and certain anticonvulsants.[11] Recent evidence suggests that multimodal analgesia significantly decreases time to discharge, unplanned hospitalizations, and postoperative opioid use in breast reduction patients.[12]

Ambulatory plastic surgery is an ideal opportunity to transition to multimodal analgesia regimens. We sought to investigate the impact that preoperative multimodal analgesia had on immediate postoperative outcomes in terms of postanesthesia care unit narcotic use, pain scores, postanesthesia care unit length of stay, rescue antiemetic use, and 30-day complications in ambulatory breast plastic surgery.

PATIENTS AND METHODS

After institutional review board approval, a retrospective review was completed for 981 patients who underwent surgery performed by one of 13 plastic surgeons at a university hospital–based ambulatory surgery center between 2012 and 2015. This patient cohort was refined to 560 patients by CPT code to include only those undergoing similar breast procedures (Table 1). (**See Table, Supplemental Digital Content 1**, which shows the distribution of CPT codes included in analysis, ***http://links.lww.com/PRS/C963***.) The procedures performed consisted predominantly of secondary breast procedures and breast reductions. Often, patients underwent multiple procedures encompassed by the CPT codes described, which is standard practice for secondary breast surgery. No primary oncologic procedures are performed at our ambulatory surgery center. As a result, the data do not include any cases of immediate reconstruction. These patients were then subdivided into four categories based on the perioperative analgesic strategy, which evolved over time based on both hospital formulary availability and newly available evidence-based medical practice. These included (1) no preoperative analgesia ($n = 333$); (2) intraoperative intravenous acetaminophen only ($n = 78$), 1000 mg or 650 mg; (3) 900 mg of preoperative oral gabapentin and 975 mg of acetaminophen ($n = 95$); or (4) 900 mg of preoperative oral gabapentin, 650 mg of acetaminophen, and 400 mg of celecoxib ($n = 54$) (Table 2).

Continuous patient demographic and clinical characteristics were compared between study groups using analysis of variance or Kruskal-Wallis tests and reported as mean (standard deviation) or median (interquartile range) where relevant. Categorical demographic and clinical variables were reported as frequency (percentage) and compared between study groups using chi-square or Fisher's exact tests where relevant. General linear models were fit to compare continuous outcomes between study groups, including postanesthesia care unit narcotic use, initial and maximum pain scores, and postanesthesia care unit

Table 1. CPT Codes Included in Analysis

CPT Code	Description
19318	Breast reduction
19325	Breast augmentation
19316	Mastopexy
11970	Exchange tissue expander for permanent implant
19340	Immediate insertion breast prosthesis
19342	Delayed insertion breast prosthesis
19357	Reconstruction of breast with tissue expander
19328	Removal intact breast implant
19330	Removal breast implant material
19380	Revision breast reconstruction

Table 2. Medication Subgroups

Medication Subgroups	No.
No preoperative analgesia	333
Intraoperative intravenous acetaminophen 1000 mg or 650 mg	78
Oral acetaminophen 975 mg and oral gabapentin 900 mg	95
Oral acetaminophen 650 mg, oral gabapentin 900 mg, and oral celecoxib 400 mg	54

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Table 3. Patient Demographics*

Characteristic	Total	No Preoperative Analgesia	IV Acetaminophen	Oral Gabapentin, Acetaminophen, and Celecoxib	Oral Gabapentin and Acetaminophen	Overall *p*
Mean age ± SD, yr	47.56 ± 12.16	48.28 ± 11.53	45.88 ± 12.6	46.41 ± 13.1	47.08 ± 13.35	0.3553
Mean BMI ± SD, kg/m^2	27.89 ± 6.09	27.43 ± 5.32	29.13 ± 7.89	28.29 ± 7.66	28.28 ± 5.89	0.1318
Length of surgery, min						
Mean	145	137	148	140.5	156	
IQR	110–183	103–179	121–180	110–191	125–194	0.0088†
ASA class 1	48 (8.62)	26 (7.85)	9 (11.69)	4 (7.41)	9 (9.47)	
ASA class 2	343 (61.58)	198 (59.82)	46 (59.74)	36 (66.67)	63 (66.32)	
ASA class 3	166 (29.80)	107 (32.33)	22 (28.57)	14 (25.93)	23 (24.21)	0.6718
Prior narcotic prescription	125 (22.32)	85 (25.53)	18 (23.08)	11 (20.37)	11 (11.58)	0.0378
Intraoperative local anesthetic	163 (29.16)	100 (30.12)	33 (42.31)	12 (22.22)	18 (18.95)	0.0053

IV, intravenous; BMI, body mass index; IQR, interquartile range; ASA, American Society of Anesthesiologists.
*Continuous variables reported as mean ± SD, except for length of surgery, which is reported as median and interquartile range; *p* values for continuous variables are from analysis of variance, except for length of surgery, which is from Kruskal-Wallis nonparametric test for overall *p* value and the Dwass-Steel-Critchlow-Fligner procedure for pairwise comparisons. Categorical variables including ASA were reported as frequency (%) and compared between groups using χ^2 tests. Note that there were significant differences between treatment groups in prior narcotic prescription and intraoperative local anesthetic.
†Significant pairwise difference between the no–preoperative analgesia group and the oral acetaminophen and gabapentin group (pairwise *p* = 0.0062) for length of surgery variable.

length of stay. Logistic regression models were fit to compare dichotomous outcomes, including rescue antiemetic use and 30-day complications between study groups. The multivariate models were adjusted for potential confounding variables including age, body mass index, American Society of Anesthesiologists class, length of surgery, prior narcotic prescription availability, and intraoperative local anesthetic use. All hypothesis testing was conducted at a 5 percent type I error rate (alpha = 0.05). SAS version 9.4 (SAS Institute, Inc., Cary, N.C.) was used to conduct all statistical analyses.

RESULTS

Demographics

Mean age was 47.6 ± 12.2 years. Mean body mass index was 27.9 ± 6.1 kg/m^2. Forty-eight patients (8.6 percent) were American Society of Anesthesiologists class 1, 343 patients (61.6 percent) were American Society of Anesthesiologists class 2, and 166 patients (29.8 percent) were American Society of Anesthesiologists class 3. Median length of surgery was 145 minutes (interquartile range, 110 to 183 minutes). Twenty-two percent of patients had a history of prior home prescription opioid availability. One hundred sixty-three procedures (29.6 percent) involved intraoperative local anesthetic. There were incidentally identified statistically significant differences between certain medication groups. Specifically, patients who received no preoperative medications or intravenous acetaminophen only had higher use of intraoperative local anesthetic (overall $p = 0.0378$). Patients with no preoperative medications had a higher incidence of prior home narcotic prescriptions (overall $p = 0.0053$) (Table 3).

Postanesthesia Care Unit Narcotic Use

In univariate analysis, both preoperative oral regimens significantly reduced postanesthesia care unit narcotic use (oral gabapentin and acetaminophen, 15.7 ± 1.4; and oral gabapentin, acetaminophen, and celecoxib, 13.3 ± 1.8; versus intravenous acetaminophen, 19.9 ± 1.5; and no drug, 19.9 ± 0.8 mg oral morphine equivalents; overall $p = 0.0014$). This was confirmed in multivariate analysis with a significant reduction in postanesthesia care unit narcotic use for both preoperative oral regimens (oral gabapentin and acetaminophen, 14.3 ± 1.7; and oral gabapentin, acetaminophen, and celecoxib, 11.9 ± 2.2; versus intravenous acetaminophen, 18.9 ± 1.8; and no drug, 19.2 ± 1.1 mg oral morphine equivalents; overall $p = 0.0006$) (Fig. 1, *left*). Patients who were given oral acetaminophen, gabapentin, and celecoxib used 62 percent of the postoperative narcotics that patients with no preoperative regimen required, equating to a reduction in narcotic use of 38 percent on average after adjusting for relevant covariates. Both oral regimens were significantly better than no medications or intravenous acetaminophen alone, but were not significantly different from each other. These findings accounted for age, body mass index, American Society of Anesthesiologists class, length of surgery, prior home narcotic prescription availability, and intraoperative local anesthetic. Postanesthesia care unit narcotic use was increased with longer operative time ($p = 0.04$), decreased with intraoperative local anesthetic use, and independent of preoperative medication subgroup ($p = 0.008$), and trended toward significance for history of narcotic prescription availability at home ($p = 0.10$). No

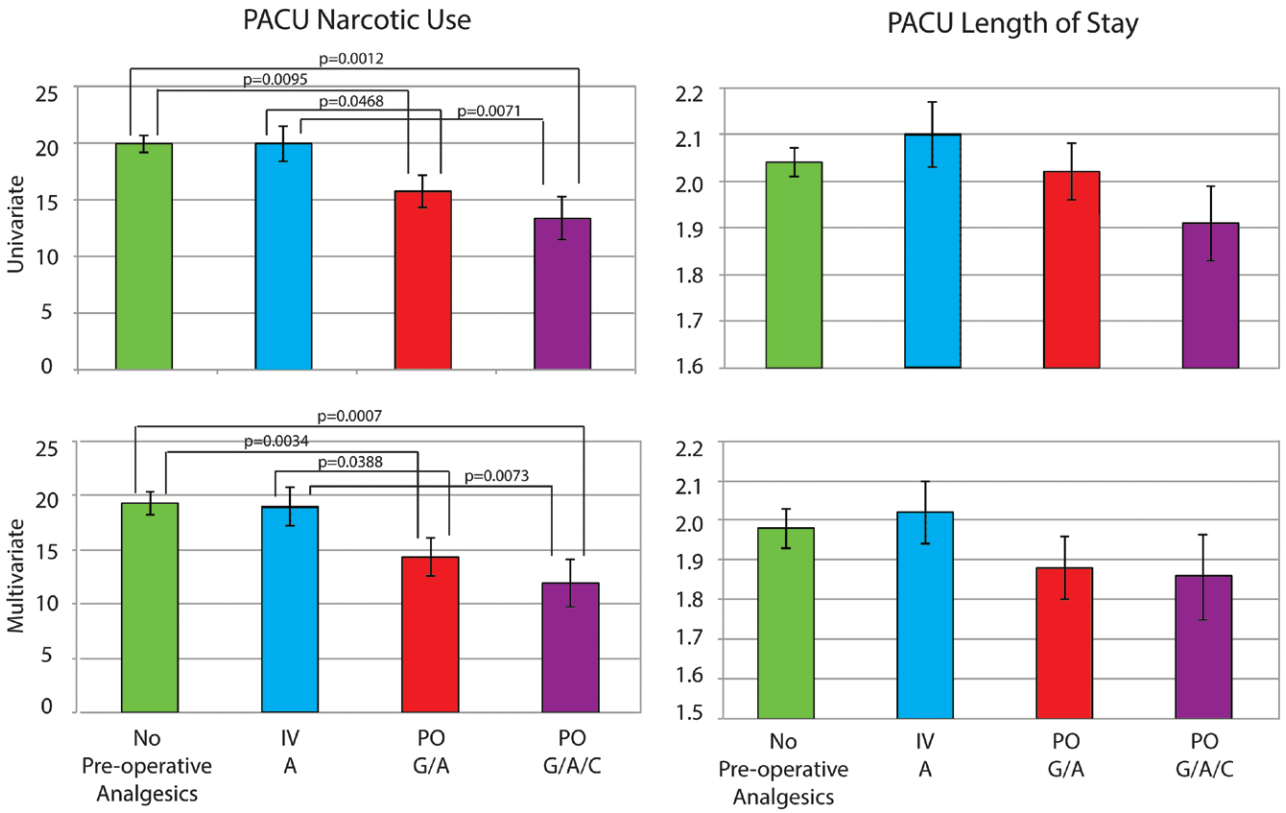

Fig. 1. Preoperative oral multimodal analgesia reduces postanesthesia care unit (*PACU*) narcotic use by comparison with no preoperative analgesia or intravenous acetaminophen alone (milligrams of oral morphine equivalents ± SEM). (*Above*, *left*) Univariate analysis; (*above*, *right*) multivariate analysis. No statistically significant differences were seen for postanesthesia care unit length of stay between the groups (hours ± SEM) (*Below*, *left*) Univariate analysis; (*below*, *right*) multivariate analysis. *IV A*, intravenous acetaminophen. *PO G/A*, oral gabapentin and acetaminophen; *PO G/A/C*, oral gabapentin, acetaminophen, and celecoxib.

difference in postanesthesia care unit narcotic use was seen with age, body mass index, or American Society of Anesthesiologists class.

Postanesthesia Care Unit Length of Stay

Postanesthesia care unit length of stay was decreased with oral preoperative pain regimens; however, these results were not statistically significant (overall $p = 0.6926$) (Fig. 1, *right*). Longer operative time resulted in longer postanesthesia care unit length of stay ($p < 0.0001$). History of prior home narcotic prescription availability trended toward significance associated with postanesthesia care unit length of stay ($p = 0.0790$). There were no other factors that impacted time to discharge, including age, body mass index, intraoperative local anesthetic, and American Society of Anesthesiologists class.

Pain Scores

Two hundred sixty-five patients had data available for analysis regarding postanesthesia care unit pain scores. In univariate analysis, both preoperative oral regimens significantly reduced initial postanesthesia care unit pain scores (oral gabapentin and acetaminophen, 4.6 ± 0.4; and oral gabapentin, acetaminophen, and celecoxib, 3.7 ± 0.6; versus intravenous acetaminophen, 5.8 ± 0.3; and no drug, 5.6 ± 0.2 on a 1 to 10 scale; overall $p = 0.0011$). This was confirmed in multivariate analysis (oral gabapentin and acetaminophen, 3.9 ± 0.4; and oral gabapentin, acetaminophen, and celecoxib, 3.4 ± 0.7; versus intravenous acetaminophen, 5.5 ± 0.4; and no drug, 5.3 ± 0.3 on a 1 to 10 scale; overall $p = 0.0002$) (Fig. 2, *left*).

Maximum postanesthesia care unit pain scores were also significantly reduced in both univariate (oral gabapentin and acetaminophen, 4.7 ± 0.4; and oral gabapentin, acetaminophen, and celecoxib, 3.7 ± 0.6; versus intravenous acetaminophen, 6.1 ± 0.3; and no drug, 6.1 ± 0.2 on a 1 to 10 scale; overall $p < 0.0001$) and multivariate (oral gabapentin and acetaminophen, 4.3 ± 0.4; and oral gabapentin, acetaminophen, and celecoxib, 3.6 ± 0.7; versus intravenous acetaminophen, 5.8 ± 0.4; and no drug, 5.9 ± 0.3 on a 1 to 10 scale; overall

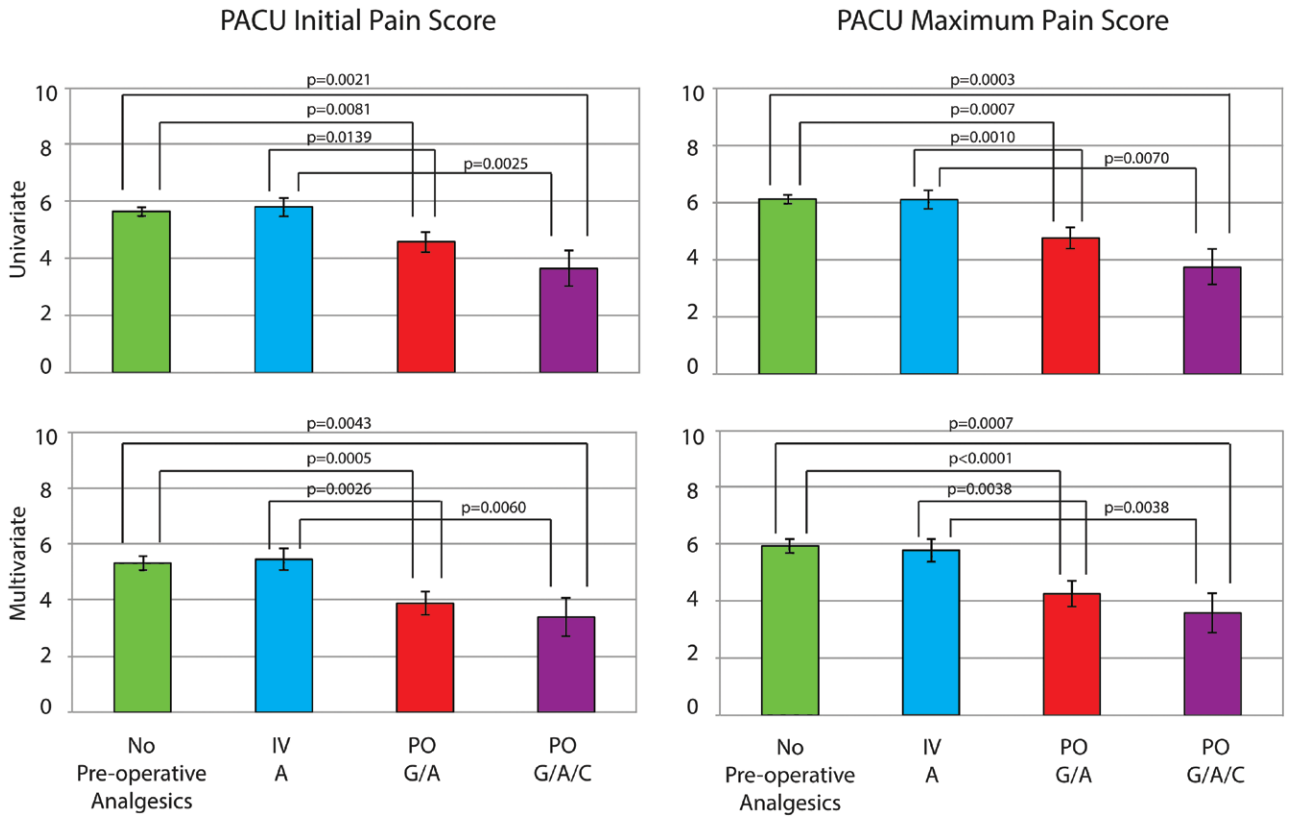

Fig. 2. Preoperative oral multimodal analgesia reduces initial (*left*) and maximum (*right*) pain scores by comparison with no preoperative analgesia or intravenous acetaminophen alone (pain score on a visual analogue scale of 1 to 10 ± SEM). (*Above*) Univariate analysis; (*below*) multivariate analysis. *PACU*, postanesthesia care unit; *IV A*, intravenous acetaminophen; *PO G/A*, oral gabapentin and acetaminophen; *PO G/A/C*, oral gabapentin, acetaminophen, and celecoxib.

$p < 0.0001$) analyses (Fig. 2, *right*). These findings accounted for age, body mass index, American Society of Anesthesiologists class, length of surgery, prior home narcotic prescription availability, and intraoperative local anesthetic use. Both initial ($p = 0.0082$) and maximum ($p = 0.0493$) pain scores were decreased with intraoperative local anesthetic use in the respective multivariate models. There were no differences in pain score when assessing history of narcotic prescription availability, American Society of Anesthesiologists class, or operative time. Increasing age was significantly associated with reduced initial postanesthesia care unit pain scores ($p = 0.0357$) but not maximum postanesthesia care unit pain scores. Body mass index trended toward being associated with maximum postanesthesia care unit pain scores ($p = 0.0743$) but not initial postanesthesia care unit pain scores.

Rescue antiemetic use in the postanesthesia care unit was not associated with preoperative medication subgroups, but was associated with longer operative time ($p = 0.01$) and trended toward an association with history of postoperative nausea and vomiting ($p = 0.09$). There were no significant findings for 30-day complications, including bleeding complications, as the study lacked the power to detect differences in these rare events.

DISCUSSION

Patients who undergo breast plastic surgery procedures performed in an ambulatory setting are generally healthy and rarely require hospital admission beyond pain control. Thus, they are an ideal population to transition to narcotic-sparing pain management regimens. This work aims to contribute to the growing body of knowledge that emphasizes the effectiveness of a multimodal approach to pain control and the need to minimize surgeon dependence on perioperative opioid use.

We evaluated the efficacy of three medications that have been proven both safe and effective for perioperative pain control: acetaminophen, gabapentin, and celecoxib. We demonstrate that preoperative administration of these medications significantly reduces opioid consumption in the

postanesthesia care unit and initial and maximum pain scores. When we secondarily analyzed the effects of local anesthetic, we also observed decreased postanesthesia care unit narcotic requirements and decreased pain scores. Therefore, we recommend the use of an oral preoperative multimodal analgesia regimen in conjunction with intraoperative local anesthetic for ambulatory breast surgery patients.[13]

Acetaminophen is well established as an effective perioperative analgesic. A recent review and meta-analysis demonstrates its efficacy for both pain control and opioid reduction across all surgical specialties.[14] The mechanism of action is not entirely known, but it is believed to function as a cyclooxygenase enzyme inhibitor within the central nervous system. Below maximum doses where hepatotoxicity can result, the safety profile of acetaminophen is favorable and the leading adverse effects including nausea, vomiting, headache, and insomnia are well tolerated. Acetaminophen is available in both oral and parenteral formulations. However, a recent meta-analysis demonstrates that there is no clear advantage of intravenous administration over oral administration for patients who are able to tolerate oral medications for the indication of perioperative pain control.[15] In the present study, we did not find an advantage to parenteral acetaminophen over oral acetaminophen in conjunction with other oral medications. We were unable to compare the two directly based on evolving hospital formulary availability, which is a limitation of our study.

Gabapentin functions as an analgesic by binding to calcium channels, causing the release of glutamate, norepinephrine, and substance P. These substances activate pathways in the dorsal horn that regulate pain signals. Studies have shown that preoperative gabapentin leads to decreased postoperative pain and opioid consumption within the 24 hours after surgery and decreased postoperative nausea and vomiting. Adverse effects are minor and include somnolence, dizziness, headaches, difficulty with balance, peripheral edema, sweating, dry mouth, and nausea and vomiting.[16,17]

Nonsteroidal antiinflammatory drugs inhibit cyclooxygenase enzymes, either cyclooxygenase-2 selectively or both cyclooxygenase-1 and cyclooxygenase-2 nonselectively, which in turn inhibits the synthesis of prostaglandins and thromboxanes. Nonsteroidal antiinflammatory drugs have the triple function of being analgesic, antipyretic, and antiinflammatory. Nonsteroidal antiinflammatory drugs reduce pain even after major operations such as total abdominal hysterectomy and total hip arthroplasty.[18,19] Selective cyclooxygenase-2 inhibitors have a more favorable profile for avoiding the side effects of gastrointestinal irritation and bleeding but must be used with caution in those with preexisting cardiovascular disease, as one of the major disadvantages is their association with higher rates of cardiovascular events. This is more concerning with certain selective cyclooxygenase-2 inhibitors over others.[20] Moreover, nonsteroidal antiinflammatory drugs should be avoided in those with acute or chronic renal disease. Surgeons remain most commonly concerned about the risk of impaired platelet function and surgical bleeding; however, there is no high-level evidence to support their contraindication in surgical patients.[21]

In light of increased awareness of the national opioid epidemic, a number of recent studies have addressed opioid-prescribing practices. Johnson et al. reported that an alarming number (13 percent) of previously opioid-naive patients continued to fill opioid prescriptions postoperatively, even 90 days after undergoing hand surgery.[22] Likewise, in a study of over 30,000 patients, Brummett et al. reported that new persistent opioid use reached 5.9 to 6.5 percent for patients undergoing minor and major surgical procedures, respectively, after receiving prescriptions for acute surgical pain.[4] Clarke et al. reported that of opioid-naive patients who were prescribed opioids in the perioperative period, nearly 50 percent continued to use opioids in the early postoperative period, with over 3 percent using these medications beyond 3 months.[23] Thus, modifying acute opioid surgical prescribing practices for even minor procedures is truly impactful and can contribute to reducing the national opioid epidemic.

Interestingly, Sekhri et al. demonstrated that the probability of refilling prescription opioids after surgery was not correlated with initial prescription strength, suggesting that surgeons could prescribe smaller amounts without influencing refill requests or adding unnecessary clinic phone call encounters.[24] Moreover, Lee et al. demonstrated that opioid prescribing practices are not related to patient satisfaction scores, allaying the concern that minimizing opioid prescribing might negatively impact the reputation of a clinical practice.[25] Ambulatory breast surgery is an opportunity for plastic surgeons to contribute to national efforts toward mitigating the opioid crisis by using multimodal strategies to minimize postoperative opioid prescription needs.

Lastly, multimodal analgesia regimens described in the present study are also inexpensive. At our academic ambulatory surgery center, the cost for each medication given was as follows:

975 mg of oral acetaminophen, $0.01; 900 mg of oral gabapentin, $2.13; and 400 mg of oral celecoxib, $0.14. Therefore, our most extensive regimen cost $2.28.

The present study was not without limitations. The medication dosing groups were not designed prospectively and patients were not randomized. Our findings reflect a retrospective review of clinical practice as it evolved over time. This was based on hospital formulary restrictions and also the evolution of current evidence-based strategies. Moreover, although we attempted to control for as many factors as possible, this list could not be entirely inclusive, given the study's retrospective nature. For example, all patients did receive intraoperative narcotics, according to standard anesthesia practice; however, this could not be controlled for in the study. Nonetheless, the large number of patients within each medication subgroup provides evidence supporting the use of the strategies presented. Given the retrospective nature of this review, we were also limited in the data that could be collected. For example, we were unable to track postdischarge opioid consumption, which would have been a valuable complement to the information presented. We are currently in the process of prospectively investigating postdischarge opioid consumption in conjunction with the concept of continued postdischarge multimodal pain regimens for ambulatory plastic surgery patients.

CONCLUSIONS

Preoperative oral multimodal analgesia reduces narcotic use and pain scores in outpatient breast plastic surgery. These regimens are inexpensive, improve pain control, and contribute to narcotic-sparing clinical practice in the setting of a national opioid epidemic.

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