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Mastectomy is no longer an indication for postoperative opioid prescription at discharge

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ABSTRACT

Background: A 10-step protocol employing multimodal analgesia was implemented in patients undergoing mastectomy to decrease the quantity of opioids prescribed at discharge.
Methods: Patients who received the Enhanced Recovery After Surgery (ERAS) protocol were compared to a control group. Inpatient and discharge prescription of opioids were compared using oral morphine equivalents (OMEs), along with postoperative pain scores.
Results: Between 2017 and 2018, fifty-seven patients were eligible for inclusion: 20 patients received ERAS and 37 received usual care (UC). The ERAS group received a mean of 2.4 (0–13) inpatient OMEs and the UC group received 13.7 (0–80) ($p = 0.002$). The ERAS group received 2.0 (0–40) OMEs at discharge and the UC group received 59.8 (0–120) ($p < 0.001$). Postoperative pain scores were significantly lower in the patients who received the ERAS protocol.
Conclusions: Patients who received the ERAS protocol required less postoperative opioids and reported lower pain scores when compared to a control group.

Introduction

Enhanced Recovery After Surgery (ERAS) protocols were developed almost two decades ago.[3] The use of ERAS protocols has gained popularity among multiple surgical subspecialties, and the goal is to expedite patients' return to equilibrium. Another main tenet of ERAS is the use of multimodal analgesia, which has the potential to minimize or eliminate the need for postoperative opioid prescription.

The U.S. Department of Health and Human Services declared the opioid epidemic a public health emergency in 2017.[1] More than one third of the overdose deaths involved prescription opioids, and the death toll continues to climb.[2] Postoperative opioid prescriptions are a major contributor to the quantity of narcotics available for diversion, and surgeons have the opportunity to effect drastic change in the course of the epidemic by re-evaluating traditional prescribing practices.

We have previously demonstrated the feasible elimination of postoperative opioid prescription using an ERAS protocol in breast conservation without compromising postoperative pain control.[4] The present study developed and implemented a similar ERAS protocol for mastectomy patients to eliminate the reflex opioid prescription at discharge.

Material and methods

Protocol development

The methods for the development of the ERAS protocol for patients undergoing lumpectomy have been previously described.[4] The Breast Surgery ERAS protocol begins in the office during the preoperative visit. Patients receive preoperative counseling, including a handout that describes perioperative pain expectations, incision and drain care, and the multimodal pain plan. Patients are also asked at the preoperative visit to have acetaminophen and ibuprofen at home. Patients found to have abnormal liver function tests during preoperative testing are encouraged to take ibuprofen but not acetaminophen, and patients with abnormal serum creatinine are encouraged to take acetaminophen but not ibuprofen. All patients on the ERAS protocol were given a phone number to call in

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1. Enhanced preoperative counseling of perioperative expectations, non-opioid analgesia
2. Clear liquids up to 2 hours preoperatively
3. Preoperative oral medication: 975mg acetaminophen, 300mg gabapentin
4. Antiemetic protocol upon induction
5. Intraoperative euvolemia and normothermia
6. Long-acting local analgesia infiltration after mastectomy (1:1 of 1.3% bupivacaine liposome suspension with 0.5% bupivacaine hydrochloride) with ≥30cc mixture into chest wall, axilla, drain site as field block (Fig. 2)
7. 15 mg intravenous ketorolac during incision closure
8. Scheduled 600 mg ibuprofen, 650 mg acetaminophen every 8 hours, alternating dose every 4 hours with first oral intake
9. 5mg oxycodone every 6 hours PRN pain score >7, IV opioid if >7 1 hour later
10. Discharge on postoperative day 1 with acetaminophen, ibuprofen for pain control

Fig. 1. 10-Step ERAS protocol for patients undergoing mastectomy without reconstruction.

the event of uncontrolled pain after surgery. Fig. 1 details the 10-step ERAS protocol for patients undergoing mastectomy without reconstruction.

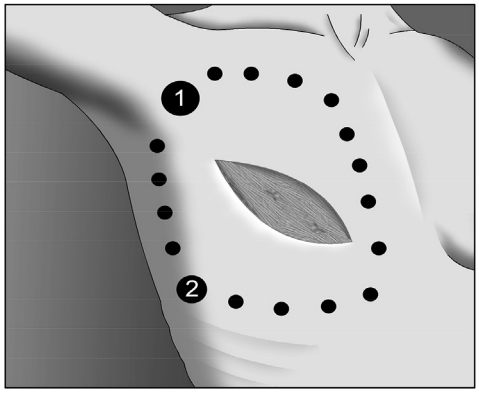
Long-acting local analgesia is used to create a field block of the chest wall and axilla (Fig. 2). After the mastectomy specimen is removed, small aliquots of the liposomal bupivacaine are injected along the periphery of the chest wall: along the sternum medially, superiorly below the clavicle with attention paid to injection at the insertion of the pectoralis major and minor at the coracoid process, laterally along the thoracic wall, and inferiorly in the serratus fascia. The subcutaneous tissue of the axilla(e) is also injected with special attention to the drain site. At least 30 cc of the mixture is used for each case. In the event of a bilateral mastectomy, 40 cc of the mixture is distributed between the two sides. In the postoperative recovery area, patients receive 2 mg of intravenous morphine if they report a pain score greater than 7. On arrival to the hospital floor, patients receive scheduled acetaminophen and ibuprofen upon demonstration of 200 cc of oral intake. Overnight, 5 mg of oxycodone is available PRN if the patient reports a pain score greater than 7. If pain persists at that level after 1 h then 2 mg of intravenous morphine is given. The protocol states that all ERAS patients are to be discharged on a regimen of alternating acetaminophen and ibuprofen, without an opioid prescription. However, if a patient explicitly asks to be discharged with an opioid, they are given a quantity of opioids based upon the inpatient postoperative OME (oral morphine equivalent) requirement. Within the present study, there was not a designated algorithm for calculating the quantity of opioids for the ERAS patient that requests a prescription. The goal was arbitrarily set at less than 10 tablets to minimize the quantity available for diversion. The protocol did stipulate that the prescribed medication should be opioid alone, not combined opioid and acetaminophen in order to encourage patients to continue scheduled acetaminophen and use the opioid as needed.

Study design

A pilot observational study including patients undergoing mastectomy without reconstruction was planned with the intent to eliminate opioid prescription at discharge. After Institutional Review Board (study #2017-09-29) approval was obtained, a database was developed using Microsoft Excel (Microsoft® Excel® for Mac 2011 v. 14.1.0) to collect patient demographics and surgical outcomes. Two breast surgeons adopted the ERAS protocol for every eligible patient and this group was named the “ERAS” cohort. A third breast surgeon proceeded with usual care, and the group was called the usual care “UC” cohort. Patients undergoing mastectomy without immediate reconstruction were eligible for inclusion within the study. Those with a prior history of chemotherapy and radiation were also included. Patients with baseline renal dysfunction were placed on the protocol but did not receive ketorolac or ibuprofen, and patients with abnormal liver function tests were not given acetaminophen.

Data collection

Patient demographics were collected and adherence to the protocol was recorded by checking the electronic medical record to ensure that protocol medications were administered. The inpatient opioid requirement did not include opioids used during induction



1. From inside the skin flap, approx. 2-3cc anesthetic mixture injected into muscle of pectoralis major at the level of the 3rd rib to anesthetize medial pectoral nerve branches
2. From the skin, approx. 2-3cc anesthetic mixture injected into skin of drain tubing exit site(s)

Fig. 2. ERAS protocol liposomal bupivacaine field block.

of anesthesia. Inpatient and prescribed opioids at discharge were quantified using oral morphine equivalents (OMEs), calculated using the ClinCalc.com Equivalent Opioid Calculator (available at http://www.clincalc.com/opioids/). All opioids were converted to oral morphine with a cross-tolerance adjusted for a 0% reduction.[5] The postoperative day one pain score was collected by nursing staff at the hospital. Pain scores were also collected at the postoperative visit 7–10 days after surgery, where the patient was asked to scale their pain on postoperative day one and during postoperative week one from 0 to 10 using the pain numeric rating scale (NRS). The postoperative day one pain score taken from the survey was preferred for the analysis, as it was collected by study personnel. The hospital pain score recorded by nursing staff during the hospital admission was used in the pain score analysis if the survey was not collected at the postoperative visit. Postoperative complications were defined as postoperative hematoma or need for postoperative transfusion, postoperative infection requiring antibiotics, emergency room visit within 10 days after surgery, or chronic seroma requiring intervention.

Statistical methods

Patient demographics were compared using student's T-test or x.[2] Protocol adherence between the ERAS and UC groups was compared using the Kruskal-Wallis test. Both in-hospital and prescribed OMEs were compared between the ERAS and the UC groups using x^2 or Fisher's exact test. Kruskal-Wallis test was used to compare the proportion of patients who received the individual ERAS protocol elements and the postoperative day one and week one pain scores. P-values <0.05 were considered statistically significant.

Results

Between September 2017 and August 2018, 758 breast surgeries were performed at a single New York City institution in the Borough of Brooklyn. Of the 153 patients who underwent mastectomy, 57 patients met inclusion criteria. Twenty patients received the ERAS protocol and 37 underwent usual care (UC). Seven percent of the patients were male, and 18% of study patients underwent bilateral mastectomy.

Groups were similar in terms of race, comorbidities, insurance type, tobacco use, receipt of neoadjuvant therapy, and laterality. All of the patients had breast malignancy, which was defined as invasive breast cancer (ductal, lobular, mucinous, tubular, and squamous cell carcinoma), ductal carcinoma in-situ, lymphoma, and malignant phyllodes. Thirty percent of all study patients underwent axillary dissection. Management of the axilla was not statistically different between the groups, although 70% of patients in the ERAS group and 60% in the UC group received sentinel lymph node biopsy, while 20% of patients in the ERAS group and 35% in the UC group underwent axillary lymph node dissection. See Table 1 for patient demographics and treatment details.

All of the patients in the ERAS group received all elements of the protocol, except for two patients who did not receive ketorolac at incision closure. None of the UC patients received ketorolac at incision closure, but almost 40% received liposomal bupivacaine mixture, although the application was not standardized in the UC group. Mean number of days in the hospital was approximately two days for both groups. Three patients in the ERAS group (15%) and one patient in the UC group (3%) went home on the day of surgery. Discharge on the day of surgery was documented as one hospital day, and discharge on postoperative day one was documented as two hospital days. Protocol adherence, along with the quantity of in-hospital and discharge opioids is shown in Table 2.

Table 1
Baseline and treatment characteristics of ERAS and UC groups.

Characteristic	ERAS (%)	Usual Care (%)	p value
Female	18 (90)	35 (94.6)	0.607
Race:			
Caucasian	4 (20)	9 (24)	0.822
African American	6 (30)	10 (27)	
Chinese	5 (25)	11 (30)	
Hispanic	1 (5)	1 (3)	
Middle Eastern	0 (0)	2 (5)	
Russian	4 (20)	2 (5)	
Other	0 (0)	1 (3)	
Insurance:			
Medicaid	6 (30)	10 (27)	0.872
Medicare	5 (25)	14 (38)	
Private	9 (45)	12 (32)	
Self-pay	0 (0)	1 (3)	
Comorbidity:			
Obesity	5 (25)	6 (16)	0.491
Cardiovascular[a]	8 (40)	21 (57)	0.274
Diabetes	6 (30)	8 (22)	0.530
Breast Cancer Diagnosis	20 (100)	37 (100)	1.000
Previous Breast Cancer	1 (5)	8 (22)	0.139
History of Other Malignancy	1 (5)	1 (3)	1.000
Tobacco Use:			
Current or Past	4 (2)	8 (22)	1.000
Unknown	0	1 (3)	
Received Neoadjuvant Therapy	5 (25)	12 (32)	0.371
Neoadjuvant Treatment Type:			
Chemotherapy	4 (20)	10 (27)	0.634
Endocrine Therapy	1 (5)	2 (5)	
Laterality:			
Right	12 (60)	13 (35)	0.480
Left	4 (20)	18 (49)	
Bilateral	4 (20)	6 (16)	
Axillary Surgery:			
Sentinel Node Biopsy	14 (70)	22 (60)	
Axillary Dissection	4 (20)	13 (35)	
None	2 (10)	2 (5)	0.364
Complications[b]	3 (15)	5 (14)	0.710

[a] Cardiovascular morbidity: hypertension, hyperlipidemia, coronary disease, arrhythmia, pulmonary embolus, deep venous thrombosis.
[b] Complication: hematoma, transfusion, postoperative infection, chronic seroma requiring intervention, ED visit or admission within 10 days postoperatively.

The ERAS cohort received a mean of 2.4 (0–13) OMEs while the UC cohort received 13.7 (0–80) ($p = 0.005$) during the hospital stay. Thirteen of 20 (65%) of the ERAS patients did not require any opioids during their hospital stay. Upon discharge, ERAS cohort received a mean of 2.0 (0–40) OMEs and the UC group received 59.8 (0–120) ($p < 0.001$) (see Table 2). All ERAS patients were discharged without an opioid prescription except for one patient, and this patient required several doses of parenteral analgesia on the postoperative floor. She was discharged with 40 OMEs, or eight tabs of oxycodone (5 mg each) in addition to alternating acetaminophen and ibuprofen. Therefore, 95% of the ERAS patients were discharged without an opioid prescription compared to 21% (8 of 37) UC patients. All of the UC patients discharged without an opioid prescription received intraoperative liposomal bupivacaine, although the method of administration was not standardized in the UC group.

The ERAS group reported a mean postoperative day one pain score of 3.1 (0–7), while the UC group reported 5.5 (0–10) ($p = 0.008$). Week one pain scores were 1.8 (0–5) in the ERAS group and 5.8 (2–10) ($p < 0.001$) in the UC group. When the two patient groups were analyzed with respect to management of the axilla, only pain scores in those who received sentinel node biopsies remained statistically different, with the postoperative day one pain scores being 2.8 (0–6) in the ERAS group and 6.1 (3–9) in the UC group ($p = 0.003$). Postoperative week one pain scores for those

Table 2
Protocol adherence and opioid use in ERAS and UC groups.

ERAS Study Element	ERAS N (% or range)	Usual Care N (% or range)	p value
Preoperative Medication:			
975 mg Acetaminophen	20 (100)	1 (3)	$p < 0.001$
300 mg Gabapentin	20 (100)	2 (5)	$p < 0.001$
Local Anesthetic with Liposomal Bupivacaine	20 (100)	14 (38)	$p < 0.001$
Ketorolac at Closure	18 (90)	0 (0)	$p < 0.001$
Mean Days in Hospital	2.1 (1–4)	2.3 (1–6)	$p = 0.588$
Mean Inpatient OMEs	2.4 (0–13)	13.7 (0–80)	$p = 0.002$
Mean Discharge OMEs	2.0 (0–40)	59.8 (0–120)	$p < 0.001$

OME: oral morphine equivalent.

undergoing mastectomy with sentinel node biopsy were 1.6 (0–5) in the ERAS group and 5.9 (3–10) in the UC group ($p < 0.001$). Day one and week one pain scores were lower in the ERAS group who underwent axillary dissection, but this difference was not significant (Table 3).

Postoperative complication rates were not significantly different between the two study groups. The ERAS group had three complications: one patient who was a heavy smoker experienced a wound dehiscence, one patient with an axillary hematoma required a blood transfusion, and one patient was admitted to the hospital on postoperative day 8 for a sepsis evaluation. Five UC patients experienced postoperative complications: two patients with hematoma required a blood transfusion, one patient experienced a postoperative infection requiring aspiration and oral antibiotics, and two patients were found to have chronic seroma formation.

Discussion

The results of the successful implementation of an opioid-sparing ERAS protocol for patients undergoing breast-conserving surgery was recently published.[4] Similar to the lumpectomy protocol, patients undergoing mastectomy in the present study received perioperative multimodal analgesia and were discharged without opioids. Despite dramatic reductions in opioid use (both inpatient administration and discharge prescription), pain scores were significantly lower in the ERAS cohort when compared to the control UC group. Pain control was not compromised with implementation of the opioid-minimizing ERAS protocol, and the superfluous opioid prescription at discharge was eliminated.

Complication rates were not different between the two groups. We observed one axillary hematoma in the ERAS group and two hematomas requiring transfusion in the UC group. None of the study patients needed reoperation for bleeding complications. Historically, the perioperative use of non-steroidal anti-inflammatory drugs such as ketorolac has been limited due to concerns regarding postoperative bleeding. Gobble et al. published a meta-analysis of 27 randomized controlled trials and found that bleeding was not significantly increased in a wide variety of procedures that utilized perioperative ketorolac.[6] The same meta-analysis also found that pain control was superior with ketorolac use. The present findings are concordant with this study. Although the FDA-approved intravenous dose of ketorolac is 30 mg, several prospective trials have demonstrated no difference in analgesic effect between 15 and 30 mg of ketorolac, and therefore 15 mg was the dose utilized in the present study.[7,8]

In the present protocol, a field block was performed using 1.3% liposomal bupivacaine mixed with 0.5% bupivacaine hydrochloride. Liposomal bupivacaine provides long acting, sustained-release local analgesia over at least 72 hours. It was first approved by the United States Food and Drug Administration in 2011 for post-surgical local analgesia, and more recently for use as a nerve block (interscalene brachial plexus block) to provide pain relief following shoulder surgery.[9,10] We did not observe any direct complications associated with the field block during our study, although careful attention should be paid to only injecting the peripheral aliquots right below the muscle fascial layer, as the risk of entering the thorax increases with deeper injection. Therefore, these injections should be performed below the mastectomy flaps under direct visualization. The injection into the pectoralis major muscle belly in the upper outer quadrant of the chest wall should also be carefully performed to limit the possibility of injury to the thoracoacromial artery running between pectoralis major and minor. It is important to note that in the present study, the 1.3% liposomal suspension was

Table 3
Postoperative day one and week one pain scores of ERAS and UC groups.

Postoperative Day One			
	ERAS	Usual Care	p value
Pain Scores Collected N (%)	18 (90)	15 (41)	n/a
All Mastectomy	3.1 (0–7)	5.5 (0–10)	$p = 0.008$
Mastectomy/SNB	2.8 (0–6)	6.1 (3–9)	$p = 0.003$
Mastectomy/AD	5 (4–7)	5 (0–10)	$p = 1.0$
Mastectomy without Axillary Surgery	1.5 (0–3)	$n = 0$	n/a
Postoperative Week One			
	ERAS	Usual Care	p value
Pain Scores Collected N (%)	19 (95)	13 (35)	n/a
All Mastectomy	1.8 (0–5)	5.8 (2–10)	$p < 0.001$
Mastectomy/SNB	1.6 (0–5)	5.9 (3–10)	$p < 0.001$
Mastectomy/AD	3.7 (2–5)	5.7 (2–10)	$p = 0.381$
Mastectomy without Axillary Surgery	0.5 (0–1)	$n = 0$	n/a

SNB: sentinel lymph node biopsy.
AD: axillary dissection.

combined with bupivacaine, but should never be combined with lidocaine. Lidocaine may cause immediate rupture of the liposomes in the liposomal bupivacaine, releasing all of the active ingredient designated for controlled release at once.[11]

ERAS protocols continue to gain acceptance across surgical subspecialties. A recent systematic review and meta-analysis reviewed the use of ERAS protocols in microsurgical breast reconstruction and found that the use of multimodal analgesia is feasible in this patient population, and complication rates are not increased with implementation in breast microsurgery. Although multimodal analgesia regimens were described, to date no study has shown the benefit of specific ERAS analgesics over others. Furthermore, there have not been any studies of patients undergoing mastectomy that have sought to completely eliminate the need for an opioid prescription at discharge.[12–15]

The present study is the first to report postoperative pain outcomes in patients undergoing mastectomy without reconstruction utilizing an opioid-minimizing multimodal ERAS protocol. Adherence to the protocol in the ERAS group was nearly 100%, which can be attributed to pre-implementation education of the medical staff involved, preoperative education of patients while in the office, and previous implementation of a similar protocol. Notably, an electronic medical record order set was created for both lumpectomy and mastectomy procedures during the design and implementation of the Breast Surgery ERAS protocols, which probably contributed to the success of the uptake, making the preoperative and postoperative medications regimens easy to order when the patient checks in for surgery.

Although the protocol was intended to eliminate the reflex opioid prescription at discharge for mastectomy patients, one patient in the ERAS group was sent home with an opioid prescription equivalent to 40 OMEs. Her care team later realized that she was likely a chronic opioid user. This dependence was not disclosed prior to her surgery; and she was included in the analysis. Including occult opioid-dependent patients makes the present study more applicable to the general population, as oftentimes the care team is not made aware of these issues prior to surgery although opioid dependence is becoming increasingly common.

The study's non-randomized multimodal approach makes it difficult to discern whether a particular element or a combination of protocol elements led to the lower pain scores in the ERAS group. While it may be tempting to assume that the use of liposomal bupivacaine attributed to the lower scores in the ERAS group, there was crossover during the study period in that some control group patients received liposomal bupivacaine during their mastectomies. However, the administration of the long-acting local anesthetic mixture was not standardized in the control group as it was in the ERAS group. Therefore, it is reasonable to assume that the multimodal approach to perioperative pain management played the most important role in lowering postoperative pain scores reported by the ERAS patients, and not necessarily a single element.

Collection of the postoperative pain scores was not 100% among the study participants. Non-collection was more common in the control group due to limitations in clinic staffing on days that the control group patients had their postoperative visits. This was partially accounted for by collecting missing postoperative day 1 scores through the nurse-reported score in the electronic medical record.

The results from the present study are encouraging and timely. The previous publication of the opioid-sparing ERAS protocol in lumpectomy patients in 2018 led to global implementation of the protocol within our Division of Breast Surgery, and almost 600 lumpectomy patients have been discharged without an opioid prescription in a 12-month period. Combined with the mastectomy

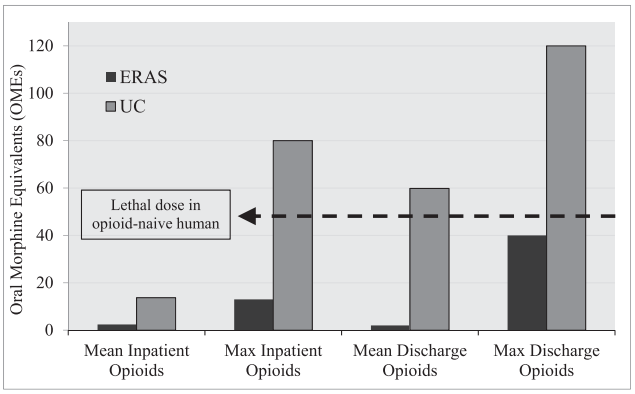


Fig. 3. Opioid use in ERAS and UC groups.

without reconstruction patients during the same period, approximately 660 breast surgery patients have been discharged without an opioid prescription. If 50 OMEs is a conservative estimate of a lethal opioid dose in an opioid-naïve human, universal implementation of the protocol has resulted in 36,288 less OMEs potentially diverted within our urban community in one year, which is equivalent to the dose required to kill more than 700 opioid-naïve humans. Fig. 3 compares the mean and maximum OMEs administered in the hospital and prescribed at discharge between the ERAS and UC mastectomy groups, and it is notable for the large differences between cohorts. Universal expansion of the opioid-sparing ERAS protocol to include all breast surgeons and all patients undergoing mastectomy without reconstruction has resulted in an even greater decrease of the contribution of opioids available for diversion within the Borough of Brooklyn.

The opioid epidemic continues to worsen and evolve.[16] On average, 130 Americans die every day from an opioid overdose.[17] Postoperative care is a common setting in which patients are first exposed to opioids. Bruomett et al. estimated that one in 16 patients become long-term users after surgery.[18] Furthermore, 45% of patients who do not take require an opioid on the last day of a surgical hospitalization are prescribed opioids at discharge. Superfluous opioid prescription increases the potential for development of addiction and provides opportunity for drug diversion.[19] Opioid-sparing multimodal analgesic regimens, along with a more tailored approach to determining necessity of postoperative opioid prescription at discharge can minimize the contribution that surgeons make to the opioid crisis.

The reflex discharge opioid prescription after mastectomy was eliminated in patients undergoing mastectomy without reconstruction. Compared to patients who received usual care, patients receiving the ERAS protocol required less opioids after surgery with significantly lower postoperative pain scores. Surgeons can take an active role in improving patient outcomes while decreasing the quantity of opioids available for diversion by promoting the adoption of similar protocols across the country.

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Conflicts of interest

Dr. P. Borgen has received speaker's honoraria from Pacira Pharmaceuticals, Inc. All other authors report no relevant commercial, financial, consultant, institutional conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.07.017.

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