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Intraoperative Ketorolac Is Associated With Risk of Reoperation After Mastectomy: A Single-Center Examination

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Abstract

Background.—Although ketorolac is an effective adjunct for managing pain in the perioperative period, it is associated with a risk of postoperative bleeding. This study retrospectively investigated the association between ketorolac use and both reoperation and postoperative opioid use among mastectomy patients.

Methods.—The study identified all women undergoing mastectomy (unilaterally or bilaterally) at our ambulatory surgery cancer center from January 2016 to June 2019. The primary outcome was reoperation for bleeding on postoperative day 0 or 1, and the secondary outcome was postoperative

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opioid use. The association between ketorolac and outcomes was assessed using multivariable regression models. The covariates were age, body mass index, breast reconstruction, bilateral surgery, peripheral nerve block, and preoperative antiplatelet and/or anticoagulation medication.

Results.—A cohort of 3469 women were identified. Ketorolac was given to 1549 (45 %) of the women, with 922 women (60 %) receiving 30 mg and 627 women (40 %) receiving 15 mg. The overall reoperation rate for bleeding was 3.1 % (1.8 % without ketorolac vs 4.8 % with ketorolac). In the multivariable analysis, ketorolac was associated with a higher risk of reoperation (odds ratio [OR], 2.43; 95 % confidence interval [CI], 1.60–3.70; $P < 0.0001$). Ketorolac also was associated with a lower proportion of patients receiving any postoperative narcotic within 24 h (15 mg: OR, 0.73; 95 % CI, 0.57–0.94; $P = 0.014$ vs 30 mg: OR, 0.52; 95 % CI, 0.42–0.66; $P < 0.0001$).

Conclusions.—Ketorolac use decreased postoperative opioid use, but this benefit was outweighed by the increased risk of bleeding requiring reoperation. This finding led to a change in practice at the authors' center, with ketorolac no longer administered in the perioperative care of the mastectomy patient.

Opioid use in the perioperative period continues to be highly scrutinized given the continued opioid epidemic. For the breast cancer patient undergoing mastectomy, enhanced recovery after surgery (ERAS) protocols are used to address the goal of improved pain control through multimodal techniques. Such pathways, which commonly use non-narcotic agents to provide analgesia, have gained significant traction and attention.[1–4] Ketorolac, a potent, injectable, non-narcotic, non-steroidal anti-inflammatory analgesic, is an effective adjunct for managing pain in the perioperative period.

Ketorolac has become a popular addition to ERAS protocols for many types of surgery despite concerns for its association with postoperative bleeding. Ketorolac, like other non-steroidal anti-inflammatory drugs (NSAIDs), is a cyclooxygenase inhibitor. The inhibition of cyclooxygenase has been linked to slow bone healing, poor postoperative kidney function, and increased perioperative bleeding.[5]

A recent study of 157 lumpectomy and 57 mastectomy patients without reconstruction found no association between ketorolac use and postoperative bleeding.[6] A meta-analysis of randomized controlled trials including 2314 patients also found no association. However, none of the trials included mastectomy patients.[7] Evidence for the safety of ketorolac administered to mastectomy patients is thus limited.

The Memorial Sloan Kettering Cancer Center (MSKCC) Josie Robertson Surgery Center is a freestanding ambulatory surgery center created for ambulatory extended recovery surgery patients that allows for a single overnight stay after surgery. At its opening in 2016, our facility instituted ERAS protocols for all common cancer surgeries.[8] The initial ERAS protocol for mastectomy with or without implant-based reconstruction included one intraoperative dose of intravenous ketorolac.

After 2½ years of applying our ERAS protocol for mastectomy, we sought to determine whether ketorolac is associated with subsequent reoperation for bleeding. We conducted a retrospective study of the association between ketorolac use and reoperation in the mastectomy cohort. Our primary hypothesis was that ketorolac use is associated with

reoperation risk. We also evaluated whether ketorolac is associated with postoperative opioid requirements.

METHODS

This retrospective observational study was approved by the Institutional Review Board of MSKCC. A prespecified analysis plan was agreed upon before statistical work began.

We identified all patients who underwent a uni- or bilateral mastectomy with or without immediate tissue expander or implant reconstruction at the ambulatory surgical center between January 2016 and June 2019. Patients were excluded if they were male, had a concurrent gynecologic procedure, or did not receive general anesthesia. If a patient had a contralateral mastectomy performed as a separate procedure, we included only the first unilateral mastectomy.

All demographic, surgical, and outcome data were retrieved from the institutional data warehouse. The existence of antiplatelet and anticoagulation home medication prescriptions was extracted from the medication reconciliation performed the morning of surgery. Antiplatelet and anticoagulation medication was held for several days before surgery as per local guidelines. Preoperative hematocrit was measured at the presurgical testing clinic when indicated by local presurgical testing guidelines. Use of a peripheral nerve block, intraoperative ketorolac dose, or intraoperative fentanyl dose was retrieved from the anesthesia record. The electronic medication administration record was used to calculate the total opioid dose during the patient's recovery period, which was converted to oral morphine milligram equivalents (MMEs).[9]

The primary outcome was reoperation, determined by examining operating room records for any subsequent urgent surgical case managed on postoperative day 0 or 1. The secondary outcome was postoperative narcotic usage, determined from the electronic medication administration record.

Clinical Protocols

Our facility ERAS protocols have been described in detail elsewhere and are briefly reviewed here.[10] Mastectomy patients are educated on the enhanced recovery pathway, beginning in the surgeon's office. Postoperative nausea risk is evaluated, and patients at high risk are given aprepitant preoperatively. Patients who elect for immediate reconstruction are given the option of preoperative paravertebral peripheral nerve blocks with or without fascial plane blocks.

Preoperative oral gabapentin 300 mg is administered to patients younger than 65 years. Patients are encouraged to drink clear liquids up to 2 h before their scheduled arrival. Patients receive a general anesthetic with either volatile anesthetic or total intravenous anesthetic at the anesthesiologist's discretion. Patients are given dexamethasone 4 mg intravenously (IV), ondansetron 4 mg IV, and acetaminophen 1 g IV. Intraoperative ketorolac IV is administered at the beginning of surgical closure, after reaffirmation of its use with the surgeon at that time.

Although ketorolac administration is part of the ERAS protocol, it is routinely avoided by some surgeons due to concerns about bleeding and selectively used by other surgeons depending on the degree of difficulty obtaining hemostasis. The dose is 30 mg IV unless the patient is older than 60 years or has renal impairment (glomerular filtration rate [GFR] between 30 and 60), in which case a 15-mg dose is used. Ketorolac is not given to patients reporting an allergy to any NSAID.

Surgical wound checks are performed in a uniform fashion for all patients. The postanesthesia care unit (PACU) nursing staff checks the surgical wound and surgical drains upon the patient's admission and postoperatively every hour during the PACU phase of care. Wound checks also are performed upon transfer of care (staff break or shift change) every 4 h during the post-PACU phase of care and at discharge. Wound concerns are referred to the advanced practice nurses and surgical providers (physician assistants or physicians). The surgical team checks all patients 4 h after surgery and before discharge, usually the morning after surgery.[11]

Postoperative pain management follows standing orders of opioid analgesia for moderate to severe pain and transitions to oral non-opioid analgesics with acetaminophen or diclofenac for moderate pain or less.

Statistical Analysis

We tested for an association between the risk of reoperation and ketorolac use (no ketorolac use vs 15 mg vs 30 mg) using a multivariable logistic regression model adjusted for age, body mass index (BMI), bilateral mastectomy procedure, use of immediate reconstruction, and preoperative prescription for an anticoagulant or antiplatelet medication. We tested whether the effect of ketorolac on reoperation differed by use of reconstruction or bilateral procedure via testing of added interaction terms in the multivariable model. We calculated the 95 % confidence interval (CI) for the adjusted risk difference using the delta method.

For the secondary hypothesis, we tested for an association between ketorolac use (no ketorolac use vs 15 mg vs 30 mg) and receipt of any opioid (intravenous or oral) within first 24 h postoperatively with a multivariable logistic regression model, adjusting for age, BMI, use of immediate reconstruction, bilateral procedure, and receipt of a peripheral nerve block. A binary outcome of postoperative opioid receipt was used instead of the MME dose because the distribution of postoperative MMEs was highly skewed right. All analyses were performed using Stata 15 (StataCorp, College Station, TX, USA).

RESULTS

The study identified 3567 patients who underwent 3591 mastectomy procedures at the ambulatory surgery center between January 2016 through June 2019. We excluded 65 male patients, 2 patients who did not receive general anesthesia, and 28 patients who had a concurrent gynecology procedure. Of the remaining patients, 22 underwent a subsequent metachronous contralateral mastectomy, and the second procedure for these patients was excluded. Ketorolac dosing information was missing for three patients, who were excluded

from the analysis. The final analysis set contained 3469 patients (1686 unilateral, 1783 bilateral).

Ketorolac was administered to 1549 of the patients (45 %). The characteristics of the patients are presented in Table 1. The patient characteristics grouped by reconstruction status are summarized in Supplementary Digital Content 1 as well as in Tables 1 and 2. The patients who underwent bilateral mastectomy, immediate tissue expander, or implant reconstruction and received a preoperative nerve block were less likely to receive ketorolac (all P values <0.0001). Otherwise, the patient characteristics were similar between the groups.

Among the patients who received ketorolac, 60 % received 30 mg and 40 % received 15 mg. The patients who were older, treated in earlier years, managed with a unilateral procedure, and treated with a shorter surgery tended to receive the lower dose (all P values ≤0.0001; Table 2). The high-dose ketorolac group more commonly had nerve blocks (60 % vs 53 %; P = 0.012) and more frequently underwent reconstruction (68 % vs 62 %; P = 0.039).

The overall risk of reoperation was 3.1 % (n = 109). Reoperation was performed for 74 patients (4.8 %) who received ketorolac and 35 patients who did not (1.8 %). The patients who underwent bilateral surgery did not have a significantly different risk of reoperation than those who underwent unilateral surgery (increased risk among unilateral cases was 0.6 %; 95 % CI, −0.6 % to 1.7 %). The risk of reoperation was higher among the patients without breast reconstruction (5 %) than among those with reconstruction (2.5 %) (risk difference, 2.5 %; 95 % CI, 0.9–4.0 %). The likelihood of receiving ketorolac was 20 % (95 % CI, 16–23 %) higher for the patients without breast reconstruction than for those with reconstruction.

The proportion of patients who received any opioids within the first postoperative 24 h was 88 % among those who did not receive ketorolac, 79 % among those who received 15 mg of ketorolac, and 80 % among those who received 30 mg of ketorolac. In the multivariable model, ketorolac was associated with a decrease in the proportion of patients receiving any opioids within the first postoperative 24 h (15 mg: odds ratio [OR] 0.73; 95 % CI, 0.57–0.94; P = 0.014 vs 30 mg: OR, 0.52; 95 % CI, 0.42–0.66; P < 0.0001). Outcomes grouped by use of intraoperative ketorolac are summarized in Supplemental Digital Content 1 and Table 3. In the multivariable analysis, the use of ketorolac was associated with an increased risk of reoperation after adjustment for age, BMI, breast reconstruction, bilateral surgery, antiplatelet medication and anticoagulation medication (OR, 2.43; 95 % CI, 1.60–3.70; P < 0.0001; Table 3). The risk of reoperation did not differ significantly between the doses (15 vs 30 mg: OR, 1.45; 95 % CI, 0.88–2.39; P = 0.14). For the outcome of reoperation, no evidence was found for an interaction between ketorolac use and reconstruction status (P = 0.6), nor between ketorolac use and bilateral procedure (P = 1.0).

Table 4 presents the predicted risk of reoperation for a typical patient (age, 52 years; BMI, 26 kg/m^2, bilateral procedure, and no antiplatelet or anticoagulation medication) separately by ketorolac and reconstruction status.

We noted that patients who received ketorolac were 12 % more likely to have received diclofenac before reoperation (60 % vs 72 %; $P < 0.0001$). To assess whether the association between ketorolac and risk of reoperation was modified by use of diclofenac in the PACU, we added receipt of diclofenac as a covariate to the multivariable logistic regression model and repeated the primary analysis. After adjustment for diclofenac use, ketorolac remained associated with an increased risk of reoperation, with an estimated increase in odds of 3.66 (95 % CI, 2.38–5.62; $P < 0.0001$).

Both the administration of ketorolac and the risk of reoperation could be related to the individual surgeon. Surgeons have different thresholds for reoperation and vary in surgical technique. To address this source of bias, we performed sensitivity analyses to adjust for surgeon and propensity to receive ketorolac. The results of these analyses did not change our findings (see Supplementary Digital Content 2 for details).

DISCUSSION

This retrospective cohort study of mastectomy patients in an ERAS program at an ambulatory surgery center found that the use of intraoperative ketorolac was associated with increased reoperation for bleeding and decreased postoperative opioid use. We believe the analgesic benefits of ketorolac are not sufficient to offset the increased risk of bleeding for mastectomy patients with or without reconstruction. For a typical mastectomy patient, the increase in risk of reoperation was 4.0 % (95 % CI, 1.8 %–6.2 %) without reconstruction and 2.2 % (95 % CI, 0.95–3.4 %) with reconstruction. The association of ketorolac with higher rates of reoperation has changed our practice, and we have discontinued the use of ketorolac during mastectomy procedures.

In the past decade, research has been published both for and against an association between ketorolac use and postoperative bleeding. A meta-analysis by Gobble et al.[7] of 27 randomized clinical trials enrolling 2314 patients across a wide range of surgical specialties reported no association (OR, 1.10; 95 % CI, 0.61–2.06; $P = 0.7$), but none of those studies included mastectomy procedures. A subset analysis of 214 patients in a prospective study of ERAS for mastectomy and lumpectomy also reported no association.[6] A meta-analysis of 981 plastic surgery patients found no statistically significant association between ketorolac and bleeding.[12] However, another meta-analysis focused on tonsillectomy studies found that the relative risk of postoperative bleeding in adults was 5.64 (95 % CI, 2.08–15.27; $P < 0.001$) despite the inclusion of five randomized clinical trials enrolled in the Gobble meta-analysis.[13] Also, a two-institution study of reduction mammaplasty procedures reported an increased risk of reoperation for patients who had received ketorolac (relative risk [RR], 3.6; 95 % CI, 1.4–9.6).[14] This study was similar to ours in both the magnitude of the finding and the motivation to study the association due to a suspected increase in reoperation for bleeding.

We expect one additional reoperation for patients treated with ketorolac versus those treated without ketorolac for every 25 patients (1/4.0 %) undergoing mastectomy without reconstruction and every 45 patients (1/2.2 %) undergoing mastectomy with reconstruction.

Although this study found that ketorolac was associated with a decreased need for any opioid during the first 24 h after surgery, the magnitude of the impact was not large.

To date, this retrospective study is the largest analysis of the association between ketorolac use and reoperation among mastectomy patients. Naturally, the key consideration is whether the observed association is causal. The decision process used by our surgeons for taking a patient back to the operating room for reoperation is affected by a number of unmeasured factors.

Although this decision process may differ from that used by other breast and plastic surgery groups, it is highly unlikely that it was influenced by whether a patient received ketorolac or not. We therefore discount bias in the end point as an explanation of our findings. It also is possible that differences in outcome reflect differences between the patients who did and those who did not receive ketorolac. There were differences in some measured confounders, with patients who received ketorolac less likely to undergo a bilateral procedure, less likely to undergo reconstruction, and less likely to be taking anticoagulant medications at home. In the case of reconstruction, we demonstrated that the association between ketorolac and reoperation was similar irrespective of reconstruction status. The other factors were not strongly associated with outcome.

Additional sensitivity analyses addressing surgeon variation found a stronger association than the primary analysis, providing additional supportive evidence for the harm of ketorolac. These analyses suggested that bias due to differences among surgeons does not account for the result. In fact, the tendency among surgeons to withhold ketorolac when concerned about the risk of bleeding would result in an underestimate of the true risk for reoperation.

The estimated effect of ketorolac was large enough to make it highly unlikely that an unmeasured confounder strongly associated with ketorolac, unassociated with measured confounders, and with a sufficient effect on reoperation exists to explain the observed association. We therefore conclude that a causal effect is the best explanation for our findings.

We deliberately chose the outcome of reoperation for bleeding instead of a more common outcome such as hematoma formation because reoperation is a more objective outcome with clear associated costs. Hematoma formation and other bleeding outcomes are more subjective.

Our experience emphasizes the importance of analyzing data after the implementation of ERAS programs to ensure that important benchmarks such as reoperation, transfer, and readmission meet expectations. If these expectations are not met, the design or implementation of the ERAS program needs to be altered.

The surgical and anesthetic leadership at our ambulatory surgery center considered it not feasible to enroll patients in a multi-year randomized controlled trial to establish causation. Instead, the decision was made to stop administering ketorolac during mastectomy surgery. To date, our group has not pursued a multicenter retrospective study, as suggested in a

recent editorial on the study of low-incidence perioperative complications.[15] Future analyses will examine whether the reoperation risk has declined as we expect. Mastectomy ERAS programs should strongly consider withholding intraoperative ketorolac and continue to track reoperation rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

Ketorolac is a potent analgesic that can increase the risk of postoperative bleeding. This large retrospective study found an association between intraoperative ketorolac use and risk of reoperation after mastectomy.

TABLE 1

Patient characteristics by receipt of ketorolac[a]

Characteristic	No ketorolac (*n* = 1920, 55 %) *n* (%)	Ketorolac (*n* = 1549, 45 %) *n* (%)	*P* Value[b]
Ketorolac dose given (mg)			
0	1920 (100)	0 (0)	
15	0 (0)	627 (40)	
30	0 (0)	922 (60)	
Female	1920 (100)	1549 (100)	
Age at surgery: years (IQR)	50 (42–60)	51 (43–60)	0.3
BMI: kg/m^2 (IQR)	25 (22–30)	25 (22–29)	0.073
ASA score			
1	25 (1.3)	16 (1.0)	0.2
2	1081 (56)	919 (59)	
3	812 (42)	614 (40)	
4	2 (0.1)	0 (0)	
Year of surgery			
2016	515 (27)	387 (25)	0.007
2017	508 (26)	435 (28)	
2018	555 (29)	505 (33)	
2019	342 (18)	222 (14)	
Surgery approach type			
Bilateral	1072 (56)	711 (46)	<0.0001
Unilateral	848 (44)	838 (54)	
Breast reconstruction	1552 (81)	1014 (65)	<0.0001
Peripheral nerve block	1368 (71)	887 (57)	<0.0001
Operating room time: min (IQR)	181 (146–218)	154 (120–190)	<0.0001
Antiplatelet medication	144 (7.5)	103 (6.6)	0.4
Anticoagulation medication	36 (1.9)	11 (0.7)	0.003
Preoperative hematocrit (*n* = 1618): % (IQR)	37 (34–40)	37 (34–39)	0.063
Intraoperative fentanyl	1832 (95)	1491 (96)	0.2
Postoperative diclofenac Before any reoperation	1155 (60)	1118 (72)	<0.0001
Total intraoperative opioids: MME (IQR)	30.0 (20.0–45.0)	30.0 (20.0–44.0)	0.075

IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; MME, oral morphine milligram equivalent

[a]Data are presented as median (IQR) or frequency (%).

[b]*P* values were determined by Wilcoxon rank sum for continuous variables and Fisher's exact test for categorical variables.

TABLE 2

Patient characteristics by ketorolac dose among those receiving ketorolac[a]

Characteristic	Ketorolac 15 mg (*n* = 627, 40 %) *n* (%)	Ketorolac 30 mg (*n* = 922, 60 %) *n* (%)	*P* Value[b]
Female	627 (100)	922 (100)	
Age at surgery: years (IQR)	59 (46–68)	48 (42–55)	<0.0001
BMI: kg/m^2 (IQR)	25 (22–29)	25 (22–29)	0.5
ASA score			
1	8 (1.3)	8 (0.9)	0.5
2	362 (58)	557 (60)	
3	257 (41)	357 (39)	
Year of surgery			
2016	195 (31)	192 (21)	<0.0001
2017	151 (24)	284 (31)	
2018	197 (31)	308 (33)	
2019	84 (13)	138 (15)	
Surgery approach type			
Bilateral	239 (38)	472 (51)	<0.0001
Unilateral	388 (62)	450 (49)	
Breast reconstruction	391 (62)	623 (68)	0.039
Peripheral nerve block	335 (53)	552 (60)	0.012
Operating room time: mins (IQR)	146 (113–185)	161 (125–193)	<0.0001
Antiplatelet medication	69 (11)	34 (3.7)	<0.0001
Anticoagulation medication	9 (1.4)	2 (0.2)	0.010
Preoperative hematocrit (*n* = 682): % (IQR)	38 (34–40)	36 (33–39)	0.0002
Intraoperative fentanyl	593 (95)	898 (97)	0.006
Postoperative diclofenac Before to any reoperation	425 (68)	693 (75)	0.002
Total intraoperative opioids: MME (IQR)	30.0 (20.0–40.0)	30.0 (20.0–45.0)	0.008

IQR, interquaratile range; BMI, body mass index; ASA, American Society of Anesthesiologists; MME, oral morphine milligram equivalent

[a]Data are presented as median (IQR) or frequency (%).

[b]*P* values were determined by Wilcoxon rank sum for continuous variables and Fisher's exact test for categorical variables.

TABLE 3

Multivariable logistic regression to predict the risk of reoperation

Variable	OR	95 % CI	*P* Value
Ketorolac given	2.43	1.60–3.70	<0.0001
Age at surgery (per year)	0.99	0.97–1.01	0.3
BMI (per kg/m^2)	1.02	0.99–1.06	0.2
Bilateral surgery	1.02	0.67–1.56	0.9
Breast reconstruction	0.52	0.33–0.81	0.004
Antiplatelet medication	0.84	0.37–1.90	0.7
Anticoagulation medication	0.67	0.09–5.05	0.7

OR, odds ratio; CI, confidence interval; BMI: body mass index

TABLE 4

Predicted risk (%) for a patient age 52 years with a BMI of 26 kg/m^2 who underwent bilateral surgery and was not previously receiving antiplatelet or anticoagulation medication corresponding to the multivariable logistic regression model illustrated in Table 3[a]

	No ketorolac % (95 % CI)	Ketorolac % (95 % CI)	Adjusted difference % (95 % CI)
No reconstruction	3.0 (1.4–4.6)	7.0 (4.1–9.9)	4.0 (1.8–6.2)
Reconstruction	1.6 (0.95–2.2)	3.7 (2.4–5.1)	2.2 (0.95–3.4)

BMI, body mass index; CI, confidence interval

[a]The adjusted difference represents the increase in risk of reoperation associated with receiving ketorolac, with confidence intervals calculated using the delta method.