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ORIGINAL ARTICLE – BREAST ONCOLOGY

Intraoperative Ketorolac Use Does Not Increase the Risk of Bleeding in Breast Surgery

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ABSTRACT

Background. The use of nonsteroidal anti-inflammatory drugs is an effective adjunct in managing perioperative pain. We sought to determine if the use of intraoperative ketorolac as part of a multimodal ERAS protocol increased the risk of bleeding complications in breast surgery.

Methods. A subset analysis of a prospective cohort study including patients undergoing lumpectomy and mastectomy compared two groups: those who received intraoperative ketorolac and those who did not. Bleeding complications were compared using Fisher's exact test or *t* test, and analyzed with respect to surgical modality. Patients undergoing immediate reconstruction were excluded.

Results. Seven hundred and fifty-eight breast surgeries were performed in a 13-month period: 157 lumpectomy patients and 57 mastectomy patients met inclusion criteria between July 2017 and August 2018. Two hundred and fourteen patients were included in the analysis: 115 received ketorolac and 99 did not. The two groups were similar with regards to sex, age, race, tobacco use, and comorbidities. When analyzed together, there was no difference in bleeding complications between the group that received intraoperative ketorolac and those who did not (2% vs. 2.6%, $p = 1.00$). No hematomas occurred in the lumpectomy patients, and three occurred in mastectomy patients: one of which received ketorolac, and two did not (5.9% vs. 5.0%, $p = 0.575$). The rates of seroma, infection, or dehiscence were not significantly different between the two groups, regardless of surgical modality.

Conclusions. The use of intraoperative ketorolac is a useful adjunct in perioperative pain management in breast surgery and does not increase the risk of bleeding.

Suboptimal pain control can worsen the quality of recovery and increase postoperative complications.[1] The use of Enhanced Recovery After Surgery (ERAS) protocols has gained popularity among multiple surgical specialties. The goals of most multidisciplinary protocols are expediting recovery, decreasing opioid use, and improving satisfaction with care. ERAS protocols typically include multimodal analgesia components and non-steroidal anti-inflammatory drugs (NSAIDs) like ketorolac or ibuprofen.[2]

Although a meta-analysis of randomized controlled trials found that postoperative bleeding was not significantly increased with the use of ketorolac, the use of perioperative NSAIDs sometimes elicit strong negative opinions from surgeons due to the fear of bleeding complications.[3] We sought to determine if the use of intraoperative ketorolac increases the incidence of bleeding complications in breast surgery.

METHODS

The methods for implementation of our institution's opioid-sparing ERAS protocol for patients undergoing lumpectomy has been previously described.[2] A similar protocol has been employed in patients undergoing mastectomy without reconstruction. In short, the protocol was designed to expedite return to equilibrium and includes enhanced preoperative counseling, pre- and intraoperative

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use of multimodal analgesia including intravenous ketorolac and liposomal bupivacaine, and postoperative scheduled ibuprofen and acetaminophen.

A subset analysis of the previously described prospective cohort study (IRB #2017-09-29) including patients undergoing lumpectomy and mastectomy was performed. In the primary study, two breast surgeons adopted the ERAS protocol, which included an intravenous injection of 15 mg of ketorolac during incision closure. A third breast surgeon proceeded with usual care. Patients undergoing lumpectomy with and without preoperative localization and re-excision were included in the study as "lumpectomy" patients. Patients undergoing mastectomy without reconstruction were also included in the study and called "mastectomy" patients. Patients with and without malignancy, and those who received prior chemotherapy and radiation were also included. Patients who were on prophylactic or therapeutic anticoagulation were also included in the present analysis, but anticoagulation was stopped 5 days prior to surgery and resumed on postoperative day 2. Patients receiving immediate reconstruction were excluded.

The subset analysis of the data revealed that a small proportion of patients who received the ERAS protocol did not receive ketorolac, and a similarly small proportion of patients in the UC group did receive ketorolac. Therefore, for the present analysis, the two arms were determined by whether or not they received intraoperative ketorolac, and both groups included lumpectomy and mastectomy patients.

A database was developed using Microsoft Excel (Microsoft® Excel® for Mac 2011 v. 14.1.0) to collect patient demographics and surgical outcomes. Demographics including race, insurance type, comorbidities, tobacco use, surgical modality, laterality, and presence of malignancy were collected. Malignancy was defined as invasive breast cancer (including ductal, lobular, mucinous, tubular, and squamous cell carcinoma), ductal carcinoma in situ, lymphoma, and malignant phyllodes. Postoperative infection was defined as receiving a prescription for antibiotics within 30 days after surgery.

The primary outcome was bleeding complications, which was defined as clinically significant bruising noted in the medical record, or hematoma formation, which may have required readmission to the hospital or postoperative ultrasounds. Secondary outcomes included seroma formation requiring aspiration, infection, and dehiscence.

Complications were compared between the two groups using Fisher's exact test or t-test, and further analyzed with respect to surgical modality. p values < 0.05 were considered statistically significant. A regression analysis was planned to determine if the dose of ketorolac, surgical modality, injection of liposomal bupivacaine, or presence of malignancy increased the risk of bleeding complications. At the time of the original analysis, the study institution did not have an in-house statistician, so this was outsourced to an outside statistician (Peter Flom Consulting).

RESULTS

In total, 758 breast surgeries were performed at a single institution in a 13-month period: 157 lumpectomies met inclusion criteria between July 2017 and February 2018 and of 153 mastectomies, 57 met inclusion criteria between September 2017 and August 2018. Data collection continued after February 2018 in order to increase the number of mastectomy without reconstruction patients in the study cohort. Two hundred and fourteen patients were included in the total cohort: 115 received intravenous intraoperative ketorolac and 99 did not. The two groups were similar with regards to age, race, tobacco use, and comorbidities. A larger proportion of patients in the no ketorolac group underwent mastectomy (40.4% v. 14.8%, $p < 0.001$), and a larger proportion of patients in the no ketorolac group had cancer (76.8% v. 53%, $p < 0.001$). There was not a significant difference in the rates of baseline anticoagulation use between the two study groups. More patients in the ketorolac group received preoperative acetaminophen, gabapentin, and subcutaneous infiltration with liposomal bupivacaine since most of the patients who received ketorolac also received the other elements of the institutional opioid-sparing ERAS protocol ($p < 0.001$). Although the protocol stipulated a 15 mg dose of ketorolac, review of the medical record found that 59 (51.3%) received 15 mg of intraoperative ketorolac, and 56 (48.7%) received 30 mg of ketorolac (Table 1).

Analyzed together, there was no difference in the rate of bleeding complications between the group that received intraoperative ketorolac and the group that did not (2.6% vs. 2.0%, $p = 1.00$). There was a greater incidence of hematomas in the group that did not receive ketorolac, although the difference was not significant. Complications were low in both groups. The rates of seroma formation, infection, or dehiscence were not significantly different between the two groups, regardless of surgical modality (Fig. 1, Table 2).

When analyzed with respect to surgical modality (lumpectomy vs. mastectomy), no hematomas occurred in patients who underwent lumpectomy. There was one lumpectomy patient with clinically significant bruising in the group that received ketorolac, but this was managed conservatively. Three hematomas occurred in mastectomy patients: two that did not receive ketorolac and one that did

TABLE 1 Patient demographics and treatment

N (% or range)	No Ketorolac *n* = 99	Ketorolac *n* = 115	*p* value
Female	97 (98.0)	111 (96.5)	0.688
Mean age (range)	59.8 (20–94)	55.9 (16–88)	0.058
	SD = 14.0	SD = 15.2	
Race			
Caucasian	41 (41.4)	60 (52.2)	0.273
African American	33 (33.3)	29 (25.2)	
Hispanic	5 (5.1)	7 (6.1)	
Chinese	15 (15.2)	10 (8.7)	
Middle Eastern	5 (5.1)	9 (7.8)	
Insurance type			
Medicare	40 (40.4)	63 (54.8)	0.374
Medicaid	24 (24.2)	21 (18.3)	
Private	28 (28.3)	22 (19.1)	
1199	3 (3.0)	6 (5.2)	
Self-pay	6 (2.0)	1 (0.9)	
Unknown	2 (2.0)	2 (1.7)	
Comorbidities			
Any comorbidity	60 (60.6)	59 (51.3)	0.214
Cardiovascular	50 (50.5)	46 (40.0)	0.132
Diabetes	16 (16.2)	19 (16.5)	1.000
Obesity	9 (9.1)	15 (13.0)	0.393
Baseline anticoagulation use			
Any	9 (9.1)	14 (12.2)	0.468
Aspirin 81 mg	8 (8.1)	14 (12.2)	0.326
Other anticoagulation	1 (1.0)	1 (0.9)	0.967
Tobacco use			
No/never	71 (71.7)	90 (78.3)	0.341
Current/past	28 (28.3)	25 (21.7)	
Surgery type			
Lumpectomy	59 (59.6)	98 (85.2)	< 0.001
Mastectomy	40 (40.4)	17 (14.8)	
Proportion with malignancy			
All	76 (76.8)	61 (53.0)	< 0.001
Lumpectomy	36 (61.0)	46 (46.9)	0.101
Mastectomy	40 (100)	17 (100)	1.000
Laterality			
Unilateral	91 (91.9)	107 (93.1)	0.883
Bilateral	8 (8.1)	8 (7.0)	
Axillary management			
None	37 (37.4)	70 (60.9)	< 0.001
Sentinel node biopsy	46 (46.5)	40 (34.8)	
Axillary dissection	16 (16.2)	5 (4.4)	
Perioperative management			
Preoperative acetaminophen	15 (15.2)	90 (78.3)	< 0.001
Preoperative gabapentin	15 (15.2)	87 (75.7)	< 0.001
Liposomal bupivacaine	29 (29.3)	93 (80.9)	< 0.001

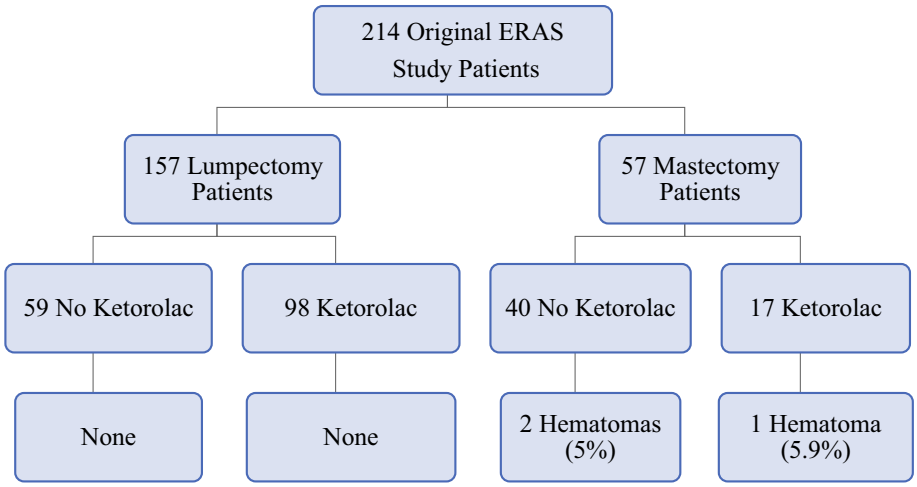

FIG. 1 Treatment groups and hematoma rates

TABLE 2 Complications among all patients (lumpectomy and mastectomy combined)

	No Ketorolac $n = 99$	Ketorolac $n = 115$	p value
Seroma	2 (2.0)	1 (0.9)	0.597
Infection	1 (1.0)	0 (0)	0.463
Dehiscence	1 (1.0)	0 (0)	0.789
Bruising	0 (0)	2 (1.7)	0.501
Hematoma	2 (2.0)	1 (0.9)	0.597
Any bleeding complication[a]	2 (2.0)	3 (2.6)	1.000
Any major complication[b]	6 (6.1)	4 (3.5)	0.519

[a]Bleeding complication includes clinically significant bruising or hematoma

[b]Major complication includes seroma, infection, dehiscence, clinically significant bruising, or hematoma

(5.0% vs. 5.9%, $p = 0.575$ for mastectomy.) All hematomas were managed non-operatively but required blood transfusion.

There were too few bleeding complications within the study cohort to determine if surgery type, presence of malignancy, or infiltration of liposomal bupivacaine increased the risk of bleeding complications. However, the likelihood of a bleeding complication does not seem to be related to the dose of intravenous ketorolac administered, since all of patients in the ketorolac group who had a bleeding complication received 15 mg of ketorolac, and none of the patients who received 30 mg of ketorolac had a bleeding complication.

DISCUSSION

Intraoperative ketorolac was not associated with an increased rate of bleeding complications in patients undergoing breast surgery. None of the patients who received 30 mg of ketorolac had a bleeding complication. The dose of 15 mg was chosen for our institution's ERAS protocol since prospective data has demonstrated a similar analgesic effect between 15 and 30 mg. A prospective, randomized noninferiority clinical trial of 50 patients undergoing spine surgery compared the effectiveness of an intraoperative dose of 15 mg with the traditional 30-mg dose. The investigators found that 30 mg of intravenous ketorolac was not superior to the 15-mg dose, although the study did not meet its prespecified definition of non-inferiority.[4] Motov et al.[5] assessed the analgesic efficacy of three single-dose regimens of ketorolac (10, 15, and 30 mg) for treating acute pain in patients in the emergency department. The investigators found that the different doses had similar analgesic efficacy.

One of the goals of our Division's Breast Surgery ERAS protocol is to decrease the amount of prescribed narcotics without compromising postoperative pain control. We have previously described that perioperative opioid use may impair immune response and increase tumor angiogenesis.[6–9] A large population-based study comparing epidural analgesia versus traditional pain management in patients undergoing colectomy found that oncologic outcomes may be inferior in patients who receive perioperative opioids.[10] Tempering the systemic inflammatory response to surgery with perioperative NSAIDs may be similarly beneficial. Retrospective data suggests that patients undergoing surgery for non-small cell lung cancer who receive postoperative NSAIDs have lower rates of recurrence and longer overall survival.[11,12] Similar findings have been reported in the breast surgery literature, demonstrating lower rates of early relapse in breast cancer patients who do not receive perioperative NSAIDs.[13,14] Retsky et al.[15] suggested that transient systemic inflammation in surgery could facilitate angiogenesis of dormant micrometastases and seeding of circulating cancer cells. Finally, a 2017 meta-analysis involving approximately 300,000 patients from 16 studies

confirmed the antineoplastic effects of NSAIDs in breast, prostate, lung, and colorectal patients, regardless of whether NSAIDs were used pre- or post-diagnosis.[16]

Inflammation is a major component of the tumor microenvironment, and inflammatory oncotaxis, or tumor growth at the site of inflammation, has been seen in patients with known or occult cancer who undergo local trauma.[17] The surgical local and systemic inflammatory response may contribute to tumor growth and metastasis, and the use of NSAIDs during this time period may attenuate this effect through anti-COX2 and anti-prostaglandin (PGE2) mechanisms. PGE2 is the only prostanoid that has demonstrated a role in tumor development, progression, and metastasis. PGE2 is also a transactivator of the epidermal growth factor receptor (EGFR) pathway, which is related to the promotion of tumor growth.[18] NSAIDS may also exhibit COX-independent antineoplastic activity through inhibition of tumor-promoting NF-KB (nuclear factor kappa-light-chain-enhancer of activated B-cells), and disruption of transforming growth factor beta 1 (TGF-β) signaling.[18–20] Although not all of the patients in the present study had breast cancer, the ability to attenuate systemic inflammation and improve postoperative pain using ketorolac as a nonopioid adjunct was not found to have deleterious effects.

Our results are in line with previous studies using NSAIDs in breast surgery. Ketorolac was used as a perioperative analgesic in 65 patients undergoing transverse rectus abdominis musculocutaneous (TRAM) flap reconstruction. The authors found that the rate of hematoma in patients treated with ketorolac was lower than in those who did not receive ketorolac, although a statistical analysis was not performed.[21] Batdorf et al. incorporated preoperative and postoperative celecoxib in 49 women who were undergoing microsurgical breast reconstruction on an ERAS protocol. The authors reported low but equal rates of breast hematoma when compared to patients who received traditional care (6% in both groups).[22] A more recent retrospective review analyzed a single institution's experience using ketorolac during implant-based breast reconstruction in 57 of 522 patients between 2008 and 2013. Two of the 57 patients who received ketorolac (4%) developed a postoperative hematoma compared with 11 of 123 (9%) controls ($p = 0.32$).[23]

The present study is the largest to report bleeding outcomes in breast surgery patients who receive ketorolac and the first to compare bleeding complications in patients undergoing both lumpectomy and mastectomy without reconstruction. Our analysis includes a comparison to a similarly large group of patients undergoing surgery at the same time. Bleeding outcomes included both hematoma and clinically significant bruising, which has not been previously reported but is certainly noted by patients and may affect their postoperative satisfaction and pain outcomes.

There were a larger proportion of lumpectomies compared to mastectomies in the cohort that did not receive ketorolac, which theoretically could have contributed to similar bleeding outcomes between the groups, because more patients in the no ketorolac group underwent more extensive surgery. To account for this, we stratified the patients according to type of surgery. Among the patients that underwent lumpectomy, there were no hematomas and only one case of bruising in the ketorolac arm. Similar findings were encountered among mastectomy patients: there was no statistically significant difference in bleeding events between the two arms (Table 3). Although the low rate of hematoma incidence in the mastectomy group that received ketorolac was similar to that of the group that did not receive ketorolac, small numbers limits this subset analysis. However, our rate of hematoma in the mastectomy group was similar to that previously reported in the literature by Batdorf et al. and therefore was included in this report as proof-of-feasibility.[22]

Like other nonrandomized studies, our analysis may be limited by confounding factors. Two surgeons initially adopted the ERAS protocol and usually used ketorolac, while a third did not. Differences in operative technique between surgeons could have potentially influenced the primary outcome. Prior use of anticoagulation medication, surgical modality, axillary management, presence of malignancy, and subcutaneous injection of liposomal bupivacaine may also

TABLE 3 Complications among patients by surgical modality

	No Ketorolac	Ketorolac	*p* value
Lumpectomy ($n = 157$)			
Seroma	0 (0)	0 (0)	n/a
Infection	0 (0)	0 (0)	n/a
Dehiscence	0 (0)	0 (0)	n/a
Bruising	0 (0)	1 (1.0)	1.000
Hematoma	0 (0)	0 (0)	n/a
Any bleeding complication[a]	0 (0)	1 (1.0)	1.000
Any major complication[b]	0 (0)	1 (1.0)	1.000
Mastectomy ($n = 57$)			
Seroma	2 (5.0)	1 (5.9)	1.000
Infection	1 (2.5)	0 (0)	1.000
Dehiscence	1 (2.5)	0 (0)	1.000
Bruising	0 (0)	1 (5.9)	0.298
Hematoma	2 (5.0)	1 (5.9)	1.000
Any bleeding complication[a]	2 (5.0)	2 (11.8)	0.575
Any major complication[b]	6 (15.0)	3 (17.7)	1.000

[a]Bleeding complication includes clinically significant bruising or hematoma

[b]Major complication includes seroma, infection, dehiscence, clinically significant bruising, or hematoma

augment the risk of bleeding complications. We attempted to investigate this, but bleeding complications were too infrequent, making a regression analysis not meaningful.

Our institution successfully implemented an ERAS protocol for patients undergoing breast surgery in 2017.[2] The original goal of the program was to expedite patient return to equilibrium. Once we learned that patients were not taking their opioids after surgery, a secondary goal of the program became eliminating the unnecessary prescription of opioids without compromising pain control. The use of single-dose intraoperative ketorolac is a key element of the protocol.

Patients who received intraoperative ketorolac during lumpectomy and mastectomy without reconstruction did not have higher rates of bleeding complications, including hematoma and bruising compared with a group that did not receive ketorolac during the same period. The use of intraoperative ketorolac is a useful adjunct for managing perioperative pain in breast surgery, may improve oncologic outcomes, and does not increase the risk of bleeding.

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REFERENCES

1. Nimmo SM, Foo ITH, Paterson HM. Enhanced recovery after surgery: pain management. *J Surg Oncol.* 2017;116:583–91.
2. Rojas K, Manasseh DM, Flom PL, Agbroko S, Bilbro N, Andaz C, Borgen PI. A pilot study of a breast surgery Enhanced Recovery After Surgery (ERAS) protocol to eliminate narcotic prescription at discharge. *Breast Cancer Res Treat*. 2018;171(3):621–6.
3. Gobbe RM, Hoang HL, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg*. 2014;133(3):741–55.
4. Duttchen KM, Lo A, Walker A, McLuckie D, De Guzman C, Roman-Smith H, Davis M. Intraoperative ketorolac dose of 15 mg versus the standard 30 mg on early postoperative pain after spine surgery: a randomized, blinded, non-inferiority trial. *J Clin Anesth*. 2017;41:11–5.
5. Motov S, Yasavolian M, Likourezos A, et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department: a randomized controlled trial. *Ann Emerg Med*. 2017;70(2):177–84.
6. Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. *Transl Perioper Pain Med*. 2016;1(1):5–13.
7. Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth metastasis. *Cancer Metastasis Rev*. 2011;30(2):225–38.
8. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, Hebbel RP. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res*. 2002;62(15):4491–8.
9. Nestler EJ, Hyman SE, Holtzman DM, Malenka RC. Molecular neuropharmacology: a foundation for clinical neuroscience, 2nd edn. New York: McGraw-Hill Medical, 2009.
10. Cummings KC, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116(4):797–806.
11. Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. *Cancer Med.* 2014;3:900–8.
12. Jiang W, Wang L, Zhang J, et al. Effects of postoperative non-steroidal anti-inflammatory drugs on long-term survival and recurrence of patients with non-small cell lung cancer. *Medicine (Baltimore)*. 2018;97(39):e12442.
13. Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, De Kock M. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesth Analg*. 2010;110(6):1630–5.
14. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. *Br J Anesth*. 2014;113:i82–7.
15. Retsky M, Demicheli R, Hrushesky W, et al. Reduction of breast cancer relapses with perioperative non-steroidal anti-inflammatory drugs: new findings and review. *Curr Med Chem.* 2013;20(33):4163–76.
16. Zhao X, Xu Z, Li H. NSAIDs Use and reduced metastasis in cancer patients: results from a meta-analysis. *Sci Rep*. 2017;7(1):1875.
17. Walter ND, Rice PL, Redente EF. Wound healing after trauma may predispose to lung cancer metastasis: review of potential mechanisms. *Am J Respir Cell Mol Biol*. 2011;44(5):591–6.
18. Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell*. 1998; 93(5):705–16.
19. Baek SJ, Okazaki R, Lee SH, et al. Nonsteroidal anti-inflammatory drug-activated gene-1 over expression in transgenic mice suppresses intestinal neoplasia. *Gastroenterology*. 2006;131:1553–60.
20. Cekanova M, Lee SH, Donnell RL, Sukhthankar M, Eling TE, Fischer SM, Baek SJ. Nonsteroidal anti-inflammatory drug-activated gene-1 expression inhibits urethane-induced pulmonary tumorigenesis in transgenic mice. *Cancer Prev Res*. 2009;2:450–8.
21. Sharma S, Chang DW, Koutz C, Evans GR, Robb GL, Langstein HN, Kroll SS. Incidence of hematoma associated with ketorolac after TRAM flap breast reconstruction. *Plast Reconstr Surg*. 2001;107(2):352–5.
22. Batdorf NJ, Lemaine V, Lovely JK, et al. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2015;68(3):395–402.
23. Mikhaylov Y, Weinstein B, Schrannk TP, Swartz JD, Ulm JP, Armstrong MB, Delaney KO. Ketorolac and hematoma incidence in postmastectomy implant-based breast reconstruction. *Ann Plast Surg*. 2018; 80(5):472–4.