

# Ketorolac May Increase Hematoma Risk in Reduction Mammoplasty: A Case-control Study

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**Background:** Ketorolac is a potent nonsteroidal anti-inflammatory drug that has valuable analgesic properties but also a hypothetical risk of increased bleeding due to inhibition of platelet activation. The clinical significance of this risk, however, is unclear when it is used after reduction mammoplasty. Our study objective was to therefore examine the association between ketorolac exposure and hematoma occurrence after breast reduction surgery. We hypothesized that there was no association between ketorolac exposure and hematoma occurrence in breast reduction surgery.

**Methods:** A case-control design was used. Data from charts of all reduction mammoplasties that developed hematomas requiring surgical evacuation (cases) at our university-based hospitals were retrieved and matched to data from charts of reduction mammoplasty patients who did not indicate this complication (controls). Matching occurred in a 1:1 ratio based on 4 criteria: age, body mass index, institution, and pre-existing hypertension. Charts were reviewed for retrospective information on exposure to ketorolac. Odds ratio (OR) was calculated with an OR > 1 favoring an association.

**Results:** From 2002 to 2016, 40 cases of hematoma met inclusion criteria and were matched with 40 controls (N = 80). Cases had a significantly lower body mass index than controls; however, the other baseline patient demographics were similar between the 2 groups. There was an association between hematoma formation and exposure to ketorolac (OR, 2.4; 95% confidence interval, 0.8–7.4;  $P = 0.114$ ) and a trend for greater risk of hematoma formation, although this was not statistically significant.

**Conclusions:** Based on this level 3 evidence, there appears to be an association between perioperative ketorolac exposure and hematoma after breast reduction surgery, but it was not statistically significant. Although this study was adequately powered, the OR of 2.4 was associated with a wide confidence interval. A larger sample size may increase the precision of the results and may also make the association definitive. (*Plast Reconstr Surg Glob Open* 2018;6:e1699; doi: 10.1097/GOX.0000000000001699; Published online 19 March 2018.)

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Ethics approval to proceed with this study was granted by the Hamilton Integrated Research Ethics Board (#1094-C). This study has been registered with ClinicalTrials.gov (NCT03280043).

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## INTRODUCTION

Breast reduction mammoplasty is a common plastic surgical procedure in the province of Ontario, Canada, with over 5,000 women in the province undergoing this procedure annually.<sup>1</sup> In the United States, 100,969 women underwent breast reduction in the year 2016.<sup>2</sup> On average, breast reduction patients rate their pain as moderate.<sup>3,4</sup> To further improve patient comfort postoperatively, various interventions have been utilized, including oral or intravenous analgesics, infiltration of local anesthetic as a field block, intercostal block, or wound infusion pumps.<sup>5–7</sup> Although each has shown efficacy, there are disadvantages with each, such as lidocaine toxicity, pneumothorax, increased cost, and medication-related adverse effects.

Among the various interventions, administration of postoperative opioids is routine and ubiquitously used by plastic surgeons. Although opioids are effective, they may

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induce vomiting, constipation, drowsiness, and in severe cases, respiratory depression. To mitigate these adverse effects, the use of nonsteroidal anti-inflammatory drug (NSAIDs), either as replacement or adjunctive therapy has been described.<sup>8</sup> Ketorolac (Toradol) is one NSAID with intriguing potential because it can decrease opioid requirements by up to 50% when used as an adjunct.<sup>9</sup> Cost analyses show higher immediate costs for ketorolac versus opioids; however, long-term savings may justify its use, as fewer resources will be spent on treating opioid-related side effects and delayed discharge.<sup>10</sup>

Although the analgesic efficacy of ketorolac has been established in pain management, there is concern among plastic surgeons regarding the risk of bleeding in the setting of reduction mammoplasty, due to the agent's antiplatelet properties.<sup>11</sup> Although several studies have suggested a link between ketorolac and breast hematomas postreduction mammoplasty, they have been limited by their retrospective nature, small sample sizes, and failure to control for confounding factors, such as premorbid hypertension.<sup>11,12</sup> The timing of ketorolac administration (ie, intra- versus postoperatively) is also inconsistent, which may also influence the outcome. For example, administering ketorolac in the postoperative period may negate the hypothetical bleeding risk, because platelets will have already been activated and adhered during primary hemostasis. Observational studies investigating ketorolac use after both subglandular breast augmentation and transverse rectus abdominis myocutaneous flap breast reconstruction did not find a correlation between NSAID use and bleeding, although the planes of tissue dissection are notably different compared with reduction mammoplasty.<sup>13,14</sup>

Given that ketorolac is a potent analgesic that can reduce opioid consumption postoperatively, it is of great interest for routine use, but there remains insufficient evidence in the literature to support this decision. The baseline incidence of hematoma after breast reduction is low, estimated at 2.4%,<sup>11</sup> hampering the ability to perform an adequately powered prospective trial. We therefore conducted a case-control study to examine the association of ketorolac exposure among patients who developed a hematoma requiring surgical exploration (cases) to those who had uncomplicated reduction mammoplasty (controls). The research question we aimed to answer was: in breast reduction patients, is there an association between the administration of ketorolac and hematoma formation? Our hypothesis was that there was no association of administration of ketorolac with hematoma formation.

### METHODOLOGY

We designed a case-control study to match patients who developed a post-reduction mammoplasty hematoma requiring surgical evacuation (cases) with patients who had uncomplicated reduction mammoplasty (controls).

The required sample size was calculated using the POWER program.<sup>15</sup> The following variables were used:  $p_0 = 0.32$  (the probability of exposure to ketorolac in controls<sup>11</sup>),  $\alpha = 0.05$ ,  $P = 0.8$ ,  $m = 1$  (matching ratio),  $\Psi = 3.6$

(reported risk ratio of developing hematoma if exposed to ketorolac<sup>11</sup>), and  $\Phi = 0.2$  (correlation coefficient for the outcome between matched cases and controls). The value for  $\Phi$  is normally retrieved from existing literature; however, because this is the first case-control study on this topic, the value 0.2 was conservatively chosen per Dupont.<sup>15</sup> Based on this calculation, a total of 25 cases matched with 25 controls were deemed necessary. Ethics approval was granted by the Hamilton Integrated Research Ethics Board before data collection (1094-C). This study is registered with ClinicalTrials.gov (NCT03280043).

Cases and controls were identified through the coding system utilized by our hospitals' electronic medical records. Coders searched "hemorrhage," "hematoma," and "plastic surgery," and all cases were identified manually from this list. Controls were pulled at random from a large pool of uncomplicated reduction mammoplasties and manually reviewed. Patients were excluded if they had a hematoma treated conservatively (needle aspiration or observation), unilateral reduction, concomitant liposuction or abdominoplasty, known coagulopathy, or documented sensitivity to NSAIDs. Cases and controls were matched in a 1:1 ratio using 4 criteria: age  $\pm 5$  years, body mass index (BMI)  $\pm 5$  kg/m<sup>2</sup>, presence of preexisting hypertension, and institution (St. Joseph's Healthcare Hamilton and Hamilton Health Sciences). At the time of matching, the primary author (J.O.B.) was blinded to ketorolac exposure and could only see the de-identified patient identifier and 4 matching variables.

Demographic data were gathered and examined for baseline differences between the two groups in nonmatching measures. Paired samples Student's *t* tests were used to statistically compare means for continuous measures, and McNemar's tests were performed for ordinal and categorical measures. Last, as our a priori primary outcome was hematoma formation, conditional logistic regression was used to examine the association between ketorolac exposure and hematoma formation controlling for the matching variables. All analyses were carried out with IBM SPSS software (IBM Corporation, Armonk, New York, version 24.0).<sup>16</sup>

### RESULTS

A total of 43 hematomas occurred at our institution. Three cases were excluded because they were managed conservatively, leading to 40 cases matched with 40 controls within the years 2002–2016 (N = 80; Table 1). Thirty-one cases occurred at St. Joseph's Healthcare Hamilton, and 9 occurred at Hamilton Health Sciences. Mean time to hematoma formation was 4.3 hours, except for 4 patients who developed a delayed-onset hematoma (> 20 hours after surgery). Fifty-five percent (22 of 40) of hematomas

**Table 1. Two-by-two Table Summarizing the Number of Cases and Controls Exposed to Ketorolac**

Ketorolac Exposure	Cases	Controls	Total
Ketorolac	20	11	31
No ketorolac	20	29	49
Total	40	40	80

**Table 2. Comparing Means of Continuous Demographic Measures between Cases and Controls**

	Cases (N = 40)	Controls (N = 40)	t-Value (df); P*
Age (mean, SD)	44.4±13.3	44.5±13.2	-2.01 (39); 0.842
BMI (mean, SD)	28.5±5.1	30.0±5.1	-2.315 (39); 0.026
Volume of tissue resected (g) (mean, SD)	Right (503±195) Left (524±201)	Right (538±300) Left (592±343)	R: -0.639 (39); 0.526 L: -1.178 (39); 0.246
Preoperative platelet count† (× 10 <sup>9</sup> /L)	268±62	288±76	-0.485 (19); 0.633

\*Paired samples *t* test.

†Platelet count data were missing in 10 cases and 15 controls, and these were excluded from this calculation.

occurred in the left breast, 42.5% (17 of 40) occurred on the right, and 1 case developed bilateral hematomas. Qualitative analysis of the operative notes for hematoma take-backs showed that surgeons described the bleeding as a generalized ooze or pulsatile approximately equally between patients who received ketorolac and those who did not.

Cases had a significantly lower BMI compared with controls (Table 2). There were otherwise no significant differences between cases and controls in the mean year of procedure, age, volume of tissue resected, and preoperative platelet count. American Society of Anesthesia scores were similar among cases and controls (McNemar-Bowker Test: chi-square = 3.533, df = 3 asymptotic 2-sided test; *P* = 0.316). From the total sample, 38.7% (31 of 80) patients received a dose of ketorolac in the perioperative time period. All 31 patients who received ketorolac were given the dose intravenously. Twenty-five patients received intraoperative administration, and 6 received the dose postoperatively (Table 3). Mean dose of ketorolac given to cases and controls was similar (27.0 ± SD 6.2, and 27.3 ± SD 6.1, respectively).

The risk of hematoma formation after exposure to ketorolac was 2.4 [odds ratio (OR), 2.4; 95% confidence interval (CI), 0.8–7.4; *P* = 0.114], after controlling for the differences in BMI and age between cases and controls. The 2.4 OR indicates that a breast reduction patient is 2.4 times more likely to develop a postoperative hematoma after being exposed to ketorolac than a patient who is not exposed. The OR of 2.4 is associated with a wide CI (0.8–7.4) and was not statistically significant indicating an inconclusive result.

## DISCUSSION

The association between perioperative ketorolac exposure and breast hematoma received attention shortly after its approval in 1989, when an anecdotal case series reported 4 hematomas within 10 days, occurring after the initiation of ketorolac use at the author's institution.<sup>17</sup> Allegedly, the hematoma rate returned to baseline after cessation of use. However, the small sample size and lack of follow-up limited the validity of this study. Subsequent to

the above case series, 2 other retrospective cohort studies have identified a positive correlation between ketorolac exposure and postoperative hematomas after reduction mammoplasty.<sup>11,12</sup>

The first, by Blomqvist et al.<sup>12</sup>, featured a retrospective cohort of 293 consecutive reduction mammoplasty patients. Among patients who received ketorolac, 60% developed a hematoma (3 of 5), which was significantly higher than the 4.7% rate among patients who did not receive an NSAID (12 of 253; *P* < 0.05, Fisher's exact test). Furthermore, patients who received diclofenac developed more hematomas compared with those who did not receive an NSAID, but this was not a statistically significant difference (14.3%; 5 of 35; *P* > 0.05, Fisher's exact test). In the study by Blomqvist et al.<sup>12</sup>, ketorolac was administered as a 30 mg intramuscular dose, and diclofenac a 75 mg intramuscular dose, and these medications were given both intra- and postoperatively. The authors adopted a broad definition of hematoma, including all bleeding managed nonoperatively and operatively. If hematomas managed conservatively were excluded, the incidence of bleeding in the 3 groups changes to 4 of 253 (1.6%), 1 of 5 (20%), and 1 of 35 (2.9%) in the non-NSAID, ketorolac, and diclofenac groups, respectively. The main drawbacks of this study were its small sample size particularly of the ketorolac group and failure to analyze comorbidities that may influence bleeding.

More recently in 2012, in a retrospective review of 379 reduction mammoplasty patients, the authors found that the incidence of hematoma requiring reoperation was 6 of 252 (2.4%) in the non-NSAID cohort, and 11 of 120 (8.7%) in the ketorolac cohort.<sup>11</sup> Most (~94%) of the patients in the ketorolac group received 30 mg intravenous ketorolac intraoperatively. The relative risk of hematoma formation requiring reoperation was statistically significant in the ketorolac group (risk ratio = 3.6; 95% CI, 1.4–9.6). There was also a higher proportion of patients with hypertension in the ketorolac group (27 of 127, 21.3%) compared with the nonketorolac group (32 of 252, 12.7%; *P* < 0.05, chi-square statistic), which may have confounded the results and predisposed the patients exposed to ketorolac to greater bleeding. The authors do report mean arterial pressures, which were measured immediately upon entering and exiting the recovery room, which were not statistically significant between the 2 groups. One may argue that these pressures are discrete points, which do not accurately reflect the flux in blood pressure over time. Similar to our results, this study had a broad CI for their risk ratio.

**Table 3. Ketorolac Administration**

	Cases (N = 40)	Controls (N = 40)
No. patients exposed to ketorolac	20	11
Intraoperative administration	18	7
Postoperative administration	2	4

There is evidence evaluating ketorolac use after other breast procedures as well, although the planes of tissue dissection differ from breast reduction techniques. Dowbak<sup>13</sup> anecdotally reported on a cohort of 105 submammary breast augmentations treated with 30 mg of intramuscular ketorolac immediately before completion of the procedure. None of the patients in their series developed a postoperative hematoma. The definition of “prior to completion of procedure” in relation to hemostasis, closure of the incision, or before reversal of general anesthesia was not specified. There was also no report on follow-up.

In another retrospective study of 215 patients undergoing transverse rectus abdominis myocutaneous flap for breast reconstruction, no differences were found in the incidence of hematoma among the groups receiving ketorolac (1 of 65, 1.5%) and those who did not (4 of 150, 2.7%).<sup>14</sup> In this study, ketorolac was only administered in the postoperative setting as part of a patient-controlled analgesia pump at a dosage of 30 mg intravenous ketorolac every 8 hours if needed. Patients who were given ketorolac had a shorter duration of use of the patient-controlled analgesia pump and inpatient stay, although this difference was not statistically significant. Hypothetically, administration of ketorolac in the postoperative setting may reduce bleeding diathesis, because primary hemostasis has already been achieved and thus the antiplatelet effect of ketorolac would be negligible. This concept has also been suggested and demonstrated in nonplastic surgery literature.<sup>18</sup>

Three prospective randomized controlled trials have also evaluated ketorolac’s analgesic properties as a wound irrigant in subpectoral breast augmentation.<sup>7,19,20</sup> Collectively, 150 patients were randomized to receive either pocket irrigation with a ketorolac and bupivacaine mixture or normal saline (1 study used no irrigant as a control<sup>7</sup>). Of the 150 patients, there were no cases of hematoma requiring surgical evacuation. It is difficult, however, to interpret these results, as the route of administration (pocket irrigation versus intramuscular or intravenous injection), and perhaps the clinical effect of ketorolac is different.

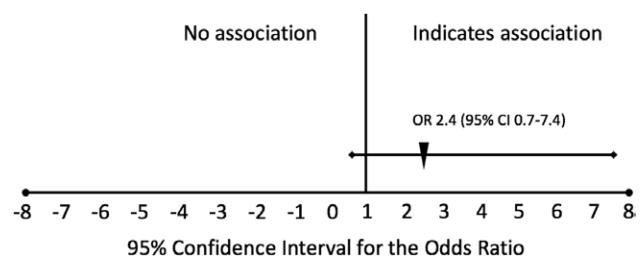
In a theoretical scenario, a randomized controlled trial, with a narrow CI, evaluating the cause-and-effect relationship between ketorolac and bleeding after reduction mammoplasty would provide us with the best evidence if ethical considerations were not an issue. The study with the closest design to a randomized controlled trial thus far has been by Marín-Bertolín et al.<sup>21</sup>, who examined a prospective cohort of 92 patients undergoing various plastic surgery procedures who were randomized to either ketorolac or metamizole groups. Their primary outcomes were pain scores and complication rates. In their study, 2 patients bled after receiving ketorolac, whereas none of the patients who received metamizole had a bleed, leading the authors to conclude that ketorolac is safe among individuals without baseline high bleeding risk. However, only 6 of the 92 randomized patients had a breast procedure, which were reconstructive in nature. The study by Marín-Bertolín et al.<sup>21</sup> was also included as part of a meta-analysis of 27 randomized controlled trials evaluating bleeding risk after ketorolac use across many procedures.<sup>22</sup> It was

the only study examining plastic surgery procedures. Notably, there were no significant differences in bleeding between ketorolac-exposed and nonexposed patients.

There are 2 main barriers to conducting a randomized controlled trial concerning this topic. First, it is unethical to randomize a patient into a group where they might incur potential harm. Second, because the baseline rate of postoperative hematoma is low (2.4% after reduction mammoplasty<sup>11</sup>), a randomized controlled trial would require a large sample size, long recruitment time, and significant resources. A case-control study design is therefore a feasible method that overcomes the low incidence of hematoma and the ethical concerns.

In our study, our primary aim was to compare the frequency of ketorolac exposure among patients who developed a hematoma after a breast reduction mammoplasty and patients who did not. Ketorolac exposure did not predict hematoma formation in our sample statistically as the *P* value did not meet our significance threshold of 0.05 (OR, 2.4; 95% CI, 0.8–7.4; *P* = 0.114). The OR of 2.4 is clinically important however. It can be interpreted that it is 2.4 times as likely for a postoperative breast reduction patient who has been exposed to ketorolac to have hematoma formation than a patient who has not been exposed. As both clinical significance and statistical significance must be established to render the results conclusive, this study remains inconclusive.

The fact that BMI was statistically different between cases and controls indicates a that the matching protocol did not work as expected. When the difference in BMIs between cases and controls was not considered in our statistical model, ketorolac exposure reached statistical significance with regard to hematoma formation. However, this significance disappeared when we accounted for the BMI difference statistically. From a clinical perspective, the OR of 2.4 suggests that patients who receive ketorolac are almost 2.4 times more likely to develop a hematoma. If this was the “truth,” most surgeons would not expose their patients to ketorolac. Our CI, however, is quite broad (0.8–7.4) indicating a lack of precision, even though our study was adequately powered based on our sample size calculation. We cannot dismiss these findings, however, as there is more weight to the right of the value OR = 1 on the CI scale, which means that there may be a clinically important association even if our study has not shown it (Fig. 1).



**Fig. 1.** Visual representation of the odds ratio with 95% confidence interval of developing a hematoma if exposed to ketorolac. The majority of the confidence interval lies greater than 1.

Among cases, the hematomas occurred with approximately the same frequencies on each side (55% left, 42.5% right), which seems to indicate that the level of training may not be related to hematoma development (in general, at our institution the resident operates on one side and the staff surgeon on the other). Anecdotally, bleeding from ketorolac has been described as “generalized ooze” and we were interested to see if staff surgeons were more likely to describe the bleeding in this way among cases exposed to ketorolac. Interestingly, their descriptions did not differ.

The primary limitation to our study is the retrospective design, which precludes cause-and-effect associations. There was also no control over the perioperative prescription patterns of ketorolac. We therefore cannot make any suggestions regarding ketorolac dosing, route, and timing (preoperative, intraoperative, or postoperative) on the risk of hematoma formation.

Last, journal editors and reviewers have traditionally accepted articles with positive results. Thankfully, this is changing, as this practice introduces bias to the scientific evidence as the results of all studies need to be published. Publishing results of all studies facilitates the pooling of results in systematic reviews and meta-analyses with more “truthful” conclusions. Although this study was inconclusive, it provides useful evidence for investigators to use in future meta-analyses. Alternatively, a larger, multi-site, case-control study can be used to provide further evidence of the association observed and its strength. Future studies could also examine the impact of ketorolac timing (preoperative, intraoperative, or postoperative administration) or dose on the risk of hematoma after reduction mammoplasty.

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