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REPORTS OF ORIGINAL INVESTIGATIONS

Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty

Analyse rétrospective de l'utilisation périopératoire de kétorolac et des saignements postopératoires dans la mammoplastie de réduction

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Abstract

Purpose *We conducted a retrospective review following concerns involving a suspected increase in the requirement for surgical re-exploration for hematoma evacuation when ketorolac was administered perioperatively in patients undergoing reduction mammoplasty.*

Methods *Following ethics approval, a retrospective chart review was conducted of all patients who underwent reduction mammoplasty at our two institutions from the time ketorolac became available in 2004 until surgeons requested its use discontinued in 2007. The data we collected included patient demographics, ketorolac administration, requirement for surgical re-exploration, documented hematoma formation not requiring surgical re-exploration, and excessive bleeding in the perioperative period. Three hundred and seventy-nine patient records were reviewed; 127 of the patients received a single intravenous dose of ketorolac (15 or 30 mg), and 252 of the patients did not receive ketorolac.*

Results *Patients who received ketorolac were at an increased risk of requiring surgical re-exploration for hematoma evacuation (relative risk [RR] = 3.6; 95% confidence interval [CI], 1.4 to 9.6) and hematoma formation not requiring re-exploration (RR = 2.2; 95% CI, 1.3 to 3.6).*

Conclusions *A single perioperative intravenous dose of ketorolac was associated with a greater than three-fold increase in the likelihood of requirement for surgical hematoma evacuation. Our data suggest that it may be prudent to consider carefully whether the potential risks associated with the use of ketorolac outweigh the potential benefits of using ketorolac in patients undergoing reduction mammoplasty.*

Author contributions *Kim E. Turner* and *John S. Davidson* contributed substantially to study conception. *Thomas R. Cawthorn, Kim E. Turner, Rachel Phelan,* and *John S. Davidson* contributed substantially to the study design and interpretation of the data, and they also played a significant role in drafting the manuscript. *Thomas Cawthorn* played a significant role in data acquisition and data analyses, and *Kim Turner and Rachel Phelan* played a significant role in revising the manuscript for intellectual content.

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Résumé

Objectif *Nous avons mené une étude rétrospective à la suite de préoccupations concernant l'augmentation suspectée des besoins de nouvelle exploration chirurgicale pour évacuation d'un hématome lorsque du kétorolac était administré en périopératoire à des patientes subissant une mammoplastie de réduction.*

Méthodes *Après accord des comités d'éthique, une analyse rétrospective a été réalisée sur tous les dossiers de patientes ayant subi une mammoplastie de réduction dans nos deux établissements entre le moment où le kétorolac a*

été disponible en 2004 et celui où les chirurgiens ont demandé l'arrêt de son utilisation en 2007. Les données que nous avons recueillies incluaient les variables démographiques des patientes, l'administration de kétorolac, la nécessité d'une nouvelle exploration chirurgicale, la constitution d'un hématome documenté ne nécessitant pas de réexploration chirurgicale et un saignement excessif au cours de la période périopératoire. Trois cent soixante-dix-neuf dossiers de patientes ont été passés en revue; 127 patientes avaient reçu une dose intraveineuse unique de kétorolac (15 ou 30 mg), et 252 patientes n'avaient pas reçu de kétorolac.

Résultats *Les patientes qui avaient reçu du kétorolac présentaient un risque accru de nouvelle exploration chirurgicale pour évacuation de l'hématome (risque relatif [RR] = 3,6; intervalle de confiance à 95 % [IC], 1,4 à 9,6) et de constitution d'un hématome ne nécessitant pas de reîntervention (RR = 2,2; IC à 95 %: 1,3 à 3,6).*

Conclusions *Une dose intraveineuse unique périopératoire de kétorolac a été associée à une probabilité multipliée par trois de formation d'un hématome nécessitant une évacuation chirurgicale. Nos données suggèrent qu'il peut être prudent d'évaluer soigneusement si les risques potentiels associés à l'utilisation du kétorolac ne dépassent pas largement les avantages éventuels de son utilisation chez des patientes subissant une mammoplastie de réduction.*

Ketorolac was introduced in 1990 in the United States and one year later in Canada. It is a non-steroidal anti-inflammatory drug (NSAID) with proven efficacy in the management of moderate to severe postoperative pain.[1-3] Ketorolac can be administered orally, parenterally, or topically[4] either alone or in combination with opioids. When used as an adjunct, there may be a 25-50% reduction in opioid requirements, which may reduce the incidence of adverse side effects associated with opioid consumption.[1,5]

Similar to other NSAIDs, ketorolac may prolong bleeding through inhibition of prostaglandin synthesis[6,7] *via* a mechanism of non-selective cyclooxygenase inhibition.[4] In 1991, shortly after the introduction of ketorolac, Garcha raised concerns surrounding an unusual cluster of postoperative hematomas following breast procedures.[8] Evidence of a potential association was strengthened by Blomqvist's report of the increased risk of bleeding-related complications following breast reduction surgery in patients who received NSAIDs.[9]

In our institution, ketorolac became available for perioperative use in 2004, and this was followed by concerns of a suspected increase in the incidence of surgical re-exploration for postoperative hematoma evacuation in patients undergoing reduction mammoplasty. In 2007, these increased concerns led to a request by our plastic surgeons to discontinue the use of ketorolac in reduction mammoplasty patients. The objective of the current investigation was to determine retrospectively whether there was an association between perioperative intravenous ketorolac administration and the requirement for surgical re-exploration for hematoma evacuation in patients undergoing elective reduction mammoplasty. We also examined the association of perioperative ketorolac administration with secondary outcome measures of hematoma formation not requiring surgical re-exploration, estimated blood loss, and transfusion requirements.

Methods

Study population and data source

Following approval from the Queen's University and Affiliated Teaching Hospital's Research Ethics Board (Queen's University, Kingston, Ontario, ANAE-166-10, approved May 31, 2010), we examined the medical records of all female patients who underwent elective reduction mammoplasty from January 2004 to December 2007 at either of our two institutions. Both bilateral and unilateral reductions were included in the study. Patients with any known hematological condition or who were undergoing concurrent surgical procedures were excluded.

Data collection and outcome measures

All medical records were examined by a single reviewer (T.R.C.) in June and July of 2010. The following demographic data were recorded and evaluated for each patient: age at surgery, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) status, preoperative hemoglobin/hematocrit/platelet count, and relevant pre-existing conditions (e.g., hypertension, hematological disorders, tobacco use, preoperative NSAIDs, anticoagulants, herbal medicines, and postoperative antibiotic prescriptions). We collected perioperative parameters, including total weight of resections, length of surgery, total intravenous intraoperative fluids, length of hospital stay, requirement for antibiotics, and blood pressure measurements entering surgery as well as entering and leaving the postanesthetic care unit (PACU). Mean arterial pressure (MAP) was calculated from recorded systolic blood pressure (SBP) and diastolic blood pressure (DBP) using the following formula: $MAP = (2(DBP) + SBP)/3$.[10]

Ketorolac administration was documented with respect to dosage and timing of administration. The primary study outcome, of hematoma formation requiring surgical evacuation, was defined as patients who developed hematomas

during the first 24 hr postoperatively, which required return to the operating room for surgical re-exploration and evacuation. Secondary outcome measures included any documented indicators of hematoma formation not requiring surgical re-exploration, intraoperative blood loss, requirement for blood transfusion, and requirement for drains to be placed. Hematoma formation was defined as specific documentation of a hematoma in the surgeon's postoperative notes or follow-up reports. Data for any documentation of the aforementioned bleeding-related complications were obtained from a review of the anesthetic record, operative report, progress reports, nursing notes, and the first postoperative clinic visit.

Statistical analysis

Analyses were conducted using SPSS® Version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences between groups in demographic data and outcome measures were examined by two-tailed Student's t tests or contingency tables using the Chi square statistic where appropriate. One-way ANOVA was used to examine differences between the four surgeons with respect to demographic and outcome data. As the number of required transfusions was low, this comparison was completed using a Yates correction. Significance level was set at $P < 0.05$. The magnitude and precision of the risk estimates were calculated using relative risk and 95% confidence intervals. The issue of missing data did not affect our primary outcome of return to the operating room for hematoma evacuation. Study subjects with missing data for the secondary outcomes related to fluid administration or intraoperative blood loss were not included in the calculation of mean values.

Results

All patients who underwent reduction mammoplasty at our institution from 2004 to 2007 and who met eligibility criteria were included in the study ($n = 379$); one patient was excluded due to known von Willebrand disease. No patients were taking NSAIDs, herbal medications, antiplatelets or anticoagulant medications prior to surgery. One hundred and twenty-seven patients (treatment group) received a single dose of perioperative intravenous ketorolac, and the 252 patients who did not receive ketorolac comprised the control group. Of the 127 patients in the treatment group, 124 received ketorolac intraoperatively (119 patients [93.7%] received 30 mg, and five patients [3.9%] received 15 mg). The remaining three patients (2.4%) received 30 mg ketorolac in the PACU within two hours of surgery.

There were no significant differences between the treatment and control groups with respect to age, BMI, ASA status, incidence of tobacco use, or preoperative hemoglobin, hematocrit, or platelet count. Significantly more patients in the treatment group were diagnosed with hypertension preoperatively ($P = 0.04$, Table 1), but no differences in mean arterial pressure were observed throughout the perioperative period (Table 2). No significant differences were observed intraoperatively between groups with respect to the weight of resection or length of surgery, but a significantly higher volume of intraoperative fluid was administered to patients who received ketorolac (Table 3). Only four patients received intraoperative pentaspan, three of whom were in the control group and one was in the ketorolac group. The remaining patients were administered crystalloids or the intraoperative fluids were unspecified.

Table 1 Demographic data and preoperative patient characteristics

	Control ($n = 252$)	Ketorolac ($n = 127$)
Parameter Mean (SD)		
Age at surgery, yr	40.0 (13.0)	42.3 (12.9)
BMI, $kg \cdot m^{-2}$	31.6 (5.9)	31.6 (6.2)
Preoperative		
Hemoglobin	136.7 (9.3)	135.8 (9.6)
Hematocrit	0.409 (0.026)	0.409 (0.026)
Platelet count	287.1 (64.8)	287.4 (68.3)
Parameter, n (%)		
ASA status		
I	62 (26.2%)	40 (32.5%)
II	133 (56.1%)	66 (53.7%)
III	42 (17.7%)	17 (13.8%)
Smoking status	49 (19.4%)	17 (13.4%)
Diagnosed hypertension	32 (12.7%)	27 (21.3%)

SD = standard deviation; ASA = American Society of Anesthesiologists; BMI = body mass index. Demographic data and preoperative characteristics for control *vs* ketorolac-treated reduction mammoplasty patients

Table 2 Mean arterial pressure (MAP) measurements at discrete time points

Measurement Time	Control	Ketorolac	P value*
Preoperative	93.5 (11.1)	93.7 (11.1)	0.80
End of surgery	80.1 (12.2)	78.5 (13.5)	0.37
Entering recovery	97.6 (13.0)	96.6 (15.7)	0.74
Leaving recovery	90.7 (11.0)	91.2 (11.5)	0.98

* Two-tailed Student's t test. Comparison of mean arterial pressure (MAP) measurements at four discrete time points. Mean (standard deviation) for control *vs* ketorolac-treated reduction mammoplasty patients. MAPs were based on blood pressure measurements taken immediately prior to surgery, at the end of surgery just before leaving the operating room, and upon entry and exit from the recovery room

Table 3 Intraoperative characteristics

Parameter Mean (SD)	Control ($n = 252$)	Ketorolac ($n = 127$)	P value*
Length of surgery, min	108.1 (34.2)	115.6 (38.7)	0.07
Intraoperative fluids, mL	1,510.9 (522.9)	1,735.9 (546.3)	< 0.001
Resection weight, g	1,327.9 (731.6)	1,311.1 (703.0)	0.83
Estimated blood loss-surgeon, mL	259.8 (101.4)	250.2 (100.1)	0.37
Estimated blood loss- anesthesiologist, mL	327.5 (168.4)	316.1 (162.3)	0.41

* Two-tailed Student's t test. SD = standard deviation. Intraoperative surgical characteristics for control *vs* ketorolac-treated reduction mammoplasty patients

Eleven patients (8.7%) in the treatment group and six patients (2.4%) in the control group required surgical hematoma evacuation (Table 4). Perioperative ketorolac administration was associated with a significantly greater relative risk (RR) of requiring surgical hematoma evacuation than the control group (RR = 3.6; 95% confidence interval [CI], 1.4 to 9.6). A number needed to harm of 16 was calculated for the primary outcome of requirement for surgical hematoma evacuation. The treatment group also experienced a significantly increased risk of hematoma formation not requiring surgical evacuation (RR = 2.2; 95% CI, 1.3 to 3.6). Three patients in the treatment group (2.4%) required a blood transfusion while no transfusions were required in the control patients (Yates correction = 3.37; $P = 0.07$).

No significant association was observed between the administration of ketorolac and recorded intraoperative blood loss (as estimated by the attending surgeon or anesthesiologist, Table 3). There were no cases of drains being required due to excessive bleeding. One surgeon placed drains in each breast routinely; however, as this was routine for this procedure, these were not considered drains required for bleeding. There were no significant differences in outcomes between the four surgeons. Since a large number of anesthesiologists were involved in the care of the study patients, we were unable to examine the differences between anesthesiologists.

The average time to hematoma identification was 3.9 hr (range 0.5-10 hr). Among the 17 cases requiring surgical evacuation, all were identified in hospital within 24 hr of the operation and were evacuated in the operating room under general anesthetic. Hematomas identified after hospital discharge were most commonly identified at the postoperative follow-up appointment (average time of 15 days) and did not require return to the operating room for surgical evacuation.

Discussion

The main objective of our study was to examine the relationship between perioperative ketorolac administration and the formation of postoperative hematomas which require evacuation in patients undergoing reduction mammoplasty. In our study, patients who received a single intravenous dose of perioperative ketorolac were at a greater than three-fold increase in the relative risk of requiring surgical hematoma evacuation compared with those who did not receive ketorolac (RR = 3.6; 95% CI, 1.4 to 9.6). Expressed differently, the calculated number needed to harm obtained from our investigation suggests that one patient for every 16 patients who undergo reduction mammoplasty and who receive a single perioperative intravenous dose of ketorolac will be required to return to

Table 4 Relative risk of complications associated with perioperative ketorolac

Event, n (%)	Control ($n = 252$)	Ketorolac ($n = 127$)	RR (95% CI)
Primary outcome			
Hematoma evacuation	6 (2.4%)	11 (8.7%)	3.6 (1.4 to 9.6)
Secondary outcomes			
Operative site bleeding	14 (5.6%)	21 (16.5%)	3.0 (1.6 to 5.7)
hematoma	23 (9.1%)	25 (19.7%)	2.2 (1.3 to 3.6)
> 2 dressing changes	10 (4.0%)	8 (6.3%)	1.6 (0.6 to 3.9)
Drains required	5 (2.0%)	2 (1.6%)	0.8 (0.2 to 4.0)
Transfusion required*	0	3 (2.4%)	N/A
Infection†	36 (14.3%)	23 (18.1%)	1.3 (0.8 to 2.0)

RR = relative risk; CI = confidence interval. * Data analyzed using the Yates continuity correction (Yates correction = 3.37; $P = 0.07$). † Infection as defined by requirement for antibiotic prescription postoperatively. Relative risk of dichotomous operative complications associated with perioperative ketorolac administration during reduction mammoplasty

the operating room for surgical re-exploration and hematoma evacuation. Three of the ketorolac-treated patients required a blood transfusion compared with none of the patients who did not receive ketorolac. In the ketorolac-treated patients, there was also a two-fold increase in the risk of developing a hematoma not requiring surgical evacuation.

Although few studies have examined ketorolac administration in breast surgery, our investigation reinforces the concern expressed in other reports. Garcha's letter to the editor documented his observation of an "unusual cluster" of bleeding in four patients following reduction mammoplasty. All patients had received 30 mg of ketorolac immediately following surgery, and two of these required subsequent hematoma evacuation in the operating room.[8] In Blomqvist's retrospective study, five patients received ketorolac 30 mg *im* pre- or postoperatively, and three of these patients (60%) were identified as developing a hematoma, defined either as a hematoma requiring surgical evacuation or as a widespread subcutaneous hematoma not suitable for reoperation but in some cases requiring drainage.[9] In contrast, in a more recent study, hematoma formation was examined following transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction, and no difference in the incidence of hematoma formation was observed in patients when treated with ketorolac postoperatively. This latter study also showed a significant reduction in self-administered (patient-controlled analgesia) morphine requirement in patients who had received postoperative ketorolac.[11] It is interesting that perioperative ketorolac administration was associated with increased bleeding complications in these reports and not in the TRAM flap breast reconstruction when the ketorolac was administered *postoperatively*. This raises the question whether ketorolac administration postoperatively, after hemostasis is achieved, may result in a lower incidence of hematoma formation compared with intraoperative administration, as has been suggested with its use in tonsillectomy patients.[12]

There are reports in the literature examining perioperative ketorolac administration and bleeding complications which show inconsistent results. For example, in a study of patients undergoing lumbar discectomy, a single dose of intraoperative intravenous ketorolac provided effective pain control with no observed difference between groups with respect to bleeding-related complications.[13] Likewise, Vitale *et al.* conducted a retrospective review of 208 children who underwent scoliosis surgery, and they determined that postoperative ketorolac administration was not associated with an increased requirement for blood transfusion or reoperation.[14] In contrast, RuDusky *et al.* (2000) described two case reports (a hysterectomy and a prostatectomy) in which a single intramuscular dose of ketorolac four or six hours postoperatively was thought to be associated with severe hemorrhage.[15] In another study looking at pediatric tonsillectomy, a single dose of ketorolac administered postoperatively (once hemostasis was achieved) revealed no significant difference in bleeding between the ketorolac and control patients, but results showed that ketorolac patients were discharged faster.[12] These results differ from other tonsillectomy studies which determined that children who underwent tonsillectomy with pre- or intraoperative ketorolac were at an increased risk of postoperative bleeding-related complications.[16,17]

Given the incongruent reports, it appears likely that many factors may influence the risk of postoperative bleeding-related complications with ketorolac administration, including timing of administration and the procedure itself. The ketorolac product insert states that "perioperative Toradol use should be avoided and postoperative use undertaken with caution when hemostasis is critical".[A] This may help to explain why no increase in bleeding was observed when ketorolac was administered postoperatively to patients undergoing TRAM flap,[11] in contrast to our patients who, for the most part, received ketorolac intraoperatively and contrary to patients of Garcha and Blomqvist who did not consistently receive their ketorolac postoperatively.[8,9] Interestingly, one of the three patients in our study who received ketorolac postoperatively required reoperation for hematoma evacuation.

It is important to understand the timeline of development of postoperative hematoma formation requiring surgical evacuation, particularly if the patient is to be discharged from hospital. Although not the primary outcome of our study, our data showed that the average time to hematoma identification was 3.9 hr (range 0.5-10 hr) among the 17 cases requiring re-exploration and surgical evacuation. This suggests that patients who have their surgery performed early in the day may be appropriate for discharge later in the day if there are no signs of bleeding and they are otherwise deemed suitable candidates for ambulatory surgery. In other studies that reported bleeding complications, the time to hematoma identification was either not specified[9] or reported to develop within ten days.[8]

Although our current investigation shows an association between perioperative ketorolac administration and an increased risk of postoperative bleeding complications following reduction mammoplasty, retrospective observational studies are subject to bias. Ketorolac administration was entirely at the discretion of the individual anesthesiologist involved in that patient's care. We were unable to

[A] *Hoffmann-La Roche Inc*. Toradol package insert. Available from URL: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9090#nlm34070-3 (accessed: January, 2012).

examine the factors that went into their decision-making. Patients are routinely instructed to discontinue all NSAIDs, aspirin, and anticoagulants five to seven days prior to their planned surgical date. While no patient reported taking these medications in the preoperative period, we cannot be certain they were not. Preoperative hemoglobin and platelet concentrations were measured but coagulation status was not assessed. We did not examine the anesthetic administered, induction agents, neuromuscular relaxants, narcotics, or events (e.g., coughing which may have occurred throughout extubation). It is interesting that three patients in the ketorolac group required transfusion, but this finding should be interpreted with caution as we were unable to examine the decision-making of the individual's ordering the transfusion, including the threshold hemoglobin concentration for transfusion. While the aforementioned factors should be seen as weaknesses in the current investigation, these factors may also serve to increase the generalizability of the results.

Although all data were extracted by a single reviewer (T.R.C.), this should not impact the primary outcome of return to the operating room for hematoma evacuation since it was an objective measure which did not require any qualitative judgement. To minimize confounding bias, demographic data were compared between the control and treatment groups to ensure that the groups were well balanced (Table 1). The only significant difference between groups was administration of significantly greater volume of intravenous fluids intraoperatively and a higher prevalence of hypertension in the treatment group. As mentioned previously, only four patients received pentaspan. All other patients either received crystalloids or the fluids administered were not specified on the anesthetic record. The administration of a greater volume of intravenous fluids in this group may have been secondary to a perceived increase in bleeding, although no significant difference was observed in blood loss between groups. Alternatively, one may argue that the higher fluid volume administered to those in the treatment group contributed to an increase in bleeding. Likewise, since alterations in blood pressure may contribute to the development of bleeding complications, an effort was made to control for this potentially confounding variable by calculating MAP for all patients at four distinct time points (i.e., preoperatively, at the end of surgery, upon admission to the PACU, and discharge from the PACU). No difference between the treatment and control groups was observed in MAP at any of the time points examined (Table 2).

Our secondary end point, of hematoma formation not requiring surgical evacuation, is a subjective measure which is difficult to examine retrospectively and should therefore be interpreted with caution. However, as both groups were equally likely to be affected by the subjectivity of these determinations, the differences observed between groups may be real, particularly in view of the fact that those making the determinations were unaware that their notes would be the subject of a future investigation. On the other hand, we are unable to confirm if the individuals making these observations knew whether or not the patient had received ketorolac; therefore, it is possible that this knowledge may have influenced the recorded notes once concerns were raised regarding the potential for bleeding.

In summary, all retrospective investigations are subject to bias and should be interpreted with caution. In this study, patients undergoing reduction mammoplasty who received a single perioperative dose of ketorolac were at a significantly increased risk of requiring return to the operating room for surgical hematoma evacuation. This finding may have significant clinical implications considering the frequency of this procedure. Estimates in 2008 were at least 88,732 reduction mammoplasties performed in the U.S[B] and more than 10,696 performed in Canada.[C] Further study is required to either confirm or refute our findings.

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Conflicts of interest None declared.

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[B] *American Society of Plastic Surgeons*. 2008 Reconstructive Surgery Procedures. Available from URL: http://www.plasticsurgery.org/Documents/news-resources/statistics/2008-statistics/2008-reconstructive-procedure-statistics.pdf (accessed January, 2012).

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