Hematoma Risks of Nonsteroidal Anti-inflammatory Drugs Used in Plastic Surgery Procedures

A Systematic Review and Meta-analysis

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Background: The opioid crisis in America has sparked a shift toward a multimodality perioperative pain regimen. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the perioperative period decreases opioid consumption and increases efficacy. However, many plastic surgeons avoid their use because of antiplatelet effects. The purpose of this article is to systematically review the plastic surgery literature to assess the risk of intraoperative or postoperative bleeding and hematoma formation.

Methods: A systematic review of articles published in PubMed was performed in September 2018 to investigate the incidence of increased bleeding and hematoma formation with use of NSAIDs in the perioperative period in plastic surgery. All articles were reviewed for primary outcome measures, and a selective literature review was performed to examine perioperative NSAID use in other surgical subspecialties. Random-effect meta-analysis was performed.

Results: Our search yielded 806 total articles, with 15 meeting inclusion criteria, and this included 3064 patients (1679 with perioperative NSAIDs, 1385 with no NSAIDs). There was no significant difference in overall incidence of bleeding/hematoma in the treatment group versus control (no NSAIDs). The overall pooled odds ratio (OR) and corresponding 95% confidence interval were 1.20 and 0.73 to 1.97 ($P = 0.48$). When separated by drug administered across all plastic surgery procedures, there were no statistically significant differences in incidences of hematoma or increased bleeding with use of ketorolac (OR, 1.48 [0.86–2.56]; $P = 0.57$), ibuprofen (OR, 0.55 [0.14–2.14]; $P = 0.87$), or celecoxib (OR, 0.22 [0.02–2.52]; $P = 0.39$). When examining NSAID use in breast surgery, there was no statistically significant difference in incidence of hematoma or increased bleeding when combining all 3 drug types (OR, 1.39 [0.82–2.37]; $P = 0.60$). Some individual studies demonstrated trends toward increased bleeding/hematoma in reduction mammoplasties.

Conclusions: Nonsteroidal anti-inflammatory drugs significantly improve pain control and decrease opioid use when used in plastic surgery. The majority of evidence in plastic surgery does not support an increased incidence of bleeding/hematoma with the use of perioperative NSAIDs.

Key Words: hematoma rate NSAIDs, bleeding risk NSAIDs, perioperative NSAIDs

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The opioid crisis in America has sparked a shift toward a multimodality pain regimen in the perioperative period. Opioids are highly addictive and have negative side effect profiles ranging from constipation and hypotension to respiratory depression and cardiac arrest, and death from overdose has tripled since the 1990s.[1] In addition to problems with dependence, issues with illicit injection of opioids have led to significant infection control issues, with spread of blood-borne disease and injection site infections.[2] Stricter guidelines for prescribers and monitoring programs are being implemented to address these issues, and additional pain control modalities will help to decrease opioid consumption without compromising perioperative pain control.

Nonsteroidal anti-inflammatory drugs (NSAIDs) include all nonsteroidal selective and nonselective COX-1 and COX-2 inhibitors. These drugs block the conversion of arachidonic acid to prostaglandins, decreasing inflammation and pain, and their use in perioperative pain regimens has been found in multiple randomized control trials to decrease opioid consumption and improve their efficacy.[3,4] The safety profiles of individual drugs in this class vary widely, with adverse gastrointestinal (GI) effects linked to COX-1 inhibition and conflicting reports of negative cardiovascular effects with long-term use.[5] Among the most feared effects of NSAIDs is a theoretic increased risk of bleeding and hematoma formation, as they also inhibit conversion of arachidonic acid to thromboxane A2, an important factor for platelet aggregation. Therefore, many surgeons have reservations in using this drug class in the perioperative period, despite much of the surgical literature supporting their safety.[6–8] The purpose of this article is to systematically review the plastic surgery literature to assess the risk of intraoperative or postoperative bleeding and hematoma formation, as well compare these risks with those identified in other surgical subspecialties.

METHODS

Literature Search

A comprehensive literature search was conducted in September 2018 according to PRIMSA guidelines for articles published after January 1, 1998, using the following terms in PubMed: "mastectomy," "reconstructive surgical procedures," "wound closure techniques," "surgery, plastic," "hand/surgery," "upper extremity surgery," "face/surgery," "craniofacial abnormalities/surgery," or "breast/surgery" AND "postoperative complications" or "anti-inflammatory agents, non-steroidal." Additional searches were performed for "mammoplasty: ketorolac," "ketorolac breast reconstruction," "celecoxib/adverse effects," "celecoxib and cardiovascular system," and "intraoperative toradol NOT cataract."[9,10]

Inclusion Criteria

All articles included were epidemiological studies, retrospective chart reviews, systematic reviews, or randomized control trials. The aforementioned search criteria were applied in PubMed, and articles were screened for duplications. After this, the resultant articles were screened by title and abstract for the primary outcome measure, intraoperative or postoperative hematoma, or bleeding risk with perioperative NSAID administration. Articles that met the inclusion criteria were evaluated for the primary outcome measure, and additional information including study type and level of evidence, NSAID used, route administered and dose used, and surgeries performed was noted.

After this, a selective literature review was performed to examine NSAID use and associated intraoperative or postoperative hematoma or

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bleeding risk from other surgical subspecialties. These articles were selected by our senior author for comparison and discussion, and this was not an exhaustive literature review as described previously. The main outcome measure was increased bleeding and hematoma, but secondary outcome measures (ie, delayed bone healing) were noted.

Exclusion Criteria

Articles that did not meet the previously mentioned search criteria, duplicate articles, and those articles in which the title or abstract did not reflect the use of NSAIDs in plastic surgery and evaluation of the primary outcome measure, intraoperative or postoperative bleeding, and hematoma risk were not included in this study.

Statistical Analysis

Meta-analysis was performed to obtain a pooled odds ratio (OR) estimate across different studies. A continuity correction of 0.5 was applied to individual studies with no bleeding events. I^2 Statistic was calculated to assess heterogeneity of the studies ($I^2 = 11.9$, $P = 0.62$). Odds ratios from the random effect models and 95% confidence interval (CI) were computed. A forest plot was used to present the individual and overall ORs (Fig. 1). All analyses were conducted in SAS 9.4 (Cary, North Carolina).

RESULTS

Our search results yielded 806 total articles, which resulted in 532 total articles after removal of duplicates. After screening for primary outcome measures by title, 31 articles remained (Fig. 2). Abstracts of the remaining articles were then screened for our primary outcome measure, resulting in 11 articles, and additional screening for article quality was performed and expert commentaries were removed, resulting in 8 articles. This included 2 systematic review articles by Stephens et al[8] and Kelley et al,[7] which evaluated hematoma rates with ketorolac and ibuprofen use in plastic surgery in 10 articles, 9 of which met our inclusion criteria, allowing for a total of 15 articles. All articles selected commented on incidence of hematoma or increased bleeding with perioperative use of NSAIDs in plastic surgery (Table 1). The 3 primary NSAID-evaluated articles chosen were ketorolac (9 total), celecoxib (2 total), and ibuprofen (4 total), with type of surgery and drug dose varying significantly from study to study.

In total, there were 3064 patients among the 15 studies selected across multiple surgical procedures including breast reduction, breast reconstruction, breast augmentation, rhytidectomy, brow lift, cutaneous oncologic surgery, and abdominoplasty as well as body contouring procedures with and without liposuction. This included 1679 patients in the treatment group, those who received perioperative or postoperative NSAIDs, and 1385 in the control group, those who were not administered NSAIDs. There was significant variation between studies in terms of drug dosage, timing of drug administration, and definition of hematoma or increased bleeding events. Overall, there was no statistically significant difference in incidence of hematoma or increased bleeding in the treatment group versus the control group (OR, 1.20 [0.73–1.97]; $P = 0.48$). When separated by drug administered across all plastic surgery procedures, there were no statistically significant differences in incidences of hematoma or increased bleeding with use of ketorolac (OR, 1.48 [0.86–2.56]; $P = 0.57$), ibuprofen (OR, 0.55 [0.14–2.14]; $P = 0.87$), or celecoxib (OR, 0.22 [0.02–2.52]; $P = 0.39$).

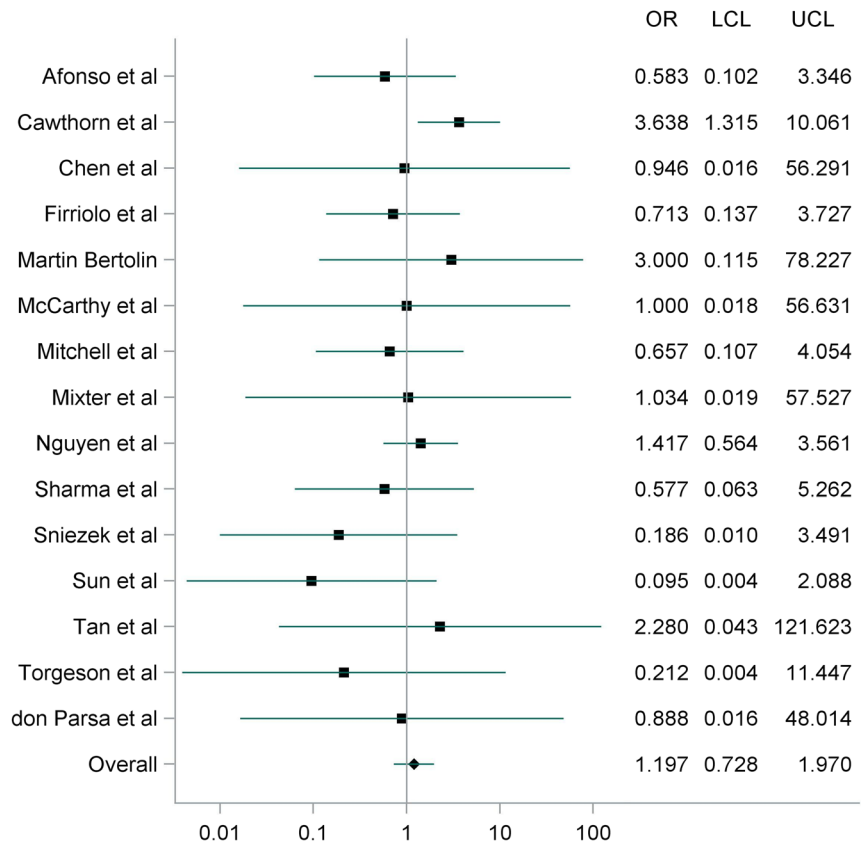

FIGURE 1. Forest plot from meta-analysis that summarizes individual ORs and the overall OR. LCL, lower confidence limit; UCL, upper confidence limit.

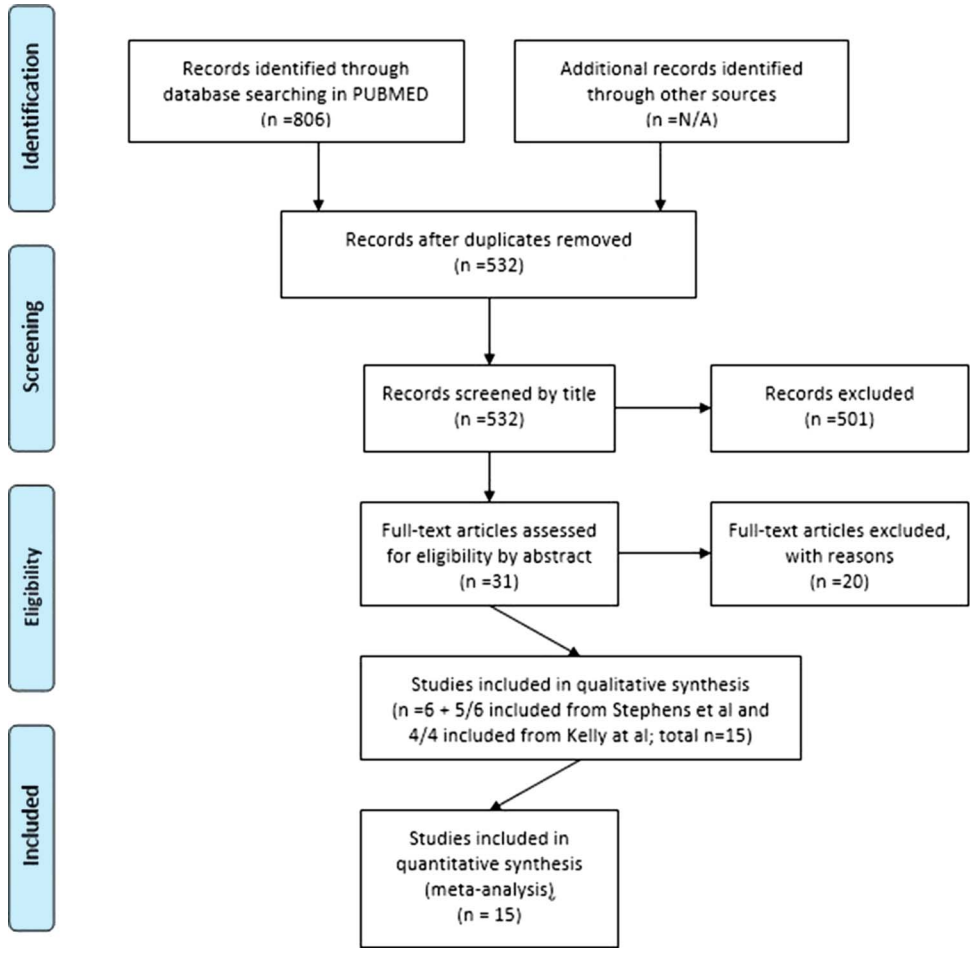

FIGURE 2. Flowchart outlining our process of study identification, and inclusion and exclusion based on PRISMA 2009 guidelines.

When examining NSAID use in breast surgery, there was no statistically significant difference in incidence of hematoma or increased bleeding when combining all 3 drug types (OR, 1.39 [0.82–2.37]; $P = 0.60$).

DISCUSSION

Nonsteroidal anti-inflammatory drugs have an enormous upside as part of a multimodality pain regimen. They have been shown to significantly improve pain control with decreased postoperative opioid use, length of stay, unplanned readmissions, and postoperative nausea and vomiting.[4,11,15,26–31] Despite this, many practitioners stray away from this drug class in the perioperative period because of fear of potential adverse effects. The black box warning for ketorolac, a common NSAID given in the perioperative setting, gives caution to use after major cardiac events in those at risk of serious bleeding or GI adverse events and in those with advanced renal dysfunction.[32] However, NSAIDs have a very safe side effect profile in the immediate perioperative period when used correctly. De Oliveira et al[33] showed this in a meta-analysis looking at the risks and benefits of a single perioperative dose of ketorolac. The review included 13 randomized control trials across multiple surgical subspecialties that examined adverse effects, postoperative pain scores, and the most effective route of administration/dose. They found a significant decrease in postoperative pain scores and postoperative nausea and vomiting with a single perioperative 60 mg intramuscular dose of ketorolac with no aggregate increase in postoperative gastritis or bleeding. Oliveri et al[34] had similar findings in a large retrospective review in 2014 that included 1309 patients receiving ketorolac for postoperative pain control in the first 72 hours after cardiac surgery. They showed no increase in GI bleeding, renal failure requiring dialysis, perioperative myocardial infarctions, or cerebrovascular incidents.

Celecoxib is also gaining popularity in its use for perioperative pain control, as it has been shown to decrease postoperative pain and increase patient satisfaction after plastic surgery procedures with no resulting platelet dysfunction or changes in serum thromboxane levels.[23,35] This selective COX-2 inhibitor was developed to circumvent the GI issues associated with long-term use of traditional COX-1/COX-2 inhibitors, but this drug class previously fell out of favor because of concerns for long-term cardiac effects. A large randomized control trial performed by Nissen et al[36] addressed this concern. This included 24,841 patients treated for either osteoarthritis or rheumatoid arthritis and compared long-term use of celecoxib to naproxen or ibuprofen, with the primary outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke. They had more than 20-month mean treatment duration and found celecoxib to have no difference with respect to cardiovascular safety, but did find it to have a significant decrease in renal events compared with ibuprofen as well as a decrease in GI events when compared with ibuprofen and naproxen. This study leads to a statement from a Food and Drug Administration Panel affirming that celecoxib has a similar safety profile to other NSAIDs in this patient population.

One of the most feared complications of perioperative NSAID administration is acute renal failure. This wariness is justified, as there have been reports of acute renal failure with short-term administration

TABLE 1. Hematoma Rates in Plastic Surgery

Study	Study Type	Drug Used/Dose Used/Route of Administration	Sex (M/F)	Mean Age at Time of Surgery, y	Timing of Administration/ Frequency and Duration	Type of Surgery	Hematoma Rate Treatment Group	Hematoma Rate Control	Definition of Hematoma	Advocate NSAID Use?
Afonso et al[11]	Retrospective chart review	Ketorolac/15 mg IV	F	51, treatment; 50, control	Intraop; postop/Q6 × 3 d, then PO equivalent × 2 d)	DIEP or muscle-sparing free TRAM	2/42 (5%)	4/49 (8%)	Hematoma noted in the first 30 d	Yes
Cawthorn et al*[12]	Retrospective chart review	Ketorolac/15–30 mg IV	F	42.3, treatment; 40.0, control	Intraop, postop/within 2 h of surgery, duration N/A)	Reduction mammaplasty	11/127 (8.7%)	6/252 (2.4%; RR, 3.6)	Required reoperation in the first 24 h	No
Chen et al†[13]	Prospective, double blind, randomized	Ibuprofen 400 mg	N/A	N/A	Postop/Q6 × 3 d	Cosmetic facial surgery	0/18 (0%)	0/17 (0%)	Not specified	Yes
Parsa et al[14]	Retrospective and prospective, nonrandomized	Celecoxib/400 mg/NA	F	34.4, all groups	Preop/30–60 min before incision	Reduction mammaplasty	0/44 (0%)	0/39 (0%)	Not specified	Yes
Firriolo et al[15]	Retrospective chart review	Ketorolac/30–90 mg IV	F	18.1, all groups	Intraop, postop/timing N/A	Reduction mammaplasty	5/389 (1.3%)	2/111 (1.8%; $P = 0.65$)	Required reoperation or aspiration	Yes
Marin-Bertolin et al[16]	Prospective, double blind, randomized	Ketorolac 30 mg IM	M = 22, F = 24	44, treatment; 46, control	Postop Q8 × 48 h	Various plastics	1/46 (2.2%)	0/46	Clinically diagnosed, regardless of intervention	Yes
McCarthy et al*†[17]	Prospective, double blind, randomized	Ketorolac 30 mg, breast pocket irrigation	F	34.4, treatment; 35.4, control	Intraop	Breast augmentations	0/25 (0%)	0/25	Not specified	Yes
Mitchell et al†[18]	Prospective, double blind, randomized	Ibuprofen 600 mg PO	F	51.3, treatment; 51.5, control	Postop, Q6 h × 7 d	Breast Surgery	2/71 (2.8%)	3/70 (4.3%)	Not specified	Yes
Mixter et al†[19]	Prospective, double blind, randomized	Ibuprofen 800 mg preop PO, 400 mg postop PO	N/A	Age range, 12–83	1 dose preop, 6 doses (1 × 4 h) postop	Herniorrhaphy	0/29 (0%)	0/30 (0%)	Not specified	Yes
Nguyen et al[20]	Retrospective chart review	Ketorolac/15–30 mg IV	F	47, treatment; 50, control	Postop (before extubation or within the first 12 h postop, then continued for up to 5 d)	Breast reduction, implant-based breast reconstruction, or autologous breast reconstruction	7/199 (3.5%)	14/564 (2.5%; $P = 0.443$)	Required reoperation	Yes
Sharma et al*[21]	Retrospective chart review	Ketorolac/N/A	F	N/A, all groups	Postop/timing N/A	TRAM flaps	1/65 (1.5%)	4/150 (2.7%; $P > 0.05$)	Not specified	Yes
Sniezek et al†[22]	Prospective, double blind, randomized	Ibuprofen 400 mg PO	N/A	63, treatment; 62/66, controls	Postop Q4 × 4 doses	Mohs reconstruction	0/68 (0%)	5/140 (3.6%)	Not specified	Yes
Sun et al[23]	Randomized control trial	Celecoxib 200–400 mg	M = 6, F = 106	42/43, treatment; 42 control	Preop/30–90 min before surgery, postop ×3 d	"Major" plastic surgery (eg, breast augmentation, abdominoplasty ± lipo)	0/76 (0%)	2/36 (5.6%)	Clinically diagnosed at first clinic follow-up or at 3 mo postop	Yes
Tan et al[24]	Retrospective chart review	Ketorolac 30 mg IV, 30 mg IM	F	28.1–32.1, all groups	Intraop/after incision, postop/end of procedure	Breast augmentations	0/37 (0%)	0/85 (0%)	Not specified	Yes
Torgerson et al*[25]	Prospective, randomized	Ketorolac 30 mg IM or injected with local anesthesia	M = 5, F = 90	N/A	Intraop	Facial aesthetics	0/120 (0%)	0/25 (0%)	Not specified	Yes

*Included in a study by Stephens et al.[8]

†Included in a study by Kelley et al.[7]

DIEP, deep inferior epigastric artery flap; F, female; Intraop, intraoperative; IM, intramuscular; IV, intravenous; M, male; N/A, not applicable; Preop, preoperative; PO, per os; Postop, postoperative; Q, every; RR, risk ratio; TRAM, transverse rectus abdominis myocutaneous flap.

TABLE 2. Hematoma Rates in Various Surgical Subspecialties

Study	LOE	Study Type	Drug Used	Specialty	Type of Surgery	Hematoma/ Bleeding Rate in the Case Group	Hematoma Rate in Controls	Other Measures of Hematoma/Bleeding Rate	Advocate NSAID Use?
Agrawal A et al[43]	3	Retrospective review	Ketorolac	ENT	Tonsillectomy ± adenoidectomy	5/213 (2.3%)	3/97 (3.1%; $P = 0.71$)	Ketorolac group, EBL 23 mL; control group, EBL 34 mL; difference was significant ($P < 0.001$)	Yes
Braganza et al[44]	2	Single-blind controlled study	Ibuprofen	Dentistry	Periodonal surgery at 2 sites	N/A	N/A	Increased intraoperative bleeding when preoperative ibuprofen given (31.93 ± 15.72 cc vs 17.80 ± 9.57 cc; $P < 0.01$)	No
Reuben et al[45]	1	Randomized double blind trial	Rofecoxib	Ortho	Knee replacement	N/A	N/A	Intraoperative blood loss: rofecoxib, 111.8 (110.0) mL vs placebo 80.5 (56.9) mL ($P = 0.30$); postoperative blood loss: 364.1 (231.3) mL vs 395.6 (286.3) mL ($P > 0.99$)	Yes
De Oliveira et al[33]	2	Meta-analysis of RCTs	Ketorolac	Multiple surgical specialties	Total hip/knee arthroplasty, lumbar discectomy, tonsillectomy, abdominal hysterectomy, gynecologic laparoscopy, prostatectomy, lap chole, gynecologic laparoscopy, orthopedics, lower abdominal surgery	N/A	N/A	Abnormal bleeding in the ketorolac group (30 and 60 mg): OR, 2.43 (95% CI, 0.5–11)	Yes
Desikan and Meena[46]	3	Literature review	Diclofenac, ketorolac, ibuprofen, tenoxicam, naproxen, indomethacin, nimosulide, or not specified	ENT	Tonsillectomy	N/A	N/A	N/A	Yes
Fransen et al[47]	1	Randomized double blind trial	Ibuprofen	Ortho	Total hip replacement or revision	21/452 (4.6%)	10/450 (2.2%)	Ibuprofen group increased risk of major bleeding complication: risk ratio, 2.09 (1.00–4.39; $P = 0.046$); no difference in RBC transfusion requirement	No
Gao et al[48]	3	Retrospective review	Ketorolac	Urology	Circumcision	N/A	N/A	OR, 2.07 (95% CI, 1.39–3.09; $P < 0.001$)	No
Gupta et al[49]	1	Prospective randomized controlled trial	Ketorolac	Cardiothoracic	Congenital heart surgery (infants/children)	13.3 mL kg^{-1} d^{-1} into chest tube	16.5 mL kg^{-1} d^{-1} into chest tube ($P = 0.05$)	N/A	Yes

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TABLE 2. *(Continued)*

Study	LOE	Study Type	Drug Used	Specialty	Type of Surgery	Hematoma/ Bleeding Rate in the Case Group	Hematoma Rate in Controls	Other Measures of Hematoma/Bleeding Rate	Advocate NSAID Use?
Magni et al[50]	3	Nested case control	Ketorolac	Neurosurgery	Elective intracranial procedures	0.50%	1.30%	Relative risk, 0.37 (95% CI, 0.17–0.79; $P = 0.007$)	Inconclusive
Marret et al[51]	2	Meta-analysis of RCTs	Ketorolac, ibuprofen	ENT	Tonsillectomy	Postoperative: 24/262 (9.2%); reoperation rate: 4.3%	Postoperative rate: 13/243 (5.3%); reoperation rate: 0.8%	Postoperative: OR, 1.8 (95% CI, 0.9–3.4); reoperation rate: OR, 3.8 (95%CI, 1.3–11.5; $P = 0.02$)	No
Møiniche et al[52]	2	Meta-analysis of RCTs	Diclofenac, ketorolac, ibuprofen, indomethacin, ketoprofen, tenoxicam, naproxen, nimesulide	ENT	Tonsillectomy	N/A	N/A	Reoperation in the NSAID group: peto-OR, 2.33 (95% CI, 1.12–4.83)	Inconclusive
Oliveri et al[34]	3	Retrospective observational study	ketorolac	Cardiothoracic	Coronary bypass (78.1%), valve (28.0%)	Reoperation: (3.9%); 1.6% of them were reopened after ketorolac	5.8% ($P = 0.15$)	Ketorolac patients received significantly fewer pRBC in perioperative period ($P < 0.0001$)	Yes
Palmer et al[53]	3	Retrospective review		Neurosurgery	Multiple procedures/not specified	N/A	N/A	30 patients with hematoma received antiplatelet therapy (43% of the cases)	No
Pickering et al[54]	1	Randomized double blind trial	Rofecoxib, ibuprofen	ENT	Tonsillectomy	Primary hemorrhage: rofecoxib 2.5%, ibuprofen 5% ($P = 0.83$); secondary hemorrhage: rofecoxib 7.5%, ibuprofen 2.5%	Primary hemorrhage 5.5%, secondary hemorrhage 11%	N/A	Yes
Schleiffarth et al[55]	2	Randomized cohort study	Ketorolac	ENT	Head and neck free tissue transfer	19.1% patients got 1+ pRBC	17.8% got 1 = pRBC ($P = 0.86$)	N/A	Yes
Sinatra et al[56]	1	Randomized double blind trial	Rofecoxib	Gynecology	Total abdominal hysterectomy or myomectomy	Mean blood loss, 386.9 mL (95% CI, 299.5–474.2)	Mean blood loss, 412.4 mL (95% CI, 327.9–496.9)	N/A	Yes
Slappendel et al[57]	1	Randomized double blind trial	Ibuprofen	Ortho	Total hip replacement	Mean blood loss, 700 mL; intraoperative blood loss + first 24 h after surgery increased 45% compared with control ($P < 0.05$)	Mean blood loss, 416 mL ($P < 0.01$)	N/A	No
Stables and Lawrence[58]	3	Literature review	Not specified	Dermatology	Skin surgery	1/21 (4.7%)	3/20 (15%)	N/A	Yes

Strom et al[59]	2	Postmarketing surveillance inception cohort study	Ketorolac	GI	Multiple procedures/not specified	N/A	N/A	Ketorolac vs opiates: OR for GI bleeding, 1.30 (95% CI, 1.11–1.52); OR for operative site bleeding, 1.02 (95% CI, 0.95–1.10). If age >75 y, OR for GI bleed, 1.66; OR for operative site bleed, 1.12; therapy >5 d; OR for GI bleed, 2.20	Yes
Thwaites et al[60]	1	Randomized double blind trial	Ketorolac	Ortho	Knee arthroscopy	N/A	N/A	No difference in platelet function (tested with bleeding time and aggremometry) after ketorolac with general anesthesia	Yes
Thwaites et al[61]	1	randomized double blind trial	Ketorolac	Ortho	Knee arthroscopy	N/A	N/A	Platelet function was impaired by single intraoperative dose of ketorolac during spinal anesthesia, unlike general anesthesia	No

ENT, ear, nose, and throat surgery; LOE, level of evidence; N/A, not applicable; Ortho, orthopedic surgery; pRBC, packed red blood cells.

of perioperative NSAIDs.[37–39] Nonsteroidal anti-inflammatory drugs as a drug class are largely, if not entirely, excreted by the kidneys, and therefore, periods of third spacing or hypotension during surgery can decrease renal perfusion, placing those with underlying renal insufficiency (ie, elderly patients, diabetic patients) at risk of renal failure.[40] However, recent studies argue for the safety of this drug class. In a retrospective cohort study that included 35 hospitals, Feldman et al[37] found that administration of ketorolac in the first 5 days postoperatively did not increase renal failure compared with opioids alone. They did find acute renal failure to occur more often with greater than 5 days of ketorolac administration as well as in those with chronic renal disease and hypotension, and with increasing age. In a randomized control trial, Qazi et al[41] examined the safety of ibuprofen administration versus oxycodone after cardiac surgery with a mean of 25 months of follow-up. They found that 9.6% of patients in the ibuprofen/lansoprazole group had postoperative creatinine levels that doubled after surgery, and this did not occur in any patients who received oxycodone alone (n = 93 [ibuprofen] vs n = 89 [oxycodone]). However, 88% of patients with elevated creatinine levels returned to normal levels within 2 weeks, and there was no significant difference in rates of long-term renal dysfunction between groups. In addition, Lee et al[42] performed a large Cochran review that included 14 total trials looking at renal dysfunction with perioperative NSAID administration. As a group, NSAIDs resulted in a transient reduction in creatinine clearance the first day after surgery compared with placebo but without a significant reduction in urine output. This was followed by a subsequent increase in creatinine clearance on the second postoperative day in the treatment group compared with placebo, with no cases of postoperative renal failure requiring dialysis. These studies suggest that true perioperative NSAID-induced renal insufficiency is extremely rare, especially if given over a short period without significant change.

Although much of the literature in both plastic surgery and other surgical subspecialties does not support an increased bleeding risk, many still have reservations in using this drug class in the perioperative setting (Table 2). In our review of more than 3000 patients, to our knowledge the largest to date, we did not find any statistically significant increase in incidence of hematoma or increased bleeding with use of NSAIDs in plastic surgery. This was consistent when broken down by NSAID type and by procedure. Although the collective incidence of increased bleeding with NSAID use in breast surgery was not significant, there are individual reports that suggest an increase with NSAID use in different subgroups. Cawthorn et al[12] performed a retrospective chart review comparing hematoma rates in patients undergoing reduction mammoplasty. One hundred twenty-seven patients received a single 15- to 30-mg intravenous dose of ketorolac versus 252 patients who did not. The treatment group had an increased risk in hematomas requiring surgical reexploration with a relative risk of 3.6 (96% CI, 1.4–9.6). In addition, Barkho et al[62] published a 2018 case-control series comparing 40 patients who underwent reduction mammoplasty and required surgical hematoma evacuations with 40 patients who underwent the same procedure and did not have a postoperative hematoma. They found a trend toward increased hematoma risk with exposure to ketorolac, but without statistical significance (OR, 2.4; 95% CI, 0.8–7.4; $P = 0.114$). Our literature review did not result in any studies that specifically discussed implant-based breast reconstruction alone, but the available literature is consistent with our results in aesthetic breast surgery and autologous breast reconstruction. Mikhaylov et al[63] performed a single-center, retrospective review that compared hematoma formation rates with and without ketorolac administration between patients who underwent prosthetic-based breast reconstruction. They found no significant difference in hematoma rates between groups, with 2 (3.5%) of the 57 patients in the treatment group versus 11 (8.9%) of the 123 patients with a postoperative hematoma ($P = 0.32$). In addition, our data did not include NSAID use in surgery of the oropharynx (ie, cleft lip/palatal surgery), and therefore, conclusions from our study about these key areas of plastic surgery cannot be made.

The literature reviewing NSAID use in surgeries of the oropharynx in otolaryngology and dentistry has varying conclusions, but there is evidence that NSAID use in the perioperative setting may increase bleeding risk. Braganza et al[44] found an increase in intraoperative bleeding (total intraoperative blood loss volume) as well as increased in bleeding time in intraoperative blood samples with administration of preoperative ibuprofen before periodontal surgery. Marret et al[51] performed a meta-analysis of multiple randomized control trials looking at bleeding risk with perioperative NSAID use during tonsillectomy. This included 7 studies with 505 adult and pediatric patients, with a collective 5.3% postoperative bleeding rate and 0.8% reoperation rate in the control group (no NSAIDs) versus 9.2% postoperative bleeding rate and 4.2% reoperation rate in the treatment group (OR, 3.8 [95% CI, 1.3–11.5]; number needed to harm, 29 [95% CI, 17–144]). This increase of greater than 4-fold in reoperation rate with tonsillectomy is consistent with the findings of Møiniche et al,[52] who also found perioperative NSAID administration to increase the risk of reoperation due to bleeding after tonsillectomy (OR, 2.33). Of note, those who received NSAIDs had approximately 9 fewer cases of postoperative nausea and vomiting per 100 patients treated. In contrast, in a double-blinded study, Pickering et al[54] compared 3 pain regimens after pediatric tonsillectomy. They advocated for addition of ibuprofen to their perioperative pain regimen, stating that it significantly reduced the need for early opioid analgesia after surgery without a significant difference in operative blood loss or complications compared with 2 other pain regimens without ibuprofen. Similarly, in a retrospective review that included 310 pediatric patients who underwent tonsillectomies with and without adenoidectomies, Agrawal et al[43] found no significant difference in postoperative hemorrhage between patients who received a single dose of intraoperative ketorolac and controls (bleeding rate: treatment group [n = 213; 2.3%] vs control group [n = 97; 3.1%]; $P = 0.71$). They also found a significant decrease in time to discharge and frequency of overnight stays in patients who received ketorolac.

With regard to NSAID effects on bone healing after facial or hand fracture fixation, there is some evidence, primarily in animal models, that suggest a detrimental effect from long-term ibuprofen in bone healing as well as contrasting reports of the effects on tendon healing. COX-2 blockade is detrimental to osteoblast differentiation from mesenchymal cells, a necessary step in fracture healing. However, there is no strong evidence of these issues with short-term postoperative NSAID analgesia.[64]

Our study is not without limitations. First, there are significant differences among studies in their definition of hematoma, which ranged from clinical diagnosis and need for transfusion to those requiring surgical exploration. Many studies did not discuss which criteria were used for hematoma diagnosis. In addition, there is a paucity of randomized control trials, with most studies consisting of case-control series and retrospective chart reviews. Because of the paucity of high-quality studies, we could not perform meaningful subgroup analysis for individual procedures in plastic surgery (ie, risk of NSAID use in facelifts, reduction mammoplasties, etc). One of the major aims of this study was to examine if the timing of NSAID use (ie, preoperative vs intraoperative, postoperative day 1 vs 5) made a difference in the overall bleeding risk. Unfortunately, there was significant variation in the timing of drug administration, and no real conclusions could be drawn. Lastly, our discussion of perioperative NSAID use does not include any articles regarding perioperative aspirin use. Although this is a widely used NSAID, this is generally not used for perioperative pain control and therefore outside the scope of this article. Despite these limitations, we feel that our study does provide results in favor of perioperative NSAID use in plastic surgery, as there are many well-documented benefits, whereas most evidence does not support an increased risk of postoperative bleeding or hematoma. The 2 exceptions would be in breast reductions and procedures of the oropharynx, in which there is some evidence of an increased bleeding risk with perioperative use. Whether this risk outweighs the benefits is up for debate and outside the scope of this study.

CONCLUSIONS

Nonsteroidal anti-inflammatory drugs significantly improve pain control and decrease opioid use when used in plastic surgery. Within plastic surgery, the majority of evidence does not support an increased incidence of hematoma or increased bleeding with the use of perioperative NSAIDs.

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