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Title

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Permalink

https://escholarship.org/uc/item/1558r341

Journal

Journal of the American College of Surgeons, 232(5)

ISSN

1072-7515

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Publication Date

2021-05-01

DOI

10.1016/j.jamcollsurg.2021.01.005

Peer reviewed

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Author manuscript

J Am Coll Surg. Author manuscript; available in PMC 2022 July 14.

Published in final edited form as:

J Am Coll Surg. 2021 May ; 232(5): 765–790.e1. doi:10.1016/j.jamcollsurg.2021.01.005.

A Systematic Review and Meta-Analysis of the Association between Non-Steroidal Anti-Inflammatory Drugs and Surgical Bleeding in the Perioperative Period

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Summary:

Introduction: It is increasingly recognized that non-opioid analgesia important analgesia in the perioperative period. Specifically, NSAIDs (nonsteroidal anti-inflammatory drugs) have been touted as an adjunct or even replacement for opioids. However, uptake of NSAIDs has been slow due to concern for side effects, including bleeding. We sought to understand the risk of bleeding caused by NSAIDs in the perioperative period.

Methods: A physician-librarian team performed a search of electronic databases (MEDLINE, EMBASE), using search terms covering the targeted intervention (use of NSAIDs) and outcomes of interest (surgical complications, bleeding), limited to English language articles of any date. We performed a systematic review and meta-analysis of the data.

Results: A total of 2,521 articles were screened and 229 were selected on the basis of title and abstract for detailed assessment. Including reference searching, 74 manuscripts met inclusion criteria spanning years 1987–2019. These studies included 151,031 patients. Studies included 12 types of NSAIDs, the most common being ketorolac, diclofenac and ibuprofen over a wide-range of procedures from ENT, breast, abdomen, plastics, and more. Over half were randomized control trials. The meta-analyses for hematoma, return to the operating room for bleeding and blood transfusions showed no difference in risk in any of three categories studied between the NSAID versus non-NSAID groups (p=0.49, p=0.79 and p=0.49, respectively). Quality scoring found a

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wide range of quality with scores ranging from lowest quality of 12 to highest quality of 25 out of a total of 27 (average=16).

Conclusions: NSAIDs are unlikely to be the cause of post-operative bleeding complications. This literature covers a large number of patients and remains consistent across types of NSAIDs and operations.

Keywords

Perioperative period; Non-steroidal anti-inflammatory drugs; Hematoma; Bleeding

Introduction

Approximately 50 million people have surgery each year in the US, making post-operative pain control an important issue. Opioids, which formed the backbone of programs to optimize pain management for hospitalized patients, have significant deleterious consequences, including delayed return of bowel function, respiratory depression, new persistent opioid use or abuse and unintentional overdose.[1] The opioid epidemic has become a major public health crisis[2] and surgeons are considered gatekeepers to opioid prescriptions.[1] Addressing new persistent opioid use following surgical care is of great import. Efforts at the local and national level have sought to better understand and address overprescribing after both emergency and elective surgical procedures.[1,3–6] In approaching opioid overprescribing, It is increasingly recognized that non-opioid analgesia is as effective as some opioid analgesia and that multimodal analgesia is better than exclusive opioid analgesia.[7–9] Specifically, nonsteroidal anti-inflammatory drugs (NSAIDs) have been encouraged as an important adjunct or replacement for opioids in certain patients and an effective strategy to curb the flow of opioids into our communities.[7–9]

Despite strong evidence to support multimodal analgesia,[10,11] uptake of this practice has proven challenging.[12,13] In fact, increasing the use of non-opioid analgesia may be more challenging than reducing opioid use, especially for the uptake of NSAIDs.[13] One barrier to use of NSAIDs for perioperative pain management is the perceived risk of bleeding associated with use.[14–16] This is of particular importance in surgical patients – a population where both risk and consequences of bleeding are increased. Therefore, we undertook a systematic review and meta-analysis of the existing literature to investigate the risk of bleeding associated with use of perioperative NSAIDs with the goal of consolidating evidence with regard to perioperative use of NSAIDs and the risk of bleeding.

Methods

Data Sources

In consultation with an experienced medical librarian (EW), we collaboratively developed a sensitive three-concept PubMed search composed of a comprehensive set of keywords and MeSH terms. The three concepts were perioperative period, NSAIDs, and bleeding (complete PubMed search string is found in eAppendix 1 in the Supplement). We adapted the MEDLINE search to work optimally in Embase using a combination of Emtree terms and keywords. Embase is a biomedical and pharmacological bibliographic database of

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published literature, and Emtree is used to index Embase content based on a hierarchically structured, controlled vocabulary for biomedicine and the related life sciences. The searches were not restricted by date, language or publication type. The end date of the search was August 29, 2019. Articles were combined and duplicates were eliminated in Zotero, an open-source reference management software to manage bibliographic data and related research materials. These articles were uploaded to Covidence for screening. Covidence is an online tool that streamlines parts of the systematic review process. It makes it easy to screen references (both title/abstract and full-text), divide up the work among a team of reviewers, and track the progress of the project.

Study Selection

Included studies evaluated the effect of administration of perioperative NSAIDs on surgery-associated bleeding in the postoperative period for adult surgical patients by reporting on rates of clinically significant surgical bleeding outcomes. We defined clinically significant bleeding as a documented hematoma, the need for a reoperation due to bleeding, and the need for a blood transfusion. Gastritis was not included because it is a known and dose-dependent complication of NSAIDs and is not necessarily related to a surgical procedure. All clinical contexts (inpatient, outpatient, clinic) and any study design were included. Studies were excluded if: (1) they were review articles, commentaries, editorials or case reports (with number of patients <5); (2) they studied the impact of the chronic use of NSAIDs or NSAIDs administered only in the preoperative period; (3) they were animal-only studies; (4) patients did not actually receive NSAIDs in the peri- or postoperative period; (5) they focused only on ophthalmologic procedures; (6) they studied only aspirin; (7) they included only pediatric populations, or (8) the report was not in English. Studies that evaluated only aspirin were excluded as aspirin is not typically used for pain control. Case-control studies were excluded from the meta-analysis because these types of studies a priori determine the number of patients in each group.

Four of us (TB, EL, YL, EW), one of whom is also a medical librarian (EW),[17] reviewed 50 randomly chosen titles and abstracts together to test the inclusion/exclusion criteria and train the reviewers for consistency. The same four independently assessed titles and abstracts, so that two reviewers independently reviewed each title and abstract. Disagreements were resolved by discussion during team meetings. The full text of articles retained for further review was then examined independently by each of the four reviewers (TB, EL, YL, EW) so that each article was fully reviewed by two reviewers.

Cited reference searching revealed additional articles not found by the original search terms, and these were added to the final set of articles for analysis. Full manuscripts were obtained for all articles not previously excluded and were independently read for inclusion in the final review by the same four reviewers (TB, EL, YL, EW). The references of all included studies were then searched manually, and the Scopus database was used to search for all studies that had subsequently cited the included studies. We also searched the references of relevant literature reviews or commentaries that broadly covered bleeding complications with perioperative NSAIDs. Additional articles of interest discovered through manual search were then subjected to the same review process for inclusion in the study.

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Data Extraction and Synthesis

Data for included studies were extracted by using a standardized form that was created after we developed and tested a data abstraction form. The final set of articles was abstracted in duplicate by the same four reviewers. This form underwent iterations as necessary to ensure it captured all relevant data. Study characteristics were then summarized based on reviewer consensus. The major study characteristics extracted for descriptive analyses included study design and duration, clinical setting, study size, type of NSAIDs used, timing and route of administration, NSAID dosing, body area of specific surgical procedures, type of complications, population demographics, years of enrollment, and study location. Since NSAIDs can be selective or non-selective in their mechanism of action,[18] we recorded this distinction. NSAIDs act by inhibiting cyclooxygenase, which has at least two different isoenzymes. Selective NSAIDs are those that have the ability to selectively inhibit the COX2 enzyme only. If patients were taking NSAIDs on a chronic basis as an outpatient, this was not independently considered a perioperative administration of NSAIDs. We considered the perioperative period to be in the immediate pre-operative holding area, intra-operative administration, or in the post-operative period.

Main Outcomes and Meta-analysis Procedures

The main outcomes extracted were the aggregate impact of NSAIDs administered in the perioperative period on surgical bleeding including presence of hematoma, the need for a return to the operating room secondary to bleeding, and the need for transfusion, which we used as a marker of blood loss. We did not include intraoperative blood loss and postoperative drain output because they are hard to accurately quantify and may have little clinical significance. We included all instances of surgical bleeding, as defined above, for two groups, the group that received NSAIDs in the perioperative period, and the group who did not receive NSAIDs in the perioperative period.

We then performed a meta-analysis on aggregated data from randomized controlled trials and cohort studies to test the association between perioperative NSAIDS and perioperative surgical bleeding. This entailed evaluating the differences in postoperative bleeding between groups who did receive perioperative NSAIDs and groups who did not. Subgroup analysis was performed based on type of bleeding complication (takeback to operating room, hematoma, need for blood transfusion) as well as a composite of all three plus two others that were studied more rarely, specifically change in hemoglobin and surgical site bleeding which were not defined more clearly than that.

All four outcomes (hematoma, return to operating room for surgical bleeding, blood transfusions and any other complication) were compared between the NSAID perioperative administration and non-NSAID administration groups using random effects models to control for heterogeneity and under the assumption that not all studies had similar patient mix and similar protocols. Sensitivity analyses were performed to examine heterogeneity for small study effects and evaluated using an influence summary. Heterogeneity across studies was tested with the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively.[19] To check the effect of various factors on the primary outcomes, we performed subgroup analyses according to each type

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of bleeding outcome (hematoma, return to operating room, blood transfusion, and any other surgical bleeding complication). We also analyzed these outcomes by year of publication. We assessed publication bias by using the Begg and Egger tests.[20,21] We then performed an influence summary, to assess if leaving out a test has an effect on the overall result. All statistical analyses were performed by Stata 16.1 (StataCorp LP, College Station, TX). The results were considered statistically significant if the corresponding 2-sided P value < 0.05.

Study quality was independently evaluated using the Downs and Black checklist, which is designed to assess quality of both randomized and non-randomized studies.[22] As has been done in prior peer-reviewed literature,[23] we omitted one checklist item because it specifically pertained to adjustment for time to event or time to follow-up that was not easily applicable to our studies.

Results

Database searches yielded a total of 2,785 articles. Three hundred and nine duplicates were identified and removed. Cited reference searching identified an additional 15 relevant abstracts not found in the database searches. Together, this represented a total of 2,521 abstracts screened. Of these, 229 were selected on the basis of the abstract text for full-text assessment. Finally, of those that underwent full-text assessment, 74 satisfied all inclusion and exclusion criteria. Thus, 74 total manuscripts representing 151,031 patients met all inclusion/exclusion criteria (see eAppendix 2 in the Supplement – PRISMA diagram) and were included in the qualitative analysis.[14,24–96] Of these, 68 were then included in the quantitative analysis (meta-analysis).

Study Characteristics

There was considerable heterogeneity among the 74 studies with regard to design, setting, scope and type of NSAID (Table 1). There were 41 randomized controlled trials (RCTs), 27 cohort studies and 6 case-control studies as detailed in Table 1. Studies were conducted in both the inpatient and ambulatory surgery settings, with follow-up occurring in both the inpatient and clinic setting, and in both academic and community hospitals. The most common categories of operations studied were breast surgery (some with reconstruction) (14), abdominal operations including open and laparoscopic (10), ear, nose, and throat procedures, which were mostly tonsillectomies (9), and orthopedic operations including joints and spine (9). Additional included studies evaluated cosmetic operations (4), thyroid/parathyroid resections (4), plastic surgery operations including microvascular free flaps (4), obstetrical/gynecologic procedures (4), and other categories that included <4 studies each, including cardiac, dental, endoscopic retrograde cholangiopancreatography, perianal, neurosurgical, and podiatric. Seven studies included a wide variety of operations over multiple body areas.

The type of NSAID used varied, as did the timing and route of administration. The types of NSAIDs studied included ketorolac (41), diclofenac (8), ibuprofen (8), celecoxib (6), ketoprofen (5), and parecoxib (4). NSAIDS in < 4 studies included flubiprofen, indomethacin, lornoxicam, meloxicam, rofecoxib, and tenoxicam, with some studies evaluating two or more NSAIDs (8). Sixty-two studies were with non-selective NSAIDs

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only, while the remainder were mixed or selective only. NSAIDs were administered at different times throughout perioperative care and sometimes at multiple times (pre/post, intra/post, etc.), including preoperatively (13), intraoperatively (24) and postoperatively (56).

In the 44 studies that reported duration of follow-up, the follow-up period ranged from 12 hours to three days. Studies with longer durations were focused on evaluating pain scores and overall complications, rather than only bleeding. Twenty-nine studies reported post-operative bleeding complications as a primary outcome. The remainder focused on pain control as a primary outcome but tracked other surgical complications, including bleeding.

Study publication dates ranged from 1987–2019, with only two in 1980s, 15 in the 1990s, 18 in the 2000s, and 39 in the 2010s, with 10 in 2018 alone. In total, 13 (18%) studies were sponsored by a pharmaceutical company.[24,29,37,38,44,46,47,50,60,66,71,76,79]

Studies were grouped by four types of surgical bleeding complication: 1) “hematoma” as defined by the study (41); 2) return to the operating room specifically because of bleeding (25); 3) need for blood transfusion in the post-operative period (18), and 4) all other ‘bleeding’ types of complications as reported by the authors (30). These ‘other’ types of bleeding included complications such as ‘surgical site bleeding’, ‘post-operative bleeding requiring compression’, and ‘perioperative bleeding’. As noted in the Methods section, we did not include measurements of drain outputs, lap pads, or estimated blood loss as a bleeding complication in our review or meta-analysis.

Findings from Meta-Analysis

Of the 74 included studies, 6 were case-control studies[58,72,92,93,95,96] and excluded from the meta-analysis. Therefore, 68 were used in the meta-analysis. The meta-analysis for hematoma included 35 studies and showed no difference in hematoma risk in the NSAID versus non-NSAID groups (p=0.492) and low heterogeneity (I^2=19.5%, p = 0.157 from the Mantel-Haenszel Q statistic) (Figure 1). The results of the Begg’s test and influence summary showed no evidence of bias and no difference between groups by leaving out each study out at a time.

The meta-analysis for return to the operating room for surgical bleeding included 19 studies and showed no difference in risk in the NSAID versus non-NSAID groups (p=0.792) and low heterogeneity (I^2=10.6%, p = 0.318 from the Mantel-Haenszel Q statistic) (Figure 2). The results of the Begg’s test and influence summary showed no evidence of bias and no difference between groups by leaving out each study out at a time.

The meta-analysis for blood transfusions included 16 studies and showed no difference in risk in the NSAID versus non-NSAID groups (p=0.492) and no heterogeneity (I^2=0.0%, p = 0.172 from the Mantel-Haenszel Q statistic) (Figure 3). The results of the Begg’s test and influence summary showed no evidence of bias and no difference between groups by leaving out each study out at a time.

The results of each meta-analysis showed similar results when performed only for RCTs. We could not perform a meta-analysis based on age or sex due to the inability to aggregate data for either of these characteristics because both age and gender were either underreported or

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not reported in a way that was assignable to the NSAID or non-NSAID group. For example, the average age of a group of patients might be provided in a table, but then stratified by age ranges or gender. Race was not reported in most studies, and so was not included in the meta-analysis. We did perform sub-analyses for both drug type and for the RCT studies only, and found no evidence for significant differences between the two groups.

Study Quality

Using a modified Downs & Black checklist of 27 items, we found that studies in this review had scores that ranged from 11/27 to 25/27, with an average score of 17 (Table 2), representing average quality overall. Studies most frequently lost points for not providing a list of principal confounders, not describing patients lost to follow-up, not adjusting for confounders in the analyses and not determining or reporting sufficient power to detect a clinically important effect where the probability for a difference being due to chance was <0.05.

Discussion

Bleeding remains a significant concern for surgeons, who must weigh the risk of post-operative bleeding with adequate analgesia in the setting of an opioid crisis. The results of our systematic review and meta-analysis show that over an inclusive range of studies on NSAIDs, many of which were published in the last 5 years,[14,77–96] NSAIDs are not significantly associated with postoperative hematomas, need for a return to the operating room, blood transfusions or other bleeding complications. The studies we reviewed were heterogeneous in nature, broadly covering a variety of different NSAIDs, doses and areas of the body, and overall, were of moderate quality.

Our study expands upon other systematic reviews and meta-analyses that sought to ascertain an association between NSAIDs and post-operative bleeding.[97,98] Prior studies were limited in scope by either part of the body or type of NSAID, for example focusing only on plastic surgery, or only on ibuprofen,[98,99] whereas our study was not limited by either. More recent systematic reviews and meta-analyses, including one published in 2018,[99] consist of older studies, only as recent as 2012. Our study incorporates the surge of publications in 2018 alone that examined use of NSAIDs for pain control and its association with postoperative bleeding. A more recent meta-analysis, published in 2019,[100] is limited in scope to hematoma only, and only evaluates plastic surgery cases. Therefore, our study is the most comprehensive in both time period, type of postoperative bleeding and body area included. Some of these prior papers come to opposite conclusions about the risk of perioperative NSAID use on surgical bleeding, perhaps due to their limited scope and smaller number of patients. Our findings are consistent with those of more recent meta-analyses, that NSAIDs are not associated with an increase in risk of clinically significant postoperative bleeding.

Our study had several limitations. First, we included observational studies rather than including only randomized controlled trials in the systematic review. However, this allowed us to include a broad range of studies and areas of the body, with more than half of the studies being RCTs. Importantly, most of the studies were quite recent and well-designed.

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Second, the definition of 'bleeding' as defined by hematoma was not uniform but based on how the study authors defined it. Third, the heterogeneity or poor reporting of age, race and gender in many studies precluded the ability to stratify our analysis by any of those characteristics based on the data presented in the published work. Fourth, two studies[38,50] had a short length of follow-up (12 hours) and therefore may have missed clinically significant bleeding. Interestingly, both of these studies were sponsored by drug companies (Roche[38] and Pfizer[50]). Finally, we did not study the effect of long-term preoperative use of NSAIDs on postoperative bleeding, so our conclusions only apply to immediate perioperative use of NSAIDs. Nonetheless, our study demonstrates that NSAIDs are not a source of clinically significant postoperative bleeding across a wide range of types of NSAIDs and body areas. Therefore, with regards to surgical bleeding, our results suggest that NSAIDs can be safely adopted as part of a multimodal analgesic strategy in the postoperative period.

Consistent adoption of multimodal analgesia is imperative to stem the opioid crisis while continuing to adequately treat patients' pain in the postoperative period. While interventions have been shown to increase uptake of acetaminophen, encouraging the use of NSAIDs has been more difficult. While barriers to NSAID use are multifactorial, one major barrier to use is the belief that NSAID use in the perioperative leads to increased surgical bleeding. Our systematic review and meta-analysis has shown that in fact, NSAID use was not associated with statistically significant postoperative bleeding.

Conclusions

The results of our systematic review and meta-analysis provide compelling evidence that NSAIDs, whether used in the preoperative, intraoperative or postoperative period, were not statistically associated with clinical bleeding in surgical patients. While other risks of NSAIDs should be taken into account, NSAID use can likely be safely adopted by many surgical specialties without fear of associated postoperative bleeding. Sustainable success in reducing opioid analgesia for diverse surgical procedures will require increased adoption of multimodal analgesia based on clear and published guidelines.[27] Dissemination of these results is critical for increased adoption and implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

We would like to acknowledge Pamela Derish, MA, who assisted with the scientific editing and revising of the manuscript.

Funding:

Dr. Steinman was funded by the National Institutes of Health (K24AG049057 and P30AG044281)

Dr. Bongiovanni was funded by grant number K12HS026383 from the Agency for Healthcare Research and Quality (AHRQ). The content is solely the responsibility of the authors and does not necessarily represent the official views of the AHRQ.

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Dr. Wick was funded by AHRQ (HHSP233201500020I). The content is solely the responsibility of the authors and does not necessarily represent the official views of the AHRQ.

References

1. Waljee JF, Li L, Brummett CM, Englesbe MJ. Iatrogenic Opioid Dependence in the United States: Are Surgeons the Gatekeepers? Ann Surg. 2017;265(4):728–730. doi:10.1097/SLA.0000000000001904 [PubMed: 27429023]
2. Economic Toll of Opioid Crisis in U.S. Exceeded $1 Trillion Since 2001. Altarum. Published September 27, 2018. Accessed August 19, 2020. https://altarum.org/news/economic-toll-opioid-crisis-us-exceeded-1-trillion-2001
3. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med. 2012;172(5):425–430. doi:10.1001/archinternmed.2011.1827 [PubMed: 22412106]
4. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348. doi:10.1136/bmj.g1251
5. Schoenfeld AJ, Nwosu K, Jiang W, et al. Risk Factors for Prolonged Opioid Use Following Spine Surgery, and the Association with Surgical Intensity, Among Opioid-Naive Patients. J Bone Joint Surg Am. 2017;99(15):1247–1252. doi:10.2106/JBJS.16.01075 [PubMed: 28763410]
6. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. J Pain Off J Am Pain Soc. 2017;18(11):1374–1383. doi:10.1016/j.jpain.2017.06.010
7. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. Jama. 2018;319(9):872–882. [PubMed: 29509867]
8. Combining Paracetamol (Acetaminophen) with Nonsteroidal Anti... : Anesthesia & Analgesia. Accessed August 19, 2020. https://journals.lww.com/anesthesia-analgesia/FullText/2010/04000/Combining_Paracetamol__Acetaminophen__with.30.aspx
9. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effectsMeta-analysis of randomized controlled trials. Anesthesiol J Am Soc Anesthesiol. 2005;102(6):1249–1260.
10. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study. Anesthesiology. 2018;128(5):891–902. doi:10.1097/ALN.0000000000002132 [PubMed: 29498951]
11. Gp J, De B, Rh E, et al. Defining new directions for more effective management of surgical pain in the United States: highlights of the inaugural Surgical Pain Congress™. Am Surg. 2014;80(3):219–228. [PubMed: 24666860]
12. Lancaster E, Bongiovanni T, Lin J, Croci R, Wick E, Hirose K. Residents as Key Effectors of Change in Improving Opioid Prescribing Behavior. J Surg Educ. 2019;76(6):e167–e172. doi:10.1016/j.jsurg.2019.05.016 [PubMed: 31155453]
13. Bongiovanni T, Hansen K, Lancaster E, O'Sullivan P, Hirose K, Wick E. Adopting best practices in post-operative analgesia prescribing in a safety-net hospital: Residents as a conduit to change. Am J Surg. 2020;219(2):299–303. doi:10.1016/j.amjsurg.2019.12.023 [PubMed: 31928779]
14. Rojas KE, Fortes TA, Flom P, Manasseh D-M, Andaz C, Borgen P. Intraoperative Ketorolac Use Does Not Increase the Risk of Bleeding in Breast Surgery. Ann Surg Oncol. Published online 2019. doi:10.1245/s10434-019-07557-8
15. Greer IA. Effects of ketorolac tromethamine on hemostasis. Pharmacotherapy. 1990;10(6 (Pt 2)):71S–76S. [PubMed: 2082316]
16. Conrad KA, Fagan TC, Mackie MJ, Mayshar PV. Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther. 1988;43(5):542–546. doi:10.1038/clpt.1988.70 [PubMed: 3259170]

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17. Rethlefsen ML, Murad MH, Livingston EH. Engaging Medical Librarians to Improve the Quality of Review Articles. JAMA. 2014;312(10):999–1000. doi:10.1001/jama.2014.9263 [PubMed: 25203078]
18. Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ Can Med Assoc J. 2002;167(10):1131–1137. [PubMed: 12427705]
19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557 [PubMed: 12958120]
20. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–634. doi:10.1136/bmj.315.7109.629 [PubMed: 9310563]
21. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–1101. [PubMed: 7786990]
22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377–384. doi:10.1136/jech.52.6.377 [PubMed: 9764259]
23. Silvestri MT, Bongiovanni TR, Glover JG, Gross CP. Impact of price display on provider ordering: A systematic review. J Hosp Med. 2016;11(1):65–76. doi:10.1002/jhm.2500 [PubMed: 26498736]
24. Hodsman NBA, Burns J, Blyth A, Kenny GNC, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia. 1987;42(9):1005–1008. doi:10.1111/j.1365-2044.1987.tb05377.x [PubMed: 3118730]
25. Manson AL. Trial of ibuprofen to prevent post-vasectomy complications. J Urol. 1988;139(5):965–966. doi:10.1016/s0022-5347(17)42732-7 [PubMed: 3283384]
26. Kristensen SS, Pedersen P, Pedersen NW, Schmidt SA, Kjaersgaard-Andersen P. Combined treatment with indomethacin and low-dose heparin after total hip replacement. A double-blind, placebo-controlled clinical trial. J BONE JT SURG SER B. 1990;72(3):447–449.
27. Tzeng JI, Mok MS Combination of intramuscular ketorolac and low dose epidural morphine for the relief of post-caesarean pain. ANN ACAD MED Singap. 1994;23(6 SUPPL.):10–13. [PubMed: 7710217]
28. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K. Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery: Pain. 1995;61(2):291–297. doi:10.1016/0304-3959(94)00184-G [PubMed: 7659440]
29. Etches RC, Warriner CB, Badner N, et al. Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty. Anesth Analg. 1995;81(6):1175–1180. doi:10.1097/00000539-199512000-00010 [PubMed: 7486100]
30. Gwirtz KH, Kim HC, Nagy DJ, et al. Intravenous ketorolac and subarachnoid opioid analgesia in the management of acute postoperative pain. Reg Anesth. 1995;20(5):395–401. [PubMed: 8519716]
31. Weale AE, Warwick DJ, Durant N, Prothero D. Is there a clinical interaction between low molecular weight heparin and non-steroidal analgesics after total hip replacement? Ann R Coll Surg Engl. 1995;77(1):35–37. [PubMed: 7717643]
32. Fragen RJ, Stulberg SD, Wixson R, Glisson S, Librojo E. Effect of ketorolac tromethamine on bleeding and on requirements for analgesia after total knee arthroplasty. J Bone Joint Surg Am. 1995;77(7):998–1002. doi:10.2106/00004623-199507000-00004 [PubMed: 7608243]
33. Milne JC, Russell JA, Woods GW, Dalton MD. Effect of ketorolac tromethamine (Toradol) on ecchymosis following anterior cruciate ligament reconstruction. Am J Knee Surg. 1995;8(1):24–27. [PubMed: 7866799]
34. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. JAMA. 1996;275(5):376–382. [PubMed: 8569017]
35. Marin-Bertolin S, De Andres J, Gonzalez-Martinez R, Valia Vera JC, Amorrortu-Velayos J. A controlled, randomized, double-blind study of ketorolac for postoperative analgesia after plastic surgery. Ann Plast Surg. 1997;38(5):478–484. [PubMed: 9160129]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

36. Bailey R, Sinha C, Burgess LPA. Ketorolac Tromethamine and Hemorrhage in Tonsillectomy: A Prospective, Randomized, Double-Blind Study. The Laryngoscope. 1997;107(2):166–169. doi:10.1097/00005537-199702000-00006 [PubMed: 9023238]
37. Balestrieri P, Simmons G, Hill D, et al. The effect of intravenous ketorolac given intraoperatively versus postoperatively on outcome from gynecologic abdominal surgery. J Clin Anesth. 1997;9(5):358–364. doi:10.1016/s0952-8180(97)00062-7 [PubMed: 9257200]
38. Barber F, Gladu D. Comparison of oral ketorolac and hydrocodone for pain relief after anterior cruciate ligament reconstruction. Arthrosc J Arthrosc Relat Surg. 1998;14(6):605–612. doi:10.1016/S0749-8063(98)70057-X
39. Mixter III CG, Meeker LD, Gavin TJ. Preemptive Pain Control in Patients Having Laparoscopic Hernia Repair: A Comparison of Ketorolac and Ibuprofen. Arch Surg. 1998;133(4). doi:10.1001/archsurg.133.4.432
40. Niemi T, Tanskanen P, Taxell C, Juvela S, Randell T, Rosenberg P. Effects of nonsteroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg Anesth. 1999;11(3):188–194.
41. Coloma M, White PF, Huber PJ Jr., Tongier WK, Dullye KK, Duffy LL The effect of ketorolac on recovery after anorectal surgery: Intravenous versus local administration. Anesth Analg. 2000;90(5):1107–1110. doi:10.1097/00000539-200005000-00019 [PubMed: 10781461]
42. Sharma S, Chang DW, Koutz C, et al. Incidence of hematoma associated with ketorolac after TRAM flap breast reconstruction. Plast Reconstr Surg. 2001;107(2):352–355. doi:10.1097/00006534-200102000-00009 [PubMed: 11214049]
43. Basto ER, Waintrop C, Mourey FD, Landru JP, Eurin BG, Jacob LP. Intravenous ketoprofen in thyroid and parathyroid surgery. Anesth Analg. 2001;92(4):1052–1057. doi:10.1097/00000539-200104000-00047 [PubMed: 11273950]
44. Tang J, Li S, White PF, et al. Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. Anesthesiology. 2002;96(6):1305–1309. doi:10.1097/00000542-200206000-00007 [PubMed: 12170040]
45. Forrest JB, Camu F, Greer IA, et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. Br J Anaesth. 2002;88(2):227–233. doi:10.1093/bja/88.2.227 [PubMed: 11883386]
46. Hegi TR, Bombeli T, Seifert B, et al. Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast cancer surgery compared with diclofenac. Br J Anaesth. 2004;92(4):523–531. doi:10.1093/bja/aeh107 [PubMed: 14977803]
47. Merry AF, Webster CS, Holland RL, et al. Clinical tolerability of perioperative tenoxicam in 1001 patients--a prospective, controlled, double-blind, multi-centre study. Pain. 2004;111(3):313–322. doi:10.1016/j.pain.2004.07.013 [PubMed: 15363875]
48. Jiménez Martínez E, Gasco García C, Arrieta Blanco JJ, Del Torno JG, Villar BB Study of the analgesic efficacy of Dexketoprofen Trometamol 25mg. vs. Ibuprofen 600mg. after their administration in patients subjected to oral surgery. Med Oral. 2004;9(2):138–148.
49. Legeby M, Sandelin K, Wickman M, Olofsson C. Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction. Acta Anaesthesiol Scand. 2005;49(9):1360–1366. doi:10.1111/j.1399-6576.2005.00811.x [PubMed: 16146476]
50. Beaussier M, Weickmans H, Paugam C, et al. A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. Anesth Analg. 2005;100(5):1309–1315. doi:10.1213/01.ANE.0000150972.88708.13 [PubMed: 15845675]
51. A randomized study of the effects of preoperative ketorolac on general anaesthesia for caesarean section. - Abstract - Europe PMC. Accessed August 19, 2020. https://europepmc.org/article/med/17459695
52. Mazaris EM, Varkarakis I, Chrisofos M, et al. Use of nonsteroidal anti-inflammatory drugs after radical retropubic prostatectomy: a prospective, randomized trial. Urology. 2008;72(6):1293–1297. doi:10.1016/j.urology.2007.12.039 [PubMed: 18329071]

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53. McKean SA, Lee MSW, Hussain SSM. Comparative study of posttonsillectomy hemorrhage with the use of diclofenac versus dihydrocodeine for postoperative analgesia and review of the literature. J Otolaryngol Head Neck Surg. 2008;37(4):577–581. [PubMed: 19128596]
54. Sun T, Sacan O, White PF, Coleman J, Rohrich RJ, Kenkel JM Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. Anesth Analg. 2008;106(3):950–958. doi:10.1213/ane.0b013e3181618831 [PubMed: 18292445]
55. Torgerson C, Yoskovitch A, Cole AFD, Conrad K. Postoperative Pain Management with Ketorolac in Facial Plastic Surgery Patients. J Otolaryngol. 2008;37(6):7.
56. Cassinelli EH, Dean CL, Garcia RM, Furey CG, Bohlman HH. Ketorolac Use for Postoperative Pain Management Following Lumbar Decompression Surgery: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial. Spine. 2008;33(12):1313–1317. doi:10.1097/BRS.0b013e31817329bd [PubMed: 18496342]
57. Chen T, Adamson PA. Comparison of ibuprofen and acetaminophen with codeine following cosmetic facial surgery. J Otolaryngol Head Neck Surg. 2009;38(5):580–586. [PubMed: 19769830]
58. Magni G, Rosa IL, Melillo G, Fioretti N, Imperiale C, Rosa G. Safety of Ketorolac in patients undergoing neurosurgical procedures. J Neurosurg Anesth. 2009;21(4):388–389. doi:10.1097/01.ana.0000358102.35410.08
59. Mowafi HA, Ismail SA Preoperative peritonsillar lornoxicam infiltration is not superior to intravenous lornoxicam for pain relief following tonsillectomy in adults. Eur J Anaesthesiol. 2010;27(9):807–811. doi:10.1097/EJA.0b013e32833c3101 [PubMed: 20613539]
60. Rawal N, Krøner K, Simin-Geertsen M, Hejl C, Likar R. Safety of lornoxicam in the treatment of postoperative pain: A post-marketing study of analgesic regimens containing lornoxicam compared with standard analgesic treatment in 3752 day-case surgery patients. Clin Drug Invest. 2010;30(10):687–697. doi:10.2165/11538860-000000000-00000
61. Blomqvist L, Sellman G, Strömbeck JO NSAID as pre- and postoperative medication - A potential risk for bleeding complications in reduction mammaplasty. EUR J PLAST SURG. 1996;19(1):26–28. doi:10.1007/BF00209787
62. Chin CJ, Franklin JH, Turner B, Sowerby L, Fung K, Yoo JH. Ketorolac in thyroid surgery: quantifying the risk of hematoma. J Otolaryngol Head Neck Surg. 2011;40(3):196–199. [PubMed: 21518639]
63. Klein M, Gögenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: Cohort study based on prospective data. BMJ Online. 2012;345(7879). doi:10.1136/bmj.e6166
64. Moeller C, Pawlowski J, Pappas AL, Fargo K, Welch K. The safety and efficacy of intravenous ketorolac in patients undergoing primary endoscopic sinus surgery: a randomized, double-blinded clinical trial. Int Forum Allergy Rhinol. 2012;2(4):342–347. doi:10.1002/alr.21028 [PubMed: 22411639]
65. Lee KT, Jeon B-J, Lim S-Y, et al. The effects of ketorolac on microvascular thrombosis in lower extremity reconstruction. Plast Reconstr Surg. 2012;129(6):1322–1327. doi:10.1097/PRS.0b013e31824ec33f [PubMed: 22327889]
66. Gan TJ, Daniels SE, Singla N, Hamilton DA, Carr DB A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: A multicenter, double-blind, randomized, multiple-dose study. Anesth Analg. 2012;115(5):1212–1220. doi:10.1213/ANE.0b013e3182691bf9 [PubMed: 22886837]
67. Cawthorn TR, Phelan R, Davidson JS, Turner KE Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty. Can J Anesth. 2012;59(5):466–472. doi:10.1007/s12630-012-9682-z [PubMed: 22434401]
68. Kim MK, Lee JW, Kim MG, Ha SY, Lee JS, Yeo SG. Analysis of prognostic factors for postoperative bleeding after tonsillectomy. Eur Arch Otorhinolaryngol. 2012;269(3):977–981. doi:10.1007/s00405-011-1697-5 [PubMed: 21779841]
69. Mitchell A, McCrea P, Inglis K, Porter G. A Randomized, Controlled Trial Comparing Acetaminophen Plus Ibuprofen versus Acetaminophen Plus Codeine Plus Caffeine (Tylenol

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3) after Outpatient Breast Surgery. Ann Surg Oncol. 2012;19(12):3792–3800. doi:10.1245/s10434-012-2447-7 [PubMed: 22713999]

70. Sun M, Liao Q, Wen L, Yan X, Zhang F, Ouyang W. Effect of perioperative intravenous flurbiprofen axetil on chronic postmastectomy pain. Zhong Nan Xue Xue Bao Yi Xue Ban. 2013;38(7):653–660. doi:10.3969/j.issn.1672-7347.2013.07.001
71. Chelly JE, Singla SK, Melson TI, Lacouture PG, Paadre S, Carr DB Safety of a Novel Parenteral Formulation of Diclofenac after Major Orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial. Pain Med. 2013;14(5):749–761. doi:10.1111/pme.12076 [PubMed: 23566212]
72. Jian M, Li X, Wang A, Zhang L, Han R, Gelb AW. Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery. Br J Anaesth. 2014;113(5):832–839. doi:10.1093/bja/aeu185 [PubMed: 24966149]
73. Oliveri L, Jerzewski K, Kulik A. Black box warning: is ketorolac safe for use after cardiac surgery? J Cardiothorac Vasc Anesth. 2014;28(2):274–279. doi:10.1053/j.jvca.2013.07.014 [PubMed: 24231193]
74. Patai A, Solymosi N, Patai AV. Does rectal indomethacin given for prevention of post-ERCP pancreatitis increase bleeding after biliary endoscopic sphincterotomy or cardiovascular mortality?: Post hoc analysis using prospective clinical trial data. Med Baltim. 2014;93(26):e159. doi:10.1097/MD.0000000000000159
75. Schleiffarth JR, Bayon R, Chang KE, Van Daele DJ, Pagedar NA Ketorolac after free tissue transfer: A comparative effectiveness study. Ann Otol Rhinol Laryngol. 2014;123(6):446–449. doi:10.1177/0003489414526849 [PubMed: 24690984]
76. Dirkmann D, Groeben H, Farhan H, Stahl DL, Eikermann M. Effects of parecoxib on analgesia benefit and blood loss following open prostatectomy: a multicentre randomized trial. BMC Anesth. 2015;15:31. doi:10.1186/s12871-015-0015-y
77. Chen H, Luo A. Safety and Efficacy Study of the Cyclooxygenase-2 Inhibitor Parecoxib Sodium Applied for Postoperative Analgesia After Endo-Nasal Operation. Pain Pr. 2016;16(4):467–472. doi:10.1111/papr.12294
78. Kim S-I, Ha K-Y, Oh I-S Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial. Eur Spine J. 2016;25(5):1614–1619. doi:10.1007/s00586-015-4216-3 [PubMed: 26324284]
79. Argoff C, McCarberg B, Gudin J, Nalamachu S, Young C. SoluMatrix® diclofenac: Sustained opioid-sparing effects in a phase 3 study in patients with postoperative pain. Pain Med. 2016;17(10):1933–1941. doi:10.1093/pm/pnw012 [PubMed: 26995799]
80. Shah S, Thompson D, Goldstein H. The effect of postoperative ketorolac on hemoglobin and postoperative pain control after vaginal surgery. Am J Obstet Gynecol. 2017;216(3):S584.
81. Oltman J, Militsakh O, D'Agostino M, et al. Multimodal analgesia in outpatient head and neck surgery a feasibility and safety study. JAMA Otolaryngol Head Neck Surg. 2017;143(12):1207–1212. doi:10.1001/jamaoto.2017.1773 [PubMed: 29049548]
82. Bonde C, Khorasani H, Hoejvig J, Kehlet H. Cyclooxygenase-2 inhibitors and free flap complications after autologous breast reconstruction: A retrospective cohort study. J Plast Reconstr Aesthet Surg. 2017;70(11):1543–1546. doi:10.1016/j.bjps.2017.06.007 [PubMed: 28822648]
83. Tan P, Martin M, Shank N, et al. A Comparison of Four Analgesic Regimens for Acute Postoperative Pain Control in Breast Augmentation Patients. Ann Plast Surg. 2017;78(6):S299–S304. doi:10.1097/SAP.0000000000001132 [PubMed: 28459704]
84. Firriolo JM, Nuzzi LC, Schmidtberg LC, Labow BI Perioperative Ketorolac Use and Postoperative Hematoma Formation in Reduction Mammaplasty: A Single-Surgeon Experience of 500 Consecutive Cases. Plast Reconstr Surg. 2018;142(5):632e–638e. doi:10.1097/PRS.0000000000004828
85. Mikhaylov Y, Weinstein B, Schrank TP, et al. Ketorolac and Hematoma Incidence in Postmastectomy Implant-Based Breast Reconstruction. Ann Plast Surg. 2018;80(5):472–474. doi:10.1097/SAP.0000000000001409 [PubMed: 29538000]

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86. Militsakh O, Lydiatt W, Lydiatt D, et al. Development of multimodal analgesia pathways in outpatient thyroid and parathyroid surgery and association with postoperative opioid prescription patterns. JAMA Otolaryngol Head Neck Surg. 2018;144(11):1023–1029. doi:10.1001/jamaoto.2018.0987 [PubMed: 30027221]
87. Nguyen B, Barta R, Heinrich C. Toradol® use in breast reconstruction: Risk of hematoma and benefit of post-operative pain control. Ann Surg Oncol. 2018;25(2):185–186. doi:10.1245/s10434-018-6534-2
88. Nguyen BN, Barta RJ, Stewart CE, Heinrich CA Toradol following Breast Surgery: Is There an Increased Risk of Hematoma? Plast Reconstr Surg. 2018;141(6):814e–817e. doi:10.1097/PRS.0000000000004361
89. Kelley BP, Chung KC, Chung T-T, et al. Postoperative Ketorolac in Breast and Body Contouring Procedures: A Nationwide Claims Analysis. Plast Reconstr Surg. 2018;142(4):472e–480e. doi:10.1097/PRS.0000000000004806
90. Fonseca ACG, Engelhardt MI, Huang ZJ, Jiang ZY, Yuksel S, Roy S. Effect of changing postoperative pain management on bleeding rates in tonsillectomy patients. Am J Otolaryngol. 2018;39(4):445–447. doi:10.1016/j.amjoto.2018.03.028 [PubMed: 29655490]
91. Trowbridge ER, Kim D, Caldwell L, et al. Use of Ketorolac after Outpatient Urogynecologic Surgery: A Randomized Control Trial. Female Pelvic Med Reconstr Surg. 2018;24(4):281–286. doi:10.1097/SPV.0000000000000459 [PubMed: 28914700]
92. Carpenter PS, Shepherd HM, McCrary H, et al. Association of celecoxib use with decreased opioid requirements after head and neck cancer surgery with free tissue reconstruction. JAMA Otolaryngol Head Neck Surg. 2018;144(11):988–994. doi:10.1001/jamaoto.2018.0284 [PubMed: 29710229]
93. Bakker N, Deelder JD, Richir MC, et al. Risk of anastomotic leakage with nonsteroidal anti-inflammatory drugs within an enhanced recovery program. J Gastrointest Surg. 2016;20(4):776–782. doi:10.1007/s11605-015-3010-1 [PubMed: 26536884]
94. Fortes T, Rojas K, Flom P, Manasseh D-M, Andaz C, Borgen P. Intraoperative ketorolac use does not increase the risk of bleeding complications in breast surgery. Ann Surg Oncol. 2019;26(2):247–248. doi:10.1245/s10434-019-07407-7
95. Lee M, Rhee J, Kim Y, Jung YH, Ahn S-H, Jeong W-J Perioperative risk factors for post-thyroidectomy hematoma: Significance of pain and ketorolac usage. Head Neck. 2019;((Lee M.; Kim Y.; Jung Y.H.; Jeong W.-J., safar@snubh.org) Department of Otorhinolaryngology–Head&Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea). doi:10.1002/hed.25895
96. Abou Zeid H, Kallab R, Najm MA, et al. Safety and Efficacy of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Used for Analgesia After Bariatric Surgery: A Retrospective Case-Control Study. Obes Surg. 2019;29(3):911–916. doi:10.1007/s11695-018-3608-y [PubMed: 30484174]
97. Davidson JS, Turner K. Ketorolac Does Not Increase Perioperative Bleeding: A Meta-Analysis of Randomized Controlled Trials. Plast Reconstr Surg. 2015;135(3). doi:10.1097/PRS.0000000000001046
98. Kelley BP, Bennett KG, Chung KC, Kozlow JH. IBUPROFEN DOES NOT INCREASE BLEEDING RISK IN PLASTIC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS. Plast Reconstr Surg. 2016;137(4):1309–1316. doi:10.1097/PRS.0000000000002027 [PubMed: 27018685]
99. Forsyth MG, Clarkson DJ, O'Boyle CP. A systematic review of the risk of postoperative bleeding with perioperative non-steroidal anti-inflammatory drugs (NSAIDs) in plastic surgery. Eur J Plast Surg. 2018;41(5):505–510. doi:10.1007/s00238-018-1410-7
100. Walker NJ, Jones VM, Kratky L, Chen H, Runyan CM. Hematoma Risks of Nonsteroidal Anti-inflammatory Drugs Used in Plastic Surgery Procedures: A Systematic Review and Meta-analysis. Ann Plast Surg. 2019;82(6S):S437. doi:10.1097/SAP.0000000000001898 [PubMed: 30950877]
101. Klein M, Stockel M, Rosenberg J, Gogenur I. Intraoperative ketorolac and bleeding after laparoscopic Roux-en-Y gastric by-pass surgery. Acta Chir Belg. 2012;112(5):369–373. [PubMed: 23175926]

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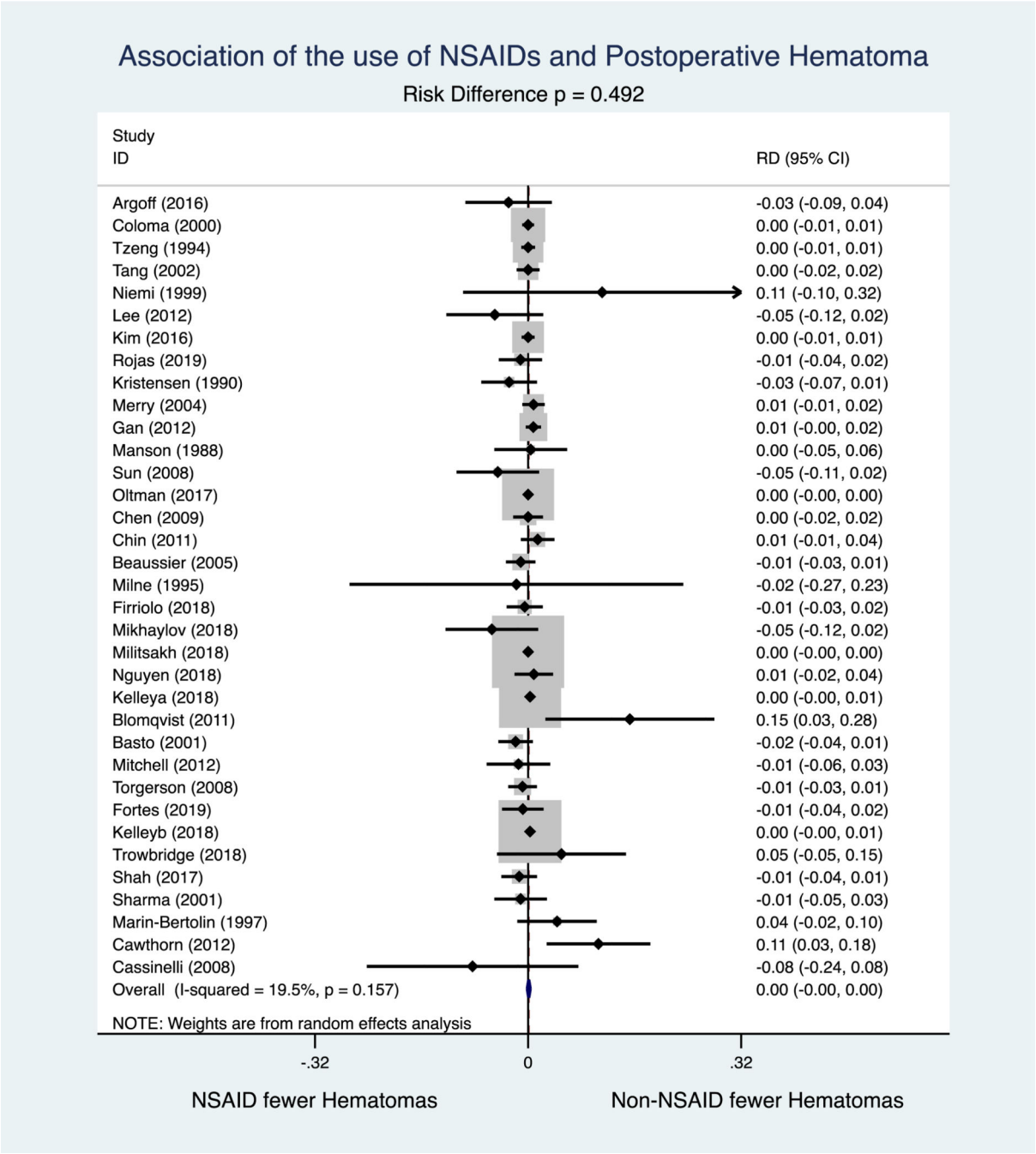

Figure 1:
Association with NSAIDs and Postoperative Hematoma (no statistically significant association)

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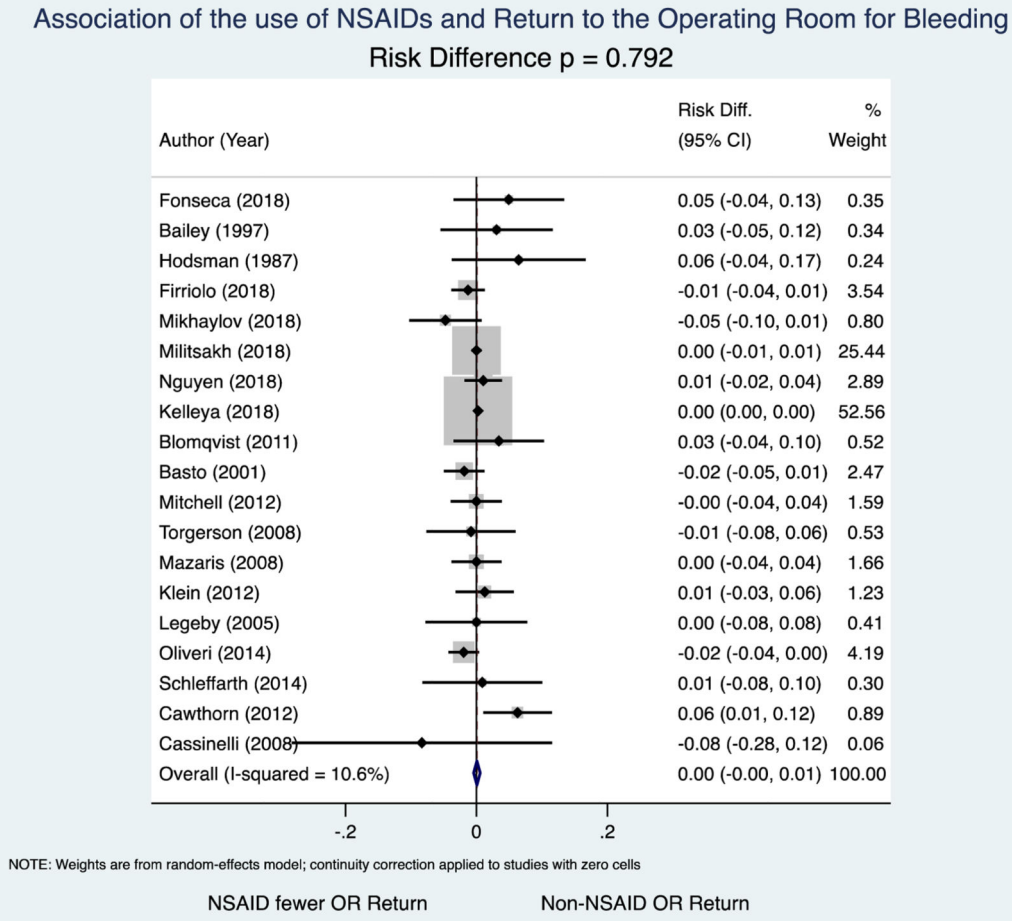

Figure 2:

Association with NSAIDs and Return to the Operating Room for Bleeding (no statistically significant association)

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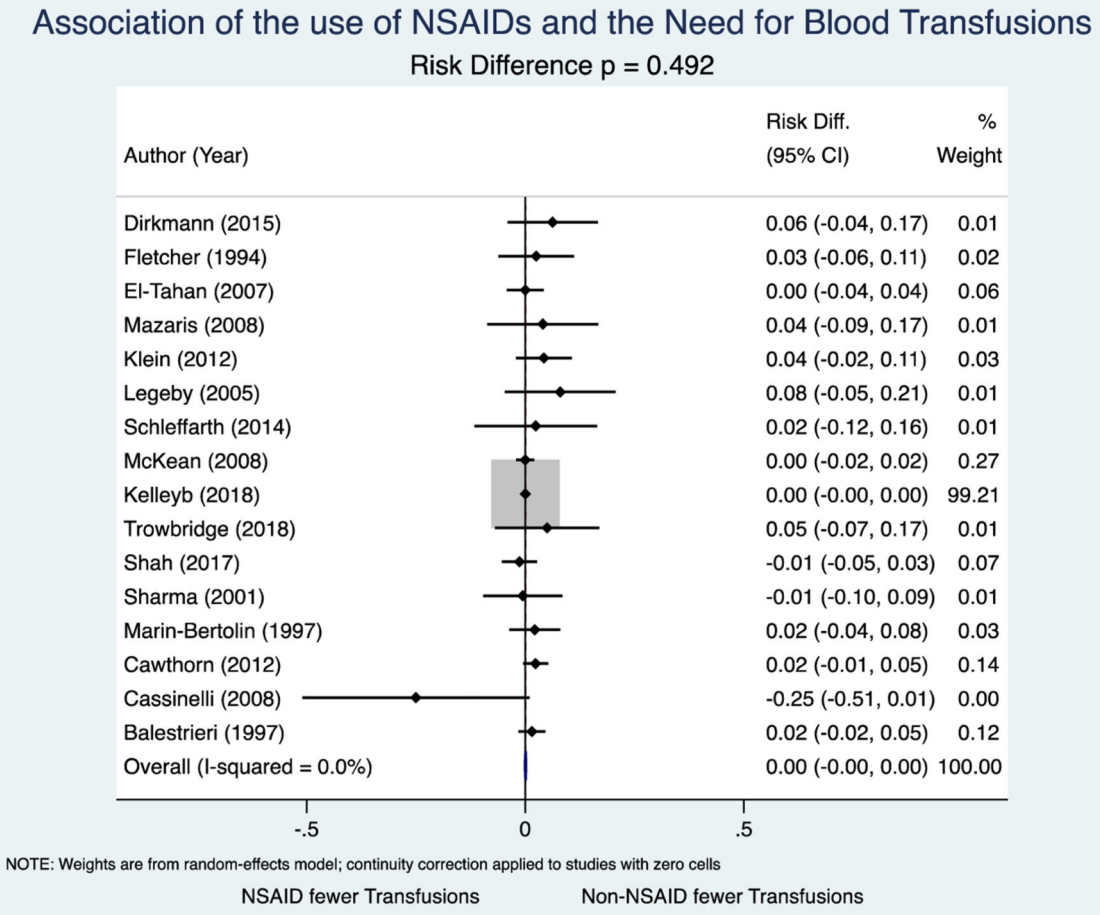

Figure 3:
Association with NSAIDs and Blood Transfusion (no statistically significant association)

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Table 1:

Titles Included in Systematic Review, with selected associated data

Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
The morphine sparing effects of Diclofenac sodium following abdominal surgery[24]	1987	Anaesthesia	RCT	Diclofenac	IM	.	18–75	62	Abdomen	1987	Ireland
Trial of ibuprofen to prevent post-vasectomy complications[25]	1988	J Urol	RCT	Ibuprofen	PO	Post	.	102	Urology	1986–1987	USA
Combined treatment with Indomethacin and low-dose heparin after total hip replacement. A double-blind, placebo-controlled clinical trial[26]	1990	J Bone Surg	RCT	Indomethacin	PO	Post	.	204	Ortho	1984–1986	Denmark
Influence of timing on the analgesic effect of intravenous Ketorolac after orthopedic surgery[28]	1994	Pain	RCT	Ketorolac	IV	Pre, Post	.	60	Ortho	before 1995	France
Combination of intramuscular Ketorolac and low dose epidural morphine for the relief of post caesarean pain[27]	1994	Ann Acad Med Singapore	RCT	Ketorolac	IM	Post	.	90	Abdomen	before 1994	Singapore
Continuous intravenous administration of Ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty[29]	1995	Anesth Analg	RCT	Ketorolac	IV	Post	50–75	174	Ortho	before 1995	Canada
Effect of Ketorolac Tromethamine on Bleeding and on Requirements for Analgesia after Total Knee Arthroplasty[32]	1995	The Journal of Bone and Joint Surgery	RCT	Ketorolac	IV	Intra, Post	.	59	Ortho	before 1995	USA
Intravenous Ketorolac and subarachnoid opioid analgesia in the management of acute postoperative pain[30]	1995	Reg Anesth	RCT	Ketorolac	IV	Intra, Post	16–72	38	Urology	before 1994	USA
Effect of Ketorolac Tromethamine (Toradol) on ecchymosis following anterior cruciate ligament reconstruction[33]	1995	Am J Knee Surg	RCT	Ketorolac	.	Intra, Post	.	64	Ortho	before 1993	USA
Is there a clinical interaction between low molecular weight heparin and non-steroidal	1995	Ann R Coll Surg Engl	RCT	Ketorolac	IM	Pre, Post	.	60	Ortho	before 1995	United Kingdom

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
analgesics after total hip replacement?[31]											
Parenteral Ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study[34]	1996	JAMA	Cohort	Ketorolac	IV or IM	Pre, Intra, Post	.	14,797	Mixed	1991–1993	USA
Ketorolac tromethamine and hemorrhage in tonsillectomy: A prospective, randomized, double-blind study[36]	1997	The Laryngoscope	RCT	Ketorolac	IM	Post	19–37	80	ENT	1992–1994	USA
The effect of intravenous Ketorolac given intraoperatively versus postoperatively on outcome from gynecologic abdominal surgery[37]	1997	Journal of Clinical Anesthesia	RCT	Ketorolac	.	Intra, Post	.	199	Gynecologic	before 1997	USA
A controlled, randomized, double-blind study of Ketorolac for postoperative analgesia after plastic surgery	1997	Ann Plast Surg	RCT	Ketorolac, Metamizol	IM	Post	18–75	92	Plastics	before 1997	Spain
Comparison of Oral Ketorolac and Hydrocodone for Pain Relief After Anterior Cruciate Ligament Reconstruction[38]	1998	Arthroscopy: The Journal of Arthroscopic and Related Surgery	RCT	Ketorolac	IV or IM, then PO	Post	18–52	125	Ortho	before 1998	USA
Preemptive Pain Control in Patients Having Laparoscopic Hernia Repair[39]	1998	Arch Surg	RCT	Ibuprofen, Ketorolac	IV or PO	Pre, Post	16–83	70	Abdomen	1994–1996	USA
Effects of nonsteroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage[40]	1999	J Neurosurg Anesthesiol	RCT	Ketoprofen	PO	Post	.	18	Mixed	before 1999	Finland
The effect of Ketorolac on recovery after anorectal surgery: Intravenous versus local administration[41]	2000	Anesth Analg	RCT	Ketorolac	IV and local	Intra	.	105	Perianal	before 2000	USA
Intravenous ketoprofen in thyroid and parathyroid surgery[43]	2001	Anesth Analg	Cohort	ketoprofen	IV	Intra, Post	.	214	Endocrine	1998–1999	France
Incidence of hematoma associated with Ketorolac after TRAM flap breast reconstruction[42]	2001	Plast Reconstr Surg	Cohort	Ketorolac	IV	Post	.	215	Breast	1988–1998	USA
Ketorolac, Diclofenac, and ketoprofen are equally safe for pain relief after major surgery[45]	2002	Br J Anaesth	RCT	Ketorolac, Diclofenac, Ketoprofen	IV/PO	Post	49	11,245	Mixed	before 2002	Europe

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
Effect of Parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control[44]	2002	Anesthesiology	RCT	Parecoxib	IV	Post	.	55	Abdomen	before 2002	USA
Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast cancer surgery compared with Diclofenac[46]	2004	Br J Anaesth	RCT	Rofecoxib	PO	Pre, Post	36–74	50	Mixed	before to 2003	Switzerland
Study of the analgesic efficacy of Dexketoprofen Trometamol 25mg. vs. Ibuprofen 600mg. after their administration in patients subjected to oral surgery[48]	2004	Med. Oral	Cohort	Ibuprofen, Dexketoprofen	PO	Post	18–65	93	Dental	2000–2001	Spain
Clinical tolerability of perioperative tenoxicam in 1001 patients--a prospective, controlled, double-blind, multi-centre study[47]	2004	Pain	RCT	Tenoxicam	IV/PO	Intra, Post	18–80	1,001	Mixed	1995–1997	New Zealand
A randomized, double-blind comparison between Parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients[50]	2005	Anesth Analg	RCT	Parecoxib	IV	Intra	18–70	182	Abdomen	2000–2003	France
Analgesic efficacy of Diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction[49]	2005	Acta Anaesthesiol Scand	RCT	Diclofenac	suppository	Pre, Post	30–72	48	Breast	1999–2001	Sweden
A randomized study of the effects of preoperative Ketorolac on general anaesthesia for caesarean section[51]	2007	International Journal of Obstetric Anesthesia	RCT	Ketorolac	IV	Intra	20–35	90	Obstetrics	2005–2006	Egypt
Ketorolac use for postoperative pain management following lumbar decompression surgery[56]	2008	Spine	RCT	Ketorolac	IV	Post	52–76	25	Ortho	2007	USA
Use of nonsteroidal anti-inflammatory drugs after radical retropubic prostatectomy: a prospective, randomized trial[52]	2008	Urology	RCT	Lornoxicam	IV	Post	.	100	Abdomen	2005–2006	Greece
Comparative study of posttonsillectomy hemorrhage with the use of Diclofenac versus dihydrocodeine for postoperative	2008	J Otolaryngol Head Neck Surg	Cohort	Diclofenac	PO	Post	16–56	193	ENT	2005	United Kingdom

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
analgesia and review of the literature[53]											
Perioperative versus postoperative Celecoxib on patient outcomes after major plastic surgery procedures[54]	2008	Anesth. Analg.	RCT	Celecoxib	PO	Pre, Post	18–75	120	Plastics	before 2007	USA
Postoperative pain management with Ketorolac in facial plastic surgery patients[55]	2008	Journal of Otolaryngology - Head & Neck Surgery	RCT	Ketorolac	IM	Intra	38–77	140	Cosmetic	before 2008	Canada
Comparison of ibuprofen and acetaminophen with codeine following cosmetic facial surgery[57]	2009	J Otolaryngol Head Neck Surg	RCT	Ibuprofen	PO	Post	.	35	Cosmetic	2006–2007	Canada
Safety of Ketorolac in patients undergoing neurosurgical procedures[58]	2009	J Neurosurg Anesthesiol	Case control	Ketorolac	IV	Post	.	60	Craniotomy	.	.
Preoperative peritonsillar lornoxicam infiltration is not superior to intravenous lornoxicam for pain relief following tonsillectomy in adults[59]	2010	Eur J Anaesthesiol	RCT	Lornoxicam	IV	Intra	.	59	ENT	before 2010	Saudi Arabia
Safety of lornoxicam in the treatment of postoperative pain: A post-marketing study of analgesic regimens containing lornoxicam compared with standard analgesic treatment in 3752 day-case surgery patients[60]	2010	Clin Drug Invest	RCT	Lornoxicam	PO	Post	13–95	1,838	Mixed	1997–1999	Europe
NSAID as pre- and postoperative medication - A potential risk for bleeding complications in reduction mammaplasty[61]	2011	Eur J Plast Surg	Cohort	Diclofenac, Ketorolac	IM	Pre, Post	16–75	293	Breast	1990–1991	Europe
Ketorolac in thyroid surgery: quantifying the risk of hematoma[62]	2011	J Otolaryngol Head Neck Surg	Cohort	Ketorolac	IV	Intra	.	799	Endocrine	2002–2007	Canada
Retrospective analysis of perioperative Ketorolac and postoperative bleeding in reduction mammoplasty[67]	2012	Can J Anesth	Cohort	Ketorolac	IV	Intra, Post	.	379	Cosmetic	2004–2007	Canada
A novel injectable formulation of Diclofenac compared with intravenous Ketorolac or placebo for acute moderate-to-severe	2012	Anesth Analg	RCT	Diclofenac, Ketorolac	IV	Post	18–65	331	Mixed	before 2012	USA

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
pain after abdominal or pelvic surgery: A multicenter, double-blind, randomized, multiple-dose study[66]											
Analysis of prognostic factors for postoperative bleeding after tonsillectomy[68]	2012	Eur Arch Otorhinolaryngol	Cohort	not specified	.	.	.	2,254	ENT	2005–2009	Korea
Intraoperative Ketorolac and bleeding after laparoscopic Roux-en-Y gastric by-pass surgery[101]	2012	Acta Chir Belg	Cohort	Ketorolac	IV	Intra	.	162	Abdomen	2006–2010	Denmark
The effects of Ketorolac on microvascular thrombosis in lower extremity reconstruction[65]	2012	Plast Reconstr Surg	Cohort	Ketorolac	IV	Post	.	128	Plastics (microvascular)	2005–2011	Korea
A randomized, controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery[69]	2012	Ann Surg Oncol	RCT	Ibuprofen	PO	Post	.	141	Breast	2006–2008	Canada
The safety and efficacy of intravenous Ketorolac in patients undergoing primary endoscopic sinus surgery: a randomized, double-blinded clinical trial[64]	2012	Int Forum Allergy Rhinol	RCT	Ketorolac	IV	Post	27–59	34	ENT	2010–2011	USA
Safety of a Novel Parenteral Formulation of Diclofenac after Major Orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial[71]	2013	Pain Med.	Cohort	Diclofenac	IV	Post	18–85	971	Abdomen	before 2013	USA
Effect of perioperative intravenous flurbiprofen axetil on chronic postmastectomy pain[70]	2013	J Cent South Univ	RCT	Flurbiprofen axetil	IV	Pre, Post	20–65	60	Breast	2010–2011	China
Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery[72]	2014	Br J Anaesth	Case control	Flurbiprofen	IV	Intra, Post	18–78	368	Craniotomy	2006–2011	China
Black box warning: is Ketorolac safe for use after cardiac surgery?[73]	2014	J Cardiothorac Vasc Anesth	Cohort	Ketorolac	not specified	Post	.	1,309	Cardiac	2006–2012	USA

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
Does rectal Indomethacin given for prevention of post-ERCP pancreatitis increase bleeding after biliary endoscopic sphincterotomy or cardiovascular mortality?: Post hoc analysis using prospective clinical trial data[74]	2014	Medicine	RCT	Indomethacin	PR	Pre	.	637	Gastroenterology	2008–2013	Hungary
Ketorolac after free tissue transfer: A comparative effectiveness study[75]	2014	Ann Otol Rhinol Laryngol	Cohort	Ketorolac	IV	Post	.	138	Plastics (microvascular)	2010–2012	USA
Effects of Parecoxib on analgesia benefit and blood loss following open prostatectomy: a multicentre randomized trial[76]	2015	BMC Anesthesiol	RCT	Parecoxib	IV	Post	46–83	96	Abdomen	2006–2010	Germany
SoluMatrix Diclofenac: Sustained Opioid-Sparing Effects in a Phase 3 Study in Patients with Postoperative Pain[79]	2016	Pain Medicine	RCT	Diclofenac, Celecoxib	PO	Post	.	428	Podiatry	before 2016	USA
Safety and Efficacy Study of the Cyclooxygenase-2 Inhibitor Parecoxib Sodium Applied for Postoperative Analgesia After Endo-Nasal Operation[77]	2016	Pain Pract	RCT	Parecoxib	IV	Intra	18–55	64	ENT	before 2015	China
Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial[78]	2016	Eur Spine J	RCT	Celecoxib	.	Pre, Post	.	80	Ortho	2012–2013	Korea
Cyclooxygenase-2 inhibitors and free flap complications after autologous breast reconstruction: A retrospective cohort study[82]	2017	J Plast Reconstr Aesthet Surg	Cohort	Celecoxib, Ibuprofen	.	Post	33–69 32–73	260	Breast	2006–2014	United Kingdom
Multimodal analgesia in outpatient head and neck surgery a feasibility and safety study[81]	2017	JAMA Otolaryngol. Head Neck Surg.	Cohort	Meloxicam, Celecoxib, Ibuprofen	PO	Pre, Post	.	222	Endocrine	2016–2017	USA
The effect of postoperative Ketorolac on hemoglobin and postoperative pain control after vaginal surgery[80]	2017	Am J Obstet Gynecol	Cohort	Ketorolac	.	.	.	129	Gynecologic	2014	USA
A comparison of 4 analgesic regimens for acute postoperative pain control in breast augmentation patients[83]	2017	Ann Plast Surg	Cohort	Ketorolac	IV/IM	Intra, Post	18–40	132	Breast	2009–2015	USA

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
Risk of anastomotic leakage with nonsteroidal anti-inflammatory drugs within an enhanced recovery program[93]	2018	J Gastrointest Surg	Case control	Ketorolac	IV	Intra, Post	.	80	Breast	2006–2013	The Netherlands
Association of Celecoxib use with decreased opioid requirements after head and neck cancer surgery with free tissue reconstruction[92]	2018	JAMA Otolaryngol. Head Neck Surg.	Case control	Celecoxib	NG	Post	.	102	ENT	2015–2017	USA
Perioperative Ketorolac Use and Postoperative Hematoma Formation in Reduction Mammaplasty: A Single-Surgeon Experience of 500 Consecutive Cases[84]	2018	Plast Reconstr Surg	Cohort	Ketorolac	IV	Intra, Post	16–20	500	Breast	2007–2017	USA
Effect of changing postoperative pain management on bleeding rates in tonsillectomy patients[90]	2018	Am J Otolaryngol	Cohort	Ibuprofen	.	Post	.	246	ENT	2013–2017	USA
Postoperative Ketorolac in Breast and Body Contouring Procedures: A Nationwide Claims Analysis[89]	2018	Plast Reconstr Surg	Cohort	Ketorolac	IV	Post	.	106,279	Cosmetic	2009–2014	USA
Ketorolac and Hematoma Incidence in Postmastectomy Implant-Based Breast Reconstruction[85]	2018	Ann Plast Surg	Cohort	Ketorolac	.	.	.	180	Breast	2008–2013	USA
Development of multimodal analgesia pathways in outpatient thyroid and parathyroid surgery and association with postoperative opioid prescription patterns[86]	2018	JAMA Otolaryngol Head Neck Surg	Cohort	Meloxicam, Ibuprofen	PO	Pre, Post	.	528	ENT	2015–2017	USA
Toradol use in breast reconstruction: Risk of hematoma and benefit of post-operative pain control[87]	2018	Ann Surg Oncol	Cohort	Ketorolac	IV	Post	.	202	Breast	2012–2016	USA
Toradol following Breast Surgery: Is There an Increased Risk of Hematoma?[88]	2018	Plast Reconstr Surg	Cohort	Ketorolac	IV	Intra, Post	.	763	Breast	2012–2014	USA
Use of Ketorolac after Outpatient Urogynecologic Surgery: A Randomized Control Trial[91]	2018	Female Pelvic Med. Reconstr. Surg.	RCT	Ketorolac	IV	Intra	.	49	Gynecologic	2012–2015	USA
Safety and Efficacy of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) Used for Analgesia After Bariatric Surgery:	2019	Obesity Surgery	Case control	Ketoprofen	IV	Post	16–63	270	Abdomen	2017	France

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Title	Year	Journal	Study Type	NSAID studied	Route	Timing	Age in range	Number of patients	Body Area	Years of Study	Country or Region
A Retrospective Case Control Study[96]											
Intraoperative Ketorolac use does not increase the risk of bleeding complications in breast surgery[94]	2019	Ann. Surg. Oncol.	Cohort	Ketorolac	IV	Intra	.	213	Breast	2017–2018	USA
Perioperative risk factors for post-thyroidectomy hematoma: Significance of pain and Ketorolac usage[95]	2019	Head Neck	Case control	Ketorolac	IV	.	33–59	88	Endocrine	2003–2012	Korea
Intraoperative Ketorolac Use Does Not Increase the Risk of Bleeding in Breast Surgery[14]	2019	Ann Surg Oncol	Cohort	Ketorolac	IV	Intra	16–94	214	Breast	2017–2018	USA

“.” = not specified or unable to determine

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Table 2:

Quality Scoring Using Downs & Black (Average score = 17)

Title	Year	Total Downs & Black Score
The morphine sparing effects of diclofenac sodium following abdominal surgery	1987	18
Trial of ibuprofen to prevent post-vasectomy complications.	1988	12
Combined treatment with indomethacin and low-dose heparin after total hip replacement. A double-blind, placebo-controlled clinical trial	1990	15
Combination of intramuscular ketorolac and low dose epidural morphine for the relief of post caesarean pain	1994	19
Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery	1994	22
Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty.	1995	25
Intravenous ketorolac and subarachnoid opioid analgesia in the management of acute postoperative pain.	1995	20
Is there a clinical interaction between low molecular weight heparin and non-steroidal analgesics after total hip replacement?	1995	15
Effect of Ketorolac Tromethamine on Bleeding and on Requirements for Analgesia after Total Knee Arthroplasty	1995	19
Effect of ketorolac tromethamine (Toradol) on ecchymosis following anterior cruciate ligament reconstruction	1995	14
Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study.	1996	17
A controlled, randomized, double-blind study of ketorolac for postoperative analgesia after plastic surgery.	1997	20
Ketorolac tromethamine and hemorrhage in tonsillectomy: A prospective, randomized, double-blind study	1997	16
The effect of intravenous ketorolac given intraoperatively versus postoperatively on outcome from gynecologic abdominal surgery	1997	15
Comparison of Oral Ketorolac and Hydrocodone for Pain Relief After Anterior Cruciate Ligament Reconstruction	1998	17
Preemptive Pain Control in Patients Having Laparoscopic Hernia Repair	1998	20
Effects of nonsteroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage.	1999	16
The effect of ketorolac on recovery after anorectal surgery: Intravenous versus local administration	2000	15
Incidence of hematoma associated with ketorolac after TRAM flap breast reconstruction.	2001	12
Intravenous ketoprofen in thyroid and parathyroid surgery.	2001	13
Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control	2002	20
Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery.	2002	19
Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast cancer surgery compared with diclofenac	2004	22
Clinical tolerability of perioperative tenoxicam in 1001 patients--a prospective, controlled, double-blind, multi-centre study.	2004	18
Study of the analgesic efficacy of Dexketoprofen Trometamol 25mg. vs. Ibuprofen 600mg. after their administration in patients subjected to oral surgery	2004	12
Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction.	2005	19

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Title	Year	Total Downs & Black Score
A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients	2005	17
A randomized stud of the effects of preoperative ketorolac on general anaesthesia for caesarean section	2007	20
Use of nonsteroidal anti-inflammatory drugs after radical retropubic prostatectomy: a prospective, randomized trial	2008	14
Comparative study of posttonsillectomy hemorrhage with the use of diclofenac versus dihydrocodeine for postoperative analgesia and review of the literature	2008	11
Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures	2008	23
Postoperative pain management with ketorolac in facial plastic surgery patients	2008	17
Ketorolac use for postoperative pain management following lumbar decompression surgery	2008	20
Comparison of ibuprofen and acetaminophen with codeine following cosmetic facial surgery	2009	18
Safety of Ketorolac in patients undergoing neurosurgical procedures	2009	14
Preoperative peritonsillar lornoxicam infiltration is not superior to intravenous lornoxicam for pain relief following tonsillectomy in adults	2010	22
Safety of lornoxicam in the treatment of postoperative pain: A post-marketing study of analgesic regimens containing lornoxicam compared with standard analgesic treatment in 3752 day-case surgery patients	2010	13
NSAID as pre- and postoperative medication - A potential risk for bleeding complications in reduction mammaplasty	2011	11
Ketorolac in thyroid surgery: quantifying the risk of hematoma	2011	12
Intraoperative ketorolac and bleeding after laparoscopic Roux-en-Y gastric by-pass surgery	2012	14
The safety and efficacy of intravenous ketorolac in patients undergoing primary endoscopic sinus surgery: a randomized, double-blinded clinical trial.	2012	21
The effects of ketorolac on microvascular thrombosis in lower extremity reconstruction.	2012	19
A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: A multicenter, double-blind, randomized, multiple-dose study	2012	18
Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty	2012	15
Analysis of prognostic factors for postoperative bleeding after tonsillectomy	2012	15
A randomized, controlled trial comparing acetaminophen plus ibuprofen	2012	25
Effect of perioperative intravenous flurbiprofen axetil on chronic postmastectomy pain	2013	21
Safety of a Novel Parenteral Formulation of Diclofenac after Major Orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial	2013	14
Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery	2014	18
Black box warning: is ketorolac safe for use after cardiac surgery?	2014	17
Does rectal indomethacin given for prevention of post-ERCP pancreatitis increase bleeding after biliary endoscopic sphincterotomy or cardiovascular mortality?: Post hoc analysis using prospective clinical trial data	2014	21
Ketorolac after free tissue transfer: A comparative effectiveness study	2014	13
Effects of parecoxib on analgesia benefit and blood loss following open prostatectomy: a multicentre randomized trial	2015	20

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Title	Year	Total Downs & Black Score
Safety and Efficacy Study of the Cyclooxygenase-2 Inhibitor Parecoxib Sodium Applied for Postoperative Analgesia After Endo-Nasal Operation.	2016	12
Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial	2016	17
SoluMatrix Diclofenac: Sustained Opioid-Sparing Effects in a Phase 3 Study in Patients with Postoperative Pain	2016	20
The effect of postoperative ketorolac on hemoglobin and postoperative pain control after vaginal surgery	2017	11
Multimodal analgesia in outpatient head and neck surgery a feasibility and safety study	2017	11
Cyclooxygenase-2 inhibitors and free flap complications after autologous breast reconstruction: A retrospective cohort study	2017	18
A comparison of 4 analgesic regimans for acute postoperative pain control in breast augmentation patients	2017	14
Perioperative Ketorolac Use and Postoperative Hematoma Formation in Reduction Mammaplasty: A Single-Surgeon Experience of 500 Consecutive Cases	2018	14
Ketorolac and Hematoma Incidence in Postmastectomy Implant-Based Breast Reconstruction	2018	14
Development of multimodal analgesia pathways in outpatient thyroid and parathyroid surgery and association with postoperative opioid prescription patterns	2018	16
Toradol use in breast reconstruction: Risk of hematoma and benefit of post-operative pain control	2018	12
Toradol following Breast Surgery: Is There an Increased Risk of Hematoma?	2018	19
Postoperative Ketorolac in Breast and Body Contouring Procedures: A Nationwide Claims Analysis	2018	17
Effect of changing postoperative pain management on bleeding rates in tonsillectomy patients	2018	15
Use of Ketorolac after Outpatient Urogynecologic Surgery: A Randomized Control Trial	2018	17
Association of celecoxib use with decreased opioid requirements after head and neck cancer surgery with free tissue reconstruction	2018	14
Risk of anastomotic leakage with nonsteroidal anti-inflammatory drugs within an enhanced recovery program	2018	21
Intraoperative ketorolac use does not increase the risk of bleeding complications in breast surgery	2019	13
Perioperative risk factors for post-thyroidectomy hematoma: Significance of pain and ketorolac usage	2019	16
Intraoperative Ketorolac Use Does Not Increase the Risk of Bleeding in Breast Surgery	2019	15
Safety and Efficacy of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) Used for Analgesia After Bariatric Surgery: A Retrospective Case Control Study	2019	14

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