Otolaryngology–Head and Neck Surgery

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY FOUNDATION

Nonopioid, Multimodal Analgesia as First-line Therapy After Otolaryngology Operations: Primer on Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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Abstract

Objective

To offer pragmatic, evidence-informed advice on nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy after surgery. This companion to the American Academy of Otolaryngology–Head & Neck Surgery (AAO-HNS) clinical practice guideline (CPG), “Opioid Prescribing for Analgesia After Common Otolaryngology Operations,” presents data on potency, bleeding risk, and adverse effects for ibuprofen, naproxen, ketorolac, meloxicam, and celecoxib.

Data Sources

National Guidelines Clearinghouse, CMA Infobase, National Library of Guidelines, NICE, SIGN, New Zealand Guidelines Group, Australian National Health and Medical, Research Council, TRIP database, PubMed, Guidelines International Network, Cochrane Library, EMBASE, CINAHL, BIOSIS Previews, ISI Web of Science, AHRQ, and HSTAT.

Review Methods

AAO-HNS opioid CPG literature search strategy, supplemented by PubMed/MEDLINE searches on NSAIDs, emphasizing systematic reviews and randomized controlled trials.

Conclusion

NSAIDs provide highly effective analgesia for postoperative pain, particularly when combined with acetaminophen. Inconsistent use of nonopioid regimens arises from common misconceptions that NSAIDs are less potent analgesics than opioids and have an unacceptable risk of bleeding. To the contrary, multimodal analgesia (combining 500 mg acetaminophen and 200 mg ibuprofen) is significantly more effective analgesia than opioid regimens (15 mg oxycodone with acetaminophen). Furthermore, selective cyclooxygenase-2 inhibition reliably circumvents antiplatelet effects.

Implications for Practice

The combination of NSAIDs and acetaminophen provides more effective postoperative pain control with greater safety than opioid-based regimens. The AAO-HNS opioid prescribing CPG therefore prioritizes multimodal, nonopioid analgesia as first-line therapy, recommending that opioids be reserved for severe or refractory pain. This state-of-the-art review provides strategies for safely incorporating NSAIDs into acute postoperative pain regimens.

Keywords

NSAID, nonsteroidal anti-inflammatory drug, opioid, opiate, analgesia, bleeding, postoperative pain, pain management, oxycodone, acetaminophen, ibuprofen,

hydrocodone, persistent opioid use, surgery, tonsillectomy, otolaryngology, guideline, NANSAID; ketorolac

Many surgeons hold strong opinions about using nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for postoperative pain. Some beliefs may be well founded, but others are grounded in historical influences that contradict current best evidence. Some surgeons regard NSAIDs as a cornerstone of postoperative pain control, while others maintain that NSAIDs lack efficacy or produce bleeding and should be avoided. The truth is likely more nuanced, and the current opioid epidemic necessitates clear, pragmatic, and evidence-informed advice now, more than ever. The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Clinical Practice Guideline (CPG), “Opioid Prescribing for Analgesia After Common Otolaryngology Operations,” which was created in response to the opioid epidemic, recommends multimodal nonopioid analgesics as first-line therapy; this recommendation puts NSAIDs front and center.

During the structured development process of the AAO-HNS CPG, “Opioid Prescribing for Analgesia After Common Otolaryngology Operations,” misconceptions and knowledge gaps relating to NSAIDs were identified, highlighting an opportunity to expand on this area. In this state-of-the-art review, we examine the research evidence underpinning the CPG recommendation for NSAID-based regimens, rather than opioids, as first-line analgesia after common otolaryngology operations. Expansion on this discussion outside the formal structure of a CPG allows more nuanced and pragmatic recommendations. In the early stages of developing the opioid-prescribing CPG, a subset of members from the guideline development group agreed to write an evidence-based review focused on NSAIDs and the role of NSAID-based multimodal regimens as an opioid alternative. **Table 1** outlines some of the common misconceptions around NSAIDs and opioid analgesia.

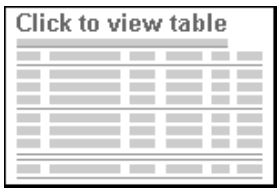

Table 1. Common Misconceptions Regarding NSAID and Opioid Analgesia.

Methods

The purpose of this review is to address—in a pragmatic and clinically relevant fashion—several misconceptions regarding NSAIDs (**Table 1**). We also synthesized the best current evidence on using NSAIDs for postoperative pain control, including multimodal therapy, an objective that was beyond the scope of the opioid CPG and inconsistent with guideline development methodology. Our starting point was the professional, systematic literature search done by an information specialist to support CPG development, which identified 3 CPGs, 40 systematic reviews, 10 randomized controlled trials (RCTs), and 53 observational studies that met predefined inclusion criteria.[2]

We searched the PubMed/MEDLINE database for relevant, additional publications related to efficacy and adverse effects of perioperative NSAIDs and opioids. Given the extensive literature on these medications, we focused this review on systematic reviews of RCTs, identifying RCTs applicable to otolaryngology wherever possible. The first literature search was done to identify systematic reviews of RCTs investigating the efficacy of commonly used analgesics. A second search was done to examine systematic reviews investigating the risks of bleeding with NSAIDs.

We selected final articles that were systematic reviews of randomized controlled trials of NSAIDs across all surgical fields, prioritizing randomized controlled trials of NSAIDs in otolaryngology. We then synthesized the data from these sources into this state-of-the-art review. Since this companion article was not a systematic review, we did not perform a formal risk-of-bias assessment for source articles, instead relying on informal consensus among the authors that the article was appropriate to include. This document was then distributed to the CPG workgroup for comment, with subsequent revisions addressing any identified areas of ambiguity. Institutional review board approval was not required for this study.

Discussion

NSAID Class of Medications

NSAIDs are a heterogeneous family of medications that inhibit cyclooxygenase (COX)

enzymes and prostaglandin production, leading to analgesic, anti-inflammatory, and antipyretic effects. NSAIDs are available in oral, parenteral, topical, intramuscular, and rectal formulations. NSAIDs differ in their relative inhibitory potentials of the COX-1 and COX-2 isoforms,[3] leading to distinct side-effect profiles. Importantly, COX-2 is the primary contributor to inflammation and pain. Selective COX-2 inhibitors counter the inflammatory process while minimizing the impact on gastrointestinal and postoperative bleeding.

The major classes of NSAIDs used for acute postoperative pain are summarized in **Table 2**. Most NSAIDs cause reversible inhibition of COX enzymes, except for aspirin. Aspirin has limited utility for acute postoperative pain control because of antiplatelet effects, and therefore it is not further discussed. Acetaminophen has little anti-inflammatory activity in peripheral tissues and so is not generally considered an NSAID[4] but will be discussed with regard to combination therapy with NSAIDs or opioids.

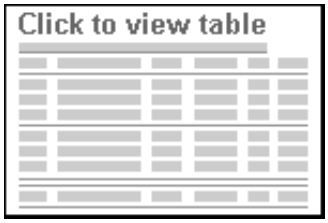

Table 2. Comparison of Classes of NSAIDs.

Analgesic Efficacy

An enduring myth is that opioids are uniquely powerful for pain control.[1] Patients often perceive that “the good stuff” is being withheld when opioids are not included in their regimen for severe pain. The evidence is clear that this belief is, in fact, a myth. After surgery, NSAIDs—alone or in combination with acetaminophen—are more likely to reduce acute postoperative pain than standard opioid regimens (**Figure 1**).[5] This analgesic efficacy is observed with both nonselective NSAIDs and selective COX-2 inhibitors (**Table 2**).

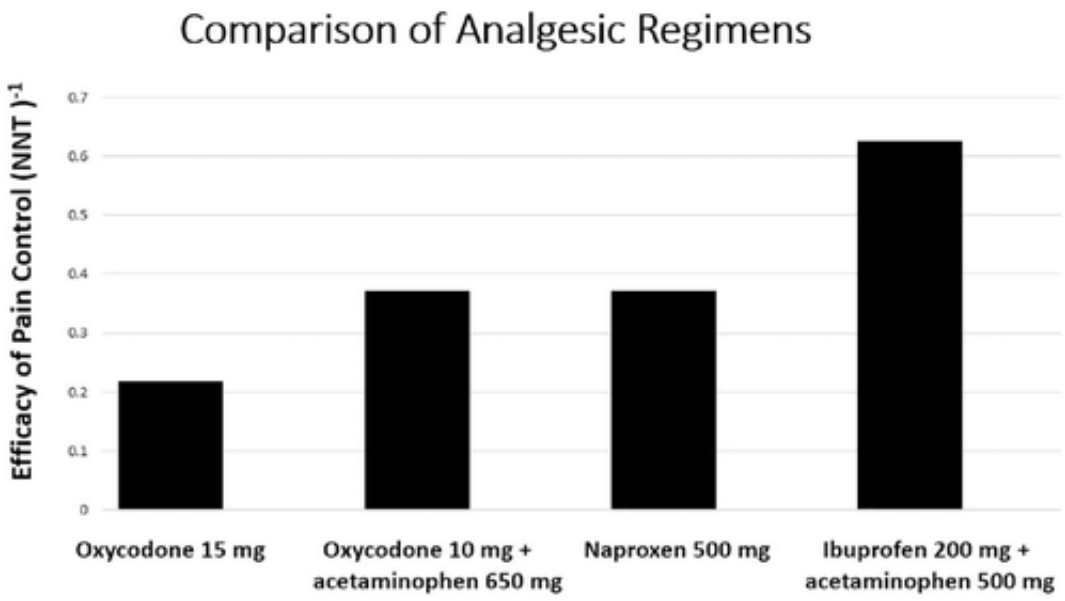

Figure 1. Efficacy of control for common surgical procedures across various analgesic regimens. Efficacy depicted on the *y*-axis is the reciprocal of number of people needed to treat for 1 person to achieve 50% pain relief (NNT).

Adverse Events With NSAIDs

The use of NSAIDs for a short duration at low dose has an excellent safety profile that compares favorably with opioids, without a risk of addiction or opioid use disorder. Adverse events of opioids include constipation, dehydration, nausea vomiting, itching, drug reactions, and opioid dependence. Moreover, opioids should be used with particular caution or avoided in individuals at risk for opioid use disorder or fatal overdose. Several of the action statements in the AAO-HNS opioid-prescribing CPG offer specific suggestions and screening tools for predicting the risk of opioid use disorder and the need for preoperative patient counseling or further assessment.

Although NSAIDs are well tolerated by most otherwise healthy patients, nonselective NSAIDs have been associated with a low incidence of dyspepsia, peptic ulcer disease, gastrointestinal bleeding, and cardiovascular thrombotic events.[6] The incidence of gastrointestinal bleeding, for example, is quite rare with NSAID use, requiring hospital admission for 122 events/100,000 person-years.[7] NSAIDs should be used with caution in patients with stage 2 chronic kidney disease and should be avoided in patients with stage 3 to 5 chronic kidney disease, because of the potential renal vasoconstriction that

results in ischemic renal insufficiency and acute interstitial nephritis.[8] In addition, NSAIDs can blunt the production of erythropoietin, causing anemia. The risk of adverse effects is increased in patients older than 65 years.[9]

The risk of adverse effects is reduced at lower doses and shorter durations. Many of the studies on adverse events from NSAIDs focus on long-term use for musculoskeletal pain. Short courses of NSAIDs prescribed for acute postoperative pain reduce the potential for adverse cardiovascular, gastrointestinal, renal, or hematologic adverse events. Furthermore, NSAIDs prescribed at low doses reduce toxicity and produce similar analgesia to higher-dose regimens because of a ceiling effect. For example, when the dose of ibuprofen for acute postoperative pain is increased to greater than 400 mg, no improvement in pain control is observed (the number needed to treat to reduce pain by 50% for ibuprofen 200, 400, and 600 mg is 2.9, 2.5, and 2.7 respectively).[5]

Acetaminophen, which lacks significant anti-inflammatory properties, is not classified as an NSAID and is often included in multimodal pain regimens. It selectively and indirectly inhibits the COX pathway in the brain but not in peripheral tissues.[10] The tissue specificity of acetaminophen illustrates the unique adverse effect profile observed with acetaminophen. Unlike NSAIDs, acetaminophen does not cause gastrointestinal effects such as ulceration or platelet inhibition. Acetaminophen is generally safe within its therapeutic range (<4 g per day in adults). Outside of its therapeutic range, acetaminophen has well-known hepatotoxicity. Acetaminophen overdose is the number one cause of acute liver failure in the United States and Europe.[11] Unintentional overdose accounts for 50% of cases of acetaminophen-induced liver toxicity.[4] Typically, unintentional acetaminophen overdose occurs from excessive use over greater than 3 days when using multiple combination formulations.[4] Acetaminophen is also associated with rare skin hypersensitivity reactions.

Bleeding

Nonspecific NSAIDs inhibit platelet function; however, the clinical impact on perioperative bleeding is low and varies with the type of NSAID and with surgical and patient factors.

Systematic reviews and meta-analyses evaluating surgical procedures with low risk of bleeding, such as plastic surgery, found no significant association between NSAID use and bleeding and/or hematoma (odds ratio [OR], 1.20; CI, 0.73-1.97).[12] For septoplasty and rhinoplasty, 5 randomized controlled trials have compared NSAIDs to alternative analgesics.[13] None of these studies reported any incidence of significant bleeding or septal hematoma with NSAIDs.[13] For thyroidectomy, 4 randomized controlled trials also compared NSAIDs to alternative analgesics and similarly found no increase in bleeding or hematoma with NSAIDs.[14-17] Similarly, large retrospective, multi-institutional studies found a similar 1% rate of hematoma with or without NSAID use.[18]

Tonsillectomy poses unique challenges with both significant postoperative pain[2] and greater concerns for postoperative bleeding. The AAO-HNS "Clinical Practice Guideline: Tonsillectomy in Children (Update)"[19] concluded that NSAIDs are safe for pain control after tonsillectomy without significantly increased risk for postoperative hemorrhage. A meta-analysis conducted by the Cochrane Collaborative including 1011 patients from randomized controlled trials did not identify a significantly increased risk of bleeding from NSAIDs, but the 95% CIs for the pooled OR were wide (CI, 0.71-4.01).[20] Other analyses that had a higher risk of bias because of observational study design identified a small but statistically significant increase in bleeding (OR, 1.38; CI, 1.11-1.72).[21] More recently, Diercks et al[22] completed a multicenter randomized controlled trial of 741 children undergoing tonsillectomy and/or adenotonsillectomy that randomized children to either ibuprofen 10 mg/kg or acetaminophen 15 mg/kg, with a primary outcome of rate of post-tonsillectomy bleeding requiring a return to the operating room. The authors found a rate of postoperative bleeding requiring a return to the operating room of 1.2% in the acetaminophen group and 2.9% in the ibuprofen group ($P = 0.12$), but all patients in the study took ibuprofen every 6 hours for 9 days, which is far in excess of what is commonly used in practice.[22] Another meta-analysis found increased bleeding with ibuprofen but required a sample size of 319,305 patients to reach significance.[21]

A historical cohort study of 6710 children after tonsillectomy found no difference in the

rate of post-tonsillectomy hemorrhage requiring surgical control (3.3% incidence) with ibuprofen (OR, 0.90; CI, 0.68-1.19), but the risk was higher if the patient was 12 years or older or had a history of tonsillitis. Of the 15 children in this study who required transfusion after surgical control of hemorrhage, the use of ibuprofen showed an increased risk (OR, 3.10; CI, 1.01-9.91), although the finding must be interpreted with the caveat that the lower limit of the 95% confidence interval approaches unity.[23]

Bleeding Risk Based on Type of NSAID

Many of these meta-analyses included multiple types of NSAIDs, and there is evidence that the type of NSAID may influence the risk of bleeding. Three NSAIDs, ketorolac, ibuprofen, and diclofenac, are available intravenously. Among these, ketorolac is the most widely available and least expensive but appears to be the most potent NSAID for perioperative bleeding complications. Meta-analysis investigating the risk of upper gastrointestinal bleeding with NSAIDs found that the risk varied 20-fold depending on the drug and 3- to 7-fold depending on the dose.[24] Risks of upper gastrointestinal bleeding were highest with ketoprofen and lowest with ibuprofen.[24]

Subgroup analysis of a Cochrane review in 2005 suggested an increased risk of bleeding with ketorolac in children post-tonsillectomy (OR, 3.12; CI, 0.53-18.38) as compared with other NSAIDs (OR, 0.67; CI, 0.20-2.24).[25] Based on this evidence, the AA-HNS 2011 CPG “Tonsillectomy in Children” recommended that ketorolac use be avoided.[26] A more recent meta-analysis in 2014 found a differential response in children and adults. They observed in adults that the relative risk of post-tonsillectomy hemorrhage with ketorolac was 5.64 (CI, 2.08-15.27), whereas in children, the relative risk was 1.39 (CI, 0.84-2.30).[27] Other studies have also shown an increased risk of bleeding in older children with NSAID use.[23,28] Meta-analysis in plastic surgery also suggested an increased risk of bleeding or hematoma with ketorolac (OR, 1.48; CI, 0.86-2.56), although with A wide interval; comparisons with ibuprofen (OR, 0.55; CI, 0.14-2.14) versus ketorolac; and celecoxib versus ketorolac (OR, 0.22; CI, 0.02-2.52),[12] which reflected a higher point estimate for ketorolac compared with ibuprofen or celecoxib, but with wide confidence intervals for all 3 drugs. The mechanism of any

differential risk of bleeding with ketorolac as compared with other NSAIDs is unclear.

Putting the Risk of Adverse Events in Perspective

Evaluating the role of NSAIDs in the management of acute postoperative pain also requires a comparison of the relative frequency of adverse events versus alternative analgesics (**Figure 2**). Adverse events are more common with opioids than with NSAIDs. A meta-analysis conducted by the Cochrane Collaborative on adverse events of analgesics including more than 35,000 participants from 350 randomized trials found that participants did not experience significantly more adverse events with NSAIDs than with placebo (risk ratio of adverse events, 0.9; CI, 0.7-1.02, with ibuprofen 200 mg).[29] However, in studies of opioids, participants were more likely to experience adverse events (risk ratio of adverse events, 1.8; CI, 1.4-2.2, for oxycodone 10 mg and acetaminophen 650 mg). Importantly, this review examined randomized trials for a single dose of analgesics.

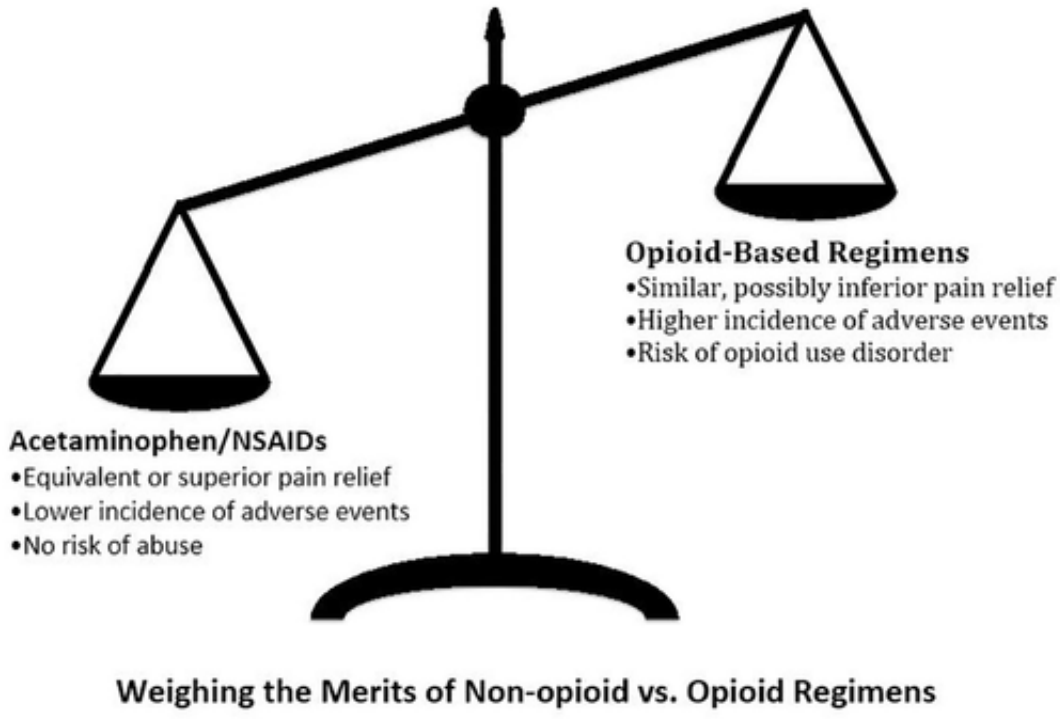

Figure 2. The balance of benefit over harm favors nonopioid regimens as first-line analgesia, as supported by a Cochrane Collaborative meta-analysis of 350 randomized trials, showing double the rate of adverse events with opioids versus nonsteroidal anti-inflammatory drugs.[29]

Common adverse events with opioids include drowsiness, respiratory depression, nausea, vomiting, and constipation.[29] Studies in elderly adults have found that compared with NSAIDs, opioids are associated with an increased risk of hospitalization and all-cause mortality.[30,31] These studies did not specifically examine risks from opioid overdose. Opioid overdose after surgical discharge remains a persistent concern,[32] with 68,306 opioid-related deaths reported in the United States in 2019.[33-35] Prior experience with surgical complications may predispose clinicians to ascribe an outsize importance to bleeding risk from NSAIDs relative to more insidious yet more pervasive harm arising from opioid diversion, overdose, and opioid use disorder. Analysis of the number needed to harm for NSAIDs (harm from excess bleeding risk) versus the number needed to harm for opioids (harm from risk of opioid use disorder) reveals a superior safety profile of NSAIDs (**Table 3**).

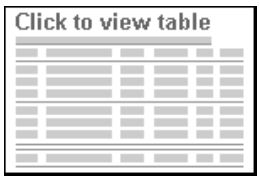

Table 3. Risk and Benefits Associated With Commonly Used Analgesic Regimens.[a]

The calculation of NSAID-specific bleeding risk depends on the base rate of bleeding in the procedure studied. The example in **Table 3** is for tonsillectomy and makes an assumption of a 3% postoperative bleeding rate. Most of the commonly performed procedures in otolaryngology have a significantly lower bleeding risk than tonsillectomy and therefore a higher number needed to harm. The number needed to harm for persistent opioid use is based on a 6% to 10% rate of persistent use, which is relatively stable across procedures but higher with a prolonged duration of opioid or patient risk factors. **Table 3** does not document all side effects of NSAIDS (eg, hypersensitivity reactions, renal insufficiency, etc) or the full range of opioid risks (eg, constipation, dehydration, nausea vomiting, itching, drug reactions, and fatal overdose). As previously noted, when accounting for all adverse events, a Cochrane Collaborative meta-analysis of 350 randomized trials showed that opioids had double the rate of adverse events of NSAIDs.[29]

Selective COX-2 Inhibitors

Selective COX-2 inhibitors were introduced in 1999 to reduce the risk of bleeding complications. In 2004, evidence of increased adverse cardiovascular outcomes with the COX-2 inhibitor rofecoxib (Vioxx) led to its withdrawal from the market.[38] However, there was evidence of differential cardiovascular risks among COX-2 inhibitors, and the Food and Drug Administration called for the PRECISION cardiovascular safety trial for the COX-2 inhibitor celecoxib.

The PRECISION trial randomized 24,081 patients with arthritis to celecoxib, ibuprofen, or naproxen with a primary endpoint of cardiovascular safety.[39] The study found that at a mean treatment duration of 20 months, celecoxib had a similar cardiovascular safety to nonselective NSAIDs (composite cardiovascular events 2.3% with celecoxib, 2.7% with ibuprofen, 2.5% with naproxen). Celecoxib reduced gastrointestinal bleeding events, conferring 49% reduction in anemia compared with ibuprofen and naproxen. Nonetheless, all NSAIDs (nonselective and selective) should be used with caution in patients with cardiovascular disease, because they carry a boxed warning of potential serious cardiovascular risk.

In otolaryngology, 3 RCTs have evaluated the outcomes of celecoxib after tonsillectomy. Two trials found that celecoxib reduced pain and co-analgesic consumption,[40,41] while a third found no significant difference.[42] The authors of the third study attributed their lack of difference to the use of 200 mg, rather than 400 mg, standard dosing or possible ceiling effects.[42] None of these trials identified any increased risk of bleeding with celecoxib. Additional RCTs investigating COX-2 inhibitor strategies are ongoing in children using celecoxib 6 mg/kg twice a day with a maximum dose of 300 mg twice a day (NCT02934191).

Overall, clinicians need to carefully assess the risks of bleeding and adverse effects of NSAIDs versus the risks of persistent opioid use and/or opioid use disorder and adverse effects associated with opioids.[43] Celecoxib is an option for surgeons receptive to opioid-sparing regimens but very concerned about risk of bleeding.

Areas for Future Research

Additional research will be necessary to explore educational interventions to promote opioid-sparing, NSAID-based multimodal analgesia. Successful efforts to reduce opioid prescriptions are predicated on informing physicians that NSAIDs are a safer and often more effective first-line option. In one study of head and neck surgery, 87% of American patients received opioids in contrast to <1% in Hong Kong.[44] This difference in practice is consistent with the more widespread use of opioids in the United States compared with the rest of the world.[34,45] More research is needed to investigate how to modify ingrained prescribing habits.

There is also a need for further research on different analgesic regimens and different types of procedures. The bulk of NSAID-related literature in otolaryngology focuses on ibuprofen, particularly as relates to bleeding risk. Tonsillectomy clinical trials also predominantly reflect studies using nonselective NSAIDs, with insufficient data on selective COX-2 inhibitors. Beyond NSAID formulations, future research is needed across a range of otolaryngology procedures besides tonsillectomy. Tonsillectomy has attracted the most randomized trials for analgesia strategies, but this literature may not generalize to other procedures in otolaryngology, given that tonsillectomy poses unique challenges related to oral intake, high postoperative pain, and proximity to vessels. Finally, research is needed on strategies that take advantage of multiple nonopioid analgesics, as in Enhanced Recovery After Surgery pathways.[46]

Implications for Practice

Opioid-sparing, NSAID-based multimodal regimens are first-line analgesia after surgery, as reflected in recommendations of the “Clinical Practice Guideline: Opioid Prescribing for Analgesia After Common Otolaryngology Operations.” This evidence-based approach to pain control after otolaryngology procedures is based on data showing a superior safety profile and the effectiveness of NSAIDs relative to opioid-based regimens. A fundamental clinical insight is that the combination of NSAIDs and acetaminophen offers at least equivalent and potentially superior pain control compared with oxycodone and acetaminophen. The implications of this recommendation are substantial because of the potential reduction in opioid prescribing. Reappraisal of data

and tradeoffs between NSAID-based versus opioid-based analgesia after surgery highlights the potential advantages of NSAIDs as a cornerstone for acute postoperative pain control.

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Author Contributions

John D. Cramer, conception, design, and drafting of the work, acquisition, analysis, and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work. **Michael L. Barnett**, drafting and analysis and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work. **Samantha Anne**, analysis and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work. **Brian T. Bateman**, analysis and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work. **Richard M. Rosenfeld**, conception, drafting, interpretation, critical revision, approval of the final submission, and agreement to be accountable for all aspects of the work. **David E. Tunkel**, analysis and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work. **Michael J. Brenner**, conception, design, and drafting of the work; analysis and interpretation of data for the work; critically revising the work for important intellectual content; approval of the final submission; agreement to be accountable for all aspects of the work.

Disclosures

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