Review

Perioperative Opioid-sparing Strategies: Utility of Conventional NSAIDs in Adults

Luc Martinez, MD[1]; Evan Ekman, MD[2,3]; and Nardine Nakhla, PharmD[4]

[1]*Former employee of the Department of General Medicine, University of Paris VI, Paris, France;* [2]*Orthopaedic Surgery, Aiken Professional Association, Aiken, NC, United States;* [3]*Edward Via College of Osteopathic Medicine, Spartanburg, NC, United States; and* [4]*University of Waterloo School of Pharmacy, Kitchener, Ontario, Canada*

ABSTRACT

Purpose: Opioids have long been used to treat acute postsurgical and postprocedural pain; however, opioid-related adverse events (AEs) contribute to poor patient outcomes. In addition, perisurgical exposure to opioids can potentially increase the risk for opioid-use disorder. NSAIDs reduce pain and inflammation by a mechanism different from that of opioid analgesics and may be useful in reducing the need for opioid drugs as part of a multimodal analgesia strategy. We conducted this review to assess the effectiveness and tolerability of adjunctive conventional NSAIDs given systemically in the perioperative setting in terms of opioid-sparing effects observed postoperatively.

Methods: Clinical trials published since 2000 that have assessed the opioid-sparing effects of conventional, nonselective NSAIDs were identified by a literature search using the PubMed search engine. Search terms were identified for the treatment of interest, the timing of the intervention, and the drugs of interest (NSAIDs). Data from studies that assessed opioid consumption outcomes with systemic NSAID administration were included in the review; data from studies in which NSAIDs were administered topically or via periarticular injection, local infiltration, or regional block were excluded.

Findings: Upon full-text review of the search results, 32 studies were chosen for inclusion in this literature review. These studies included those that assessed diclofenac, ketorolac, ibuprofen, ketoprofen, dexketoprofen, flurbiprofen, lornoxicam, tenoxicam, meloxicam, and piroxicam. In studies in which NSAIDs were associated with opioid-sparing effects within the setting of patient-controlled analgesia, opioid use was reduced by 17%−~50% with diclofenac, 9%−66% with ketorolac, 22%−46% with ibuprofen, 34%−66% with ketoprofen, 36%−50% with dexketoprofen, 38%−41% with tenoxicam, 36%−54% with lornoxicam, and ~50% with flurbiprofen. No opioid-sparing effect was noted with meloxicam (1 study). The majority of studies that reported on pain-score changes revealed either pain reductions with NSAIDs versus placebo or similar pain scores between groups, indicating that NSAIDs did not compromise pain control. Although many studies found no difference in the prevalence of AEs in NSAID-treated patients compared with controls, several studies noted lower rates of nausea, vomiting, sedation, and pruritus with NSAIDs versus placebo. Conversely, NSAID-related AEs were few overall but included gastrointestinal bleeding, injection site reactions, transient oliguric renal failure, and dizziness. No surgery-related bleeding complications were observed.

Implications: NSAIDs have the potential to play an important role in reducing postoperative opioid requirements. Reducing the amount of opioids used could be expected to reduce opioid-related side effects and contribute to reversing the opioid epidemic. (*Clin Ther*. 2019;41:2612−2628) © 2019 Elsevier Inc. All rights reserved.

Key words: Multimodal analgesia, NSAID, opioid, opioid-sparing, patient-controlled analgesia, postsurgical pain.

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INTRODUCTION

Opioids have long been used to treat acute postsurgical and postprocedural pain; however, multiple studies have shown that opioid-related adverse events (AEs) contribute to poor patient health outcomes.[1] In a recent retrospective review of clinical and admin istrative data from >135,000 patients treated with opioids after in-hospital surgical or endoscopic procedures, 10.6% of patients had opioid-related AEs, and these AEs were associated with negative outcomes, including increased inpatient mortality, prolonged length of stay, and higher 30-day readmission rates.[2] In addition, in studies of data from administrative and insurance claims, patients who underwent minor and major surgical procedures and who had opioid prescriptions filled peri operatively were at an increased risk for chronic opioid-use disorder.[3,4] When compared with those in nonsurgical patients, odds ratios (ORs) for the development of opioid-use disorder were highest in those who underwent total knee arthroplasty (OR = 5.10; 95% CI, 4.67−5.58; $P < 0.001$), open cholecystectomy (OR = 3.60; 95% CI, 2.80−4.62; $P < 0.001$), simple mastectomy (OR = 2.65; 95% CI, 2.28−3.08; $P < 0.001$), and total hip arthroplasty (OR = 2.52; 95% CI, 2.11−3.01; $P < 0.001$).[3]

Opioid abuse is a widespread condition that presents a serious threat to public health. In 2015, it was estimated that nearly 6% of the US population aged 15−64 years was abusing opioids.[5] By 2016, opioid-use disorder had become the 7th leading cause of disability-adjusted life-years after having been the 11th leading cause in 1990.[6] In the United States, current estimates of the prevalence of addiction in patients treated with long-term opioid therapy range from 20% to 33%.[7] Between 2014 and 2016, the average life expectancy in the United States declined, largely due to the opioid crisis among young adults.[8]

Partly in response to the well-publicized North American epidemic of opioid abuse, there has been increasing interest in multimodal analgesia pain-management strategies in an effort to reduce opioid use. Multimodal analgesia involves a process by which different procedures or techniques and/or medications with differing mechanisms of action are used to achieve adequate pain control while minimizing the potential complications of opioid use. NSAIDs, which reduce pain and inflammation by blocking the production of prostaglandins via the inhibition of cyclooxygenase enzymes,[9] are an increasingly common component of multimodal therapy because they have analgesic efficacy comparable to that of opioid drugs but are not associated with many of the most concerning complications of opioid use.[10] As such, NSAIDs may present a viable alternative to opioid analgesia in the perioperative setting.

This review was conducted to assess the effectiveness and tolerability of adjunctive conventional NSAIDs given systemically in the perioperative setting. The primary outcome of interest was the opioid-sparing effects of NSAIDs, as measured by the reduction in morphine-equivalents required postoperatively. Secondary outcomes of interest included effects on pain scores, AE rates (both NSAID-related and opioid-related), and associated morbidities.

MATERIALS AND METHODS

We conducted a literature search of MEDLINE using PubMed to identify clinical trials published since 2000 that have evaluated the use of systemic, conventional NSAIDs as part of a multimodal perioperative pain-management strategy in adults. The search included key words for multimodal pain management, NSAIDs, opioid-sparing, and peri surgical settings, and the exact search string used was "(multimodal pain management OR multimodal analgesia OR opioid sparing) AND (NSAIDs OR dexketoprofen OR diclofenac OR dipyrone OR metamizole OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR lornoxicam OR meloxicam OR naproxen OR oxaprozin OR piroxicam) AND (surgical OR perioperative OR postoperative OR patient-controlled analgesia)." The results were limited to clinical trials in patients ≥18 years of age; published from January 1, 2000, through August 31, 2018; and published in English.

Abstracts of the publications identified by the PubMed search were examined for relevance and inclusion in the review. Articles were included in the review if they reported at least 1 outcome of interest, including outcomes related to opioid consumption (dose requirements for patient-controlled analgesia [PCA], dosage of rescue analgesics, or dosage of titrated opioids), pain scores, AE rates, and time to recovery or discharge, as applicable. As this review

was focused on the adjunctive use of systemic, conventional NSAIDs, studies that used NSAIDs administered via periarticular injections, local infiltration, or regional blocks were excluded. Given that conventional NSAIDs were the focus of this review, we excluded studies that compared an opioid/placebo versus either a selective cyclooxygenase 2 inhibitor or acetaminophen alone. However, if a study assessed several interventions and included a conventional NSAID (eg, ibuprofen, celecoxib, and placebo arms), it was included as long as at least 1 of the outcomes of interest for the conventional NSAID was reported. If a determination of inclusion could not be made solely from the abstract, the full text of the publication was reviewed to determine its suitability for this review.

RESULTS

The original search using PubMed and the prespecified limits generated a list of 202 potentially relevant results. Of these, 148 were excluded upon abstract review and 22 were excluded after full text review. Reasons for study exclusion included that: the conventional NSAID was not the focus of the study (n = 130; 76%); the study reported on the nonsystemic (eg, topical) use of a conventional NSAID (n = 19; 11%); the outcomes of interest were not reported (n = 17; 10%); and the identified article was not a clinical study (n = 4; 2%). In total, 32 published clinical trials met the inclusion criteria for this analysis. Some of the included studies (n = 8) examined >1 NSAID of interest. The NSAIDs examined in the review are shown in the Figure and included diclofenac (n = 12), ketorolac (n = 7), ibuprofen (n = 5), ketoprofen (n = 4), dexketoprofen (n = 3), lornoxicam (n = 2), tenoxicam (n = 2), meloxicam (n = 1), flurbiprofen (n = 1), and piroxicam (n = 1).

In the majority of the studies included in this review (26 of 32), opioids were administered via PCA, and the opioid-sparing effects of NSAIDs were captured as a percentage-reduction in morphine-equivalents required. PCA morphine was most commonly used, although there were some variations, including oxycodone[11] and ketobemidone.[12] Also, a single study used meperidine epidural PCA.[13] Of the studies that did not employ PCA, opioid-sparing effects were assessed by measurement of the patient's consumption of oral opioid rescue medication. Hydrocodone/acetaminophen or oxycodone/acetaminophen tablets were used in 2 studies,[14,15] and in the final 3 studies, IV morphine,[16] IV tramadol,[17] and IM pethidine[18] were administered until patient-reported pain scores fell below predetermined thresholds.

All included trials were conducted in populations aged 18 years or older, and 1 study was conducted specifically in a population over 65 years of age.[19] All studies were conducted in the surgical setting, and common surgeries in the trials reviewed included gynecologic surgery/

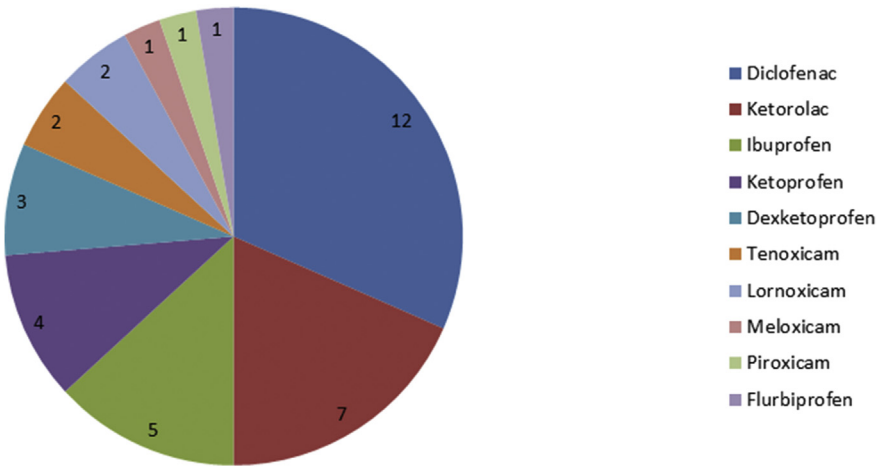

Figure. Distribution of data sets by drug.

cesarean delivery (n = 15),[12,13,18,20–26] orthopedic/arthroscopic surgery (n = 10),[11,14,19,27–33] and spinal surgery (n = 4).[34–37] Findings on individual NSAIDs are presented.

Diclofenac

Diclofenac was the most frequently tested NSAID among the trials in this review; results from these studies are summarized in Table I.[11,12,14,18–20,23,24,26,31,33,38] The total daily dose of diclofenac administered as a component of multimodal analgesia ranged from a low of 54 mg[14] to a high of 225 mg[11] across the 12 studies reviewed. In 9 of the 10 studies that evaluated the effects of diclofenac versus placebo in the setting of PCA opioid use,[11,12,20,23,24,26,31,33,38] diclofenac was associated with a 17%−~50% reduction in opioid use; no difference between diclofenac and placebo was noted in the remaining study of patients 65 years of age and older who underwent open reduction and internal fixation for subcapital femur fracture.[19]

Pain control versus that with placebo was assessed in each of the 12 trials. In 6 of these, pain scores were significantly lower (ie, improved) in the diclofenac treatment groups than in the placebo groups,[11,12,18,23,31,38] while 5 studies found no difference in pain scores between treatment groups[19,20,24,26,33]; that is, there was no compromise in pain relief with diclofenac added to PCA morphine versus those receiving PCA morphine alone. Pain score changes were not reported in 1 study.[14]

In total, 5 of the trials that tested diclofenac versus placebo reported no significant differences in the prevalence or nature of AEs in either group.[12,14,20,24,33] In the 5 trials that reported significant differences in AEs, Alexander et al[31] reported a greater prevalence of postoperative nausea and vomiting (PONV) and pruritus in patients who received placebo versus diclofenac, Ng et al[23] found significantly higher sedation and nausea scores in the placebo group than in the diclofenac group, Al-Waili[18] showed that diclofenac-treated patients were less sedated than those in the placebo group, Fayaz et al[38] found higher rates of PONV with placebo, and Silvanto et al[11] found that diclofenac was associated with less nausea and more injection site irritation versus placebo. Other reported AEs in diclofenac-treated patients included a single case of epigastric pain and melena[38] and a bladder perforation.[26]

Ketorolac

Seven studies examined ketorolac at various doses as an opioid-sparing strategy, and results from these studies are summarized in Table II.[13,16,21,25,31,39,40] Each study evaluated ketorolac treatment against a control group that did not receive the NSAID, and all of these studies reported significant opioid-sparing effects with ketorolac. Opioid-sparing effects were determined versus a background of PCA opioids in 6 of the 7 studies,[13,21,25,31,39,40] and versus morphine titrated to pain level as rescue medication in the remaining study.[16] Ketorolac use was associated with a reduction in PCA opioid use ranging from 9% to 66% in 6 studies[13,21,25,31,39,40] and a 59% reduction in rescue medication use compared with placebo in the remaining study.[16]

Pain scores were assessed in each of the 7 ketorolac trials reviewed. No statistically significant differences in pain scores between ketorolac-treated patients and control patients were noted in 2 trials.[13,39] Three studies reported significantly lower pain levels in patients treated with ketorolac at 2 and 24 h after surgery,[21,25,31] and 1 additional study found a significant reduction in pain on movement on postoperative day 3 only.[40] In contrast, Cepeda et al[16] found significantly greater pain in the ketorolac group during the first 30 min after surgery (a time at which patients had received ketorolac but no morphine) compared with those who received morphine alone, but these differences were not sustained at any point thereafter.

All 7 ketorolac studies in this review reported tolerability results, and 3 found no significant difference in AEs between patients treated with ketorolac compared with other treatments used.[25,39,40] Of the 4 studies reporting differences in AEs, ketorolac was significantly better tolerated in terms of rates of pruritus[16,31] and nausea.[21,31] In contrast, the final study found significantly more pruritus in the ketorolac-treated group than in the placebo group.[13]

Ibuprofen

The opioid-sparing effects of ibuprofen were assessed in 5 placebo-controlled trials, and the results are shown in Table III.[15,28,30,32,36] The doses tested ranged from 1200 to 3200 mg/d, and all 5 studies reported positive results for opioid-sparing outcomes.

In the United States, White et al[15] found a statistically significant decrease in opioid-containing rescue medication (hydrocodone/acetaminophen tablets) over 48 and 72 h postoperatively, and Pinar et al[36] reported significant decreases in morphine use with ibuprofen versus placebo at 2, 4, 8, 12, and 48 h after surgery (all $P < 0.05$). However, neither study quantified the opioid-sparing effect further. In the 3 remaining trials, ibuprofen treatment was associated with significant decreases in the consumption of PCA morphine ranging from 22% to 46% compared with placebo.[28,30,32] A single study tested 2 doses of ibuprofen, 1600 and 3200 mg/d, and found a significant morphine-sparing effect (22% reduction) with the higher dose from hours 1 to 24 after surgery ($P = 0.030$), while the effect with the lower dose was not significantly different from that with placebo.[32]

Each of the 5 studies[15,28,30,32,36] found that ibuprofen was associated with significantly lower pain scores than was placebo, and 3 of the studies[28,30,36] reported no differences in the AEs reported by patients in the ibuprofen and placebo groups. A study using a relatively low prescription dose of ibuprofen (1200 mg/d; also the maximum daily over-the-counter dose allowed) in patients following ambulatory surgery found significantly less postoperative constipation in patients receiving ibuprofen versus placebo,[15] while the study by Southworth et al[32] found significant decreases in pyrexia, nausea, and gastrointestinal AEs in patients receiving either 1600 or 3200 mg/d ibuprofen compared with placebo. However, the higher ibuprofen dose was also associated with an increase in the prevalence of dizziness in that study.

Ketoprofen and Dexketoprofen

The racemic NSAID ketoprofen and its *S*(+)-enantiomer, dexketoprofen,[41] were assessed in 6 total trials[11,17,27,29,35,42] (1 study reported on both agents[27]), and the results are summarized in Table IV. Ketoprofen was given at a dose of 100 mg in 4 trials,[11,17,27,42] while dexketoprofen was administered at 50 mg in 2 studies[27,29] and 25 mg in the final study.[35]

All trials testing ketoprofen reported that it was associated with opioid-sparing effects. Patients who received ketoprofen and PCA opioids after abdominal or orthopedic surgery used 36%−55% less morphine[27,42] and 34%−66% less oxycodone[11] than did placebo-treated control patients. In the remaining study, ketoprofen-treated patients used 18% less tramadol and metamizole rescue medication for postsurgical pain than did controls.[17] All studies testing dexketoprofen, likewise, found significant reductions in the consumption of PCA morphine by postsurgical patients compared with those receiving placebo. The reductions in morphine use associated with dexketoprofen ranged from 36% to 50%.[27,29,35]

Ketoprofen was associated with significantly lower pain scores in 3 of the 4 studies,[11,17,27] whereas no difference in pain scores between patients in the treatment and control groups was observed by Rao et al.[42] In 2 studies that evaluated pain levels in patients after orthopedic surgery, pain levels were significantly lower in dexketoprofen-treated patients compared with those receiving placebo.[27,29] However, Kesimci et al[35] found no difference in postsurgical pain levels in patients who received oral dexketoprofen or placebo after laminectomy.

Of the 5 ketoprofen/dexketoprofen trials that reported tolerability outcomes, 3 noted numeric reductions in PONV in active versus control groups,[17,27,42] but the difference in PONV was not significant in any study. A significantly increased prevalence of irritation at the infusion site with ketoprofen versus placebo was noted in 1 study.[11] One patient taking ketoprofen developed transient oliguric renal failure.[42] Additionally, Hanna et al[27] reported a single ketoprofen-treated patient and 2 dexketoprofen-treated patients with gastrointestinal bleeding.

Other NSAIDs

In addition to the more commonly tested NSAIDs discussed, several drugs were examined in 2 or fewer trials, including flurbiprofen, lornoxicam, tenoxicam, meloxicam, and piroxicam; results with these analgesics are detailed in Table V.[22,24,29,34,37,43]

One study tested pre- and postsurgical administration of flurbiprofen in patients undergoing spinal surgery and found that PCA morphine consumption was significantly reduced, by ~50%, and that pain was significantly reduced, over the 24-h study period with presurgical flurbiprofen (1 mg/kg) versus either the postsurgical or placebo groups from 0 to 6 h after surgery.[37]

Two studies tested tenoxicam, including one that used a dose of 40 mg in patients undergoing spinal

Table I. Opioid-sparing studies of diclofenac.

Study/Condition	Study Design/ Population	Intervention Arm(s)	Control Arm	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Al-Waili 2001; cesarean delivery[18]	RCT in female subjects aged 18–40 y	Diclofenac 75 mg IM (n = 60) postoperatively and PRN after 12 h from last injection up to 2 injections/d	PBO (n = 60)	Pethidine 100 mg IM as rescue medication	In total, diclofenac group used 2800 mg of pethidine vs 22,700 mg in PBO group ($P < 0.05$) over 48 h; represents an 88% reduction over this time period	Pain scores were significantly reduced with diclofenac vs PBO	Patients in PBO group reported significantly more sedation than diclofenac group ($P < 0.05$)
Alexander et al, 2002; major orthopedic surgery[31]	RCT in ASA physical status I or II patients aged 18 to 80 y scheduled for prosthetic hip or knee replacement	Single-dose diclofenac 75 mg IV (n = 36) or ketorolac 60 mg IV (n = 31) before induction of anesthesia	PBO (n = 32)	PCA morphine 1 mg bolus, 5-min lockout (maximum in 4 h, 30 mg); morphine 2 mg (rescue)	Diclofenac 24-h morphine use 30% lower than PBO group ($P < 0.01$)	Compared with PBO, diclofenac group mean VAS pain scores 22% lower ($P = 0.018$); verbal pain scores 21% lower ($P = 0.047$)	PONV more frequent in PBO group ($P < 0.05$); pruritus more common in PBO group ($P < 0.01$)
Anwari et al, 2008; abdominal hysterectomy[24]	RCT in ASA physical status I or II women aged 25–60 y	Single-dose diclofenac 100 mg PR (n = 24) or meloxicam 15 mg PR (n = 23)	PBO (n = 23)	PCA morphine 1.5 mg bolus, 10-min lockout, basal infusion of 1 mg/h	Diclofenac group 24-h morphine use 17% lower than PBO group ($P < 0.05$)	No statistically significant difference between groups	No statistically significant difference between groups in sedation or PONV
Argoff et al, 2016; bunionectomy[14]	RCT in men and women aged 18–65 y experiencing moderate to severe pain following bunionectomy surgery	Diclofenac 18 mg TID (n = 109); diclofenac 35 mg TID (n = 107); celecoxib 400 mg loading dose + 200 mg BID (n = 106); up to 48 h	PBO (n = 106)	Rescue medication: hydrocodone/ acetaminophen or oxycodone/ acetaminophen tablets	Mean rescue medication use was significantly less in diclofenac 18 mg group (2.3 tablets) and diclofenac 35 mg group (2.0 tablets) vs PBO group (3.7 tablets) (both, $P < 0.001$)	NR	No statistically significant difference between groups reported
Costello et al, 2010; laparoscopic excision of endometriosis[26]	Prospective RCT in women aged 18–45 y	Diclofenac 100 mg PR BID until discharge + 0.75% ropivacaine to port sites, excision sites, and topically intraoperatively (n = 30)	PBO (n = 36)	PCA morphine 1 mL bolus, 5-min lockout	The amount of opioids used by the treatment group through 5 days postoperatively were 45% lower than control group ($P = 0.017$)	No statistically significant difference between groups	A bladder perforation in 1 treatment-group patient was only AE reported during trial
Fayaz et al, 2004; cardiac surgery[38]	Prospective RCT in adults undergoing elective coronary artery bypass grafting; mean age, 62.6 years	Diclofenac 100 mg PR + acetaminophen 1 g PR for 24 h (n = 17); diclofenac 100 mg PR (n = 17) for 18 h	PBO (n = 20)	PCA morphine 1 mg bolus, 5-min lockout	Morphine use reduced by 27% in diclofenac group and 41% in diclofenac + acetaminophen group compared with PBO ($P < 0.05$)	Pain scores were significantly lower in treatment groups than controls after 24 h ($P < 0.05$)	One case of epigastric pain and melena in diclofenac group and 4 cases of severe PONV in PBO group

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Table I. (*Continued*)

Study/Condition	Study Design/ Population	Intervention Arm(s)	Control Arm	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Fredman et al, 2000; major orthopedic surgery in geriatric patients[19]	RCT in ASA physical status I–III geriatric patients aged ≥65 y	Diclofenac 0.7 mg/kg IV + constant infusion diclofenac 0.15 mg/kg/h during surgery (n = 20)	PBO (n = 20)	PCA morphine 1 mg bolus, 6-min lockout	No difference between groups in PCA attempts or morphine delivered	No statistically significant difference between groups	NR
Gombotz et al, 2010; hip arthroplasty[33]	RCT in ASA physical status I–III adults aged 18–85 y	Diclofenac/orphenadrine combination 2 × 250 mL infusions (n = 60) during first 24 h postoperatively	PBO (n = 60)	PCA morphine 2 mg bolus or piritramide 2.9 mg bolus, 10-min lockout; maximum 5 boluses/h	Treatment group used 31% less morphine than PBO group ($P = 0.0004$)	No statistically significant difference between groups	No significant difference in AEs; 3 serious AEs in 2 patients in PBO group, none in treatment group
Ng et al, 2002; abdominal hysterectomy[23]	RCT in ASA physical status I or II adults aged 20–60 y	Diclofenac 75 mg PR (n = 18) during three 12-hourly intervals	PBO (n = 16)	PCA morphine (no further information provided)	Mean morphine consumption was 47% lower in diclofenac group than PBO group ($P = 0.02$)	Pain scores were significantly lower in treatment groups than controls after 24 h ($P = 0.04$)	Sedation and nausea scores were significantly higher in PBO group
Olofsson et al, 2000; cesarean delivery[12]	RCT in healthy women; mean age, 31.6 y	Diclofenac 3 × 50 mg PR (n = 25) during first 24 h postoperatively	PBO (n = 25)	PCA ketobemidone 1 mg bolus, 6-min lockout, 10 mg/h maximum	Total ketobemidone dose 39% less in diclofenac group ($P < 0.01$) vs PBO group	Significantly lower pain scores in diclofenac group up to 3 h postoperatively	No complications due to postoperative bleeding
Silvanto et al, 2002; knee arthroplasty[11]	RCT in ASA physical status I–III adults; mean age, 65.4 y	Diclofenac 75 mg IV + 50 mg po TID (n = 24); ketoprofen 100 mg IV + 100 mg po TID (n = 24) until the third postoperative day	PBO (n = 16)	PCA oxycodone 30 μg/kg bolus, 12-min lockout	Oxycodone use by diclofenac group was about half that of the PBO group 25–60 h postoperatively ($P < 0.05$)	Pain scores were significantly lower in diclofenac group than PBO group	Significantly more irritation at injection site and fewer cases of nausea in diclofenac group vs PBO
Thaweekul et al, 2011; laparoscopic gynecologic surgery[20]	RCT in adults scheduled for laparoscopic gynecologic surgery; mean age, 44.3 y	Single-dose diclofenac 75 mg IM postoperatively (n = 23)	PBO (n = 23)	PCA morphine 1 mg bolus; 5-min lockout	Median morphine consumption was 41% lower in the diclofenac group than in PBO group ($P = 0.041$)	No statistically significant difference between groups at 24 h	No significant difference in AEs

AEs = adverse events; ASA = American Society of Anesthesiologists (I, normal healthy patient; II, patient with mild systemic disease; and III, patient with severe systemic disease); NR = not reported; PBO = placebo; PCA = patient-controlled analgesia; PONV = postoperative nausea and vomiting; RCT = randomized, controlled trial; VAS = visual analog scale.

Table II. Opioid-sparing studies of ketorolac.

Study/Condition	Study Design/ Population	Intervention Arm(s)	Control Arm	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Alexander et al, 2002; major orthopedic surgery[31]	RCT in ASA physical status I or II patients aged 18 to 80 y scheduled for prosthetic hip or knee replacement	Single dose ketorolac 60 mg IV (n = 31); diclofenac 75 mg IV (n = 36) before induction of anesthesia	PBO (n = 32)	PCA morphine 1 mg bolus, 5-min lockout (maximum in 4 h, 30 mg); morphine 2 mg (rescue)	Ketorolac 24-h morphine use 9% lower than PBO group ($P < 0.01$)	Compared with PBO, ketorolac group mean VAS pain scores 18% lower ($P = 0.025$); verbal pain scores 20% lower ($P = 0.048$)	PONV more frequent in PBO group ($P < 0.05$); pruritus more common in PBO group ($P < 0.01$)
Cepeda et al, 2005; surgery[16]	RCT in adult subjects aged 18–60 y	Ketorolac 30 mg IV + morphine 0.1 mg/kg IV (n = 503) until pain intensity of ≤4 on numeric rating scale on which 0 represents no pain and 10 represents the worst pain imaginable	Morphine 0.1 mg/kg IV (n = 500)	Morphine 2.5 mg/ 10 min until pain intensity ≤4 given as rescue	Ketorolac group required 59% less morphine than morphine-only group ($P = 0.00001$)	Pain significantly greater in ketorolac group during initial 30 min (a time when this treatment group had only received ketorolac); both groups received morphine thereafter, and no pain difference was observed thereafter	Fewer patients in the morphine-only group reported no AEs ($P = 0.007$), and the morphine-only group had a higher prevalence of sedation, dizziness, and pruritus
Chen et al, 2005; colorectal resection[39]	RCT in ASA physical status I or II subjects aged 35–75 y	PCA with ketorolac (1.2 mg/mL) + morphine (1 mg/mL; n = 39) until VAS for pain on movement was <3 on 2 consecutive evaluations	PCA morphine 1 mg/mL (n = 35)	PCA 2 mL bolus, 10-min lock	Morphine consumption 24% lower in ketorolac + morphine group than in morphine-only group ($P < 0.05$)	No statistically significant difference between groups	No statistically significant difference between groups
Chen et al, 2009; colorectal resection[40]	Prospective RCT in ASA physical status I–III subjects aged 30–80 y	PCA with ketorolac (1.2 mg/mL) + morphine (1 mg/mL; n = 52) until VAS for pain on movement was <3 on 2 consecutive evaluations	PCA morphine 1 mg/mL (n = 50)	PCA 2 mL bolus, 10-min lockout	Morphine consumption in first 3 d was 18% lower in ketorolac + morphine group than in morphine-only group ($P < 0.05$)	No statistically significant difference between groups except for VAS on movement on third postoperative day	No statistically significant difference between groups
Lu et al, 2006; laparoscopic-assisted vaginal hysterectomy[25]	RCT in ASA physical status I or II subjects; mean age, 45.4 y	Perioperative ketorolac 60 mg IV + dextromethorphan 40 mg IM (n = 20); perioperative ketorolac 60 mg IV alone (n = 20); perioperative dextromethorphan 40 mg alone (n = 20)	PBO (n = 20)	Chlorpheniramine 20 mg IM; PCA morphine 1 mg bolus, 5-min lockout	Patients in the combination group used 66% less morphine ($P = 0.0001$) and the ketorolac group used 31% less morphine ($P = 0.004$) than the control group	Significantly lower pain scores in combination and ketorolac-only groups through 2 h postoperatively	No significant difference in AEs

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Table II. (*Continued*)

Study/Condition	Study Design/ Population	Intervention Arm(s)	Control Arm	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Pavy et al, 2001; cesarean delivery[13]	RCT in ASA physical status I or II women; mean age, 31 y	Ketorolac 30 mg IV, then 120 mg IV over 24 h (n = 24)	PBO (n = 20)	PCEA meperidine 24 mg incremental dose, 15-min lockout	Ketorolac group used 36% less meperidine in the 24 h postoperatively ($P < 0.05$)	No statistically significant difference between groups at 24 h	Significantly fewer patients free of pruritus at 48 h in ketorolac group (4%) than in PBO group (40%; $P = 0.006$)
Sousa AM et al, 2016; laparoscopic gynecologic surgery[21]	RCT in ASA physical status I or II women; mean age, 49.3 y	Periprocedural ketorolac 30 mg IV (n = 18); periprocedural magnesium sulfate 20 mg/kg (n = 18)	PBO (n = 18)	PCA morphine 2 mg bolus, 10-min lockout + metamizole 30 mg/kg bolus	Patients in ketorolac group used 59.6% less morphine than the PBO group ($P = 0.002$)	Significantly less pain in ketorolac group at 24 h than PBO ($P < 0.001$)	Fewer patients in ketorolac group experienced nausea than in PBO group ($P = 0.01$)

AEs = adverse events; ASA = American Society of Anesthesiologists (I, normal healthy patient; II, patient with mild systemic disease; and III, patient with severe systemic disease); PBO = placebo; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PONV = postoperative nausea and vomiting; RCT = randomized, controlled trial; VAS = visual analog scale.

surgery[34] and one that studied tenoxicam 20 mg in women undergoing cesarean delivery.[22] De Decker et al[34] reported a 41% reduction in PCA morphine use and significantly lower pain scores with tenoxicam 40 mg compared with controls, and Yeh et al[22] found a similar 38% reduction in morphine use and significantly lower pain from uterine cramping following cesarean delivery with tenoxicam 20 mg, but only among primiparous women. In the study by De Decker et al,[34] tenoxicam was administered either IV or IM. Patients who received tenoxicam IV had significantly fewer urinary retention events requiring catheterization than did placebo-treated patients. This study also included a piroxicam arm (40 mg), but no opioid-sparing effects were observed with piroxicam.

The opioid-sparing effects of lornoxicam were also assessed in 2 placebo-controlled trials that administered a dose of 8 mg to postoperative patients and used PCA to measure morphine consumption.[29,43] These studies reported that morphine consumption was 36%[29] and 54%[43] lower in lornoxicam-treated patients; lornoxicam provided a significant reduction in pain scores in 1 study.[29] There were no differences in AEs between the lornoxicam-only and placebo groups in the 1 study in which this outcome was reported.[43]

The NSAID meloxicam 15 mg was tested in 1 trial that assessed opioid use versus PCA morphine.[24] Meloxicam treatment was not associated with decreased morphine consumption or decreased pain levels compared with placebo.[24]

DISCUSSION

In this review, we examined data from 32 studies that were conducted since the turn of the century and that investigated the utility of NSAIDs as a component of multimodal analgesia in postsurgical patients, in terms of opioid-sparing effects, pain control, and AEs. The studies reviewed showed that NSAIDs were consistently associated with reductions in opioid requirements in the treatment of postoperative pain; the only exceptions were meloxicam and piroxicam, although only 1 trial that assessed each agent was found for this review. While some studies of perioperative multimodal analgesia evaluated >1 NSAID product, they are too few to draw any firm conclusions. Although ketoprofen and dexketoprofen provided similar rates of opioid sparing,

Table III. Opioid-sparing studies of ibuprofen.

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Gago Martínez et al, 2016; abdominal and orthopedic surgery[30]	RCT in subjects aged 18–80 y	Ibuprofen 800 mg IV q6h (n = 87) for 24 h (abdominal surgery), 48 h (hip, shoulder, ligament surgery), and 72 h (knee and spine surgery)	PBO (n = 79)	PCA morphine 1 mg bolus, 5-min lockout; max 30 mg in 4 h	Patients in the ibuprofen group used 46% less morphine than the PBO group ($P = 0.01$)	Ibuprofen group had significantly lower pain scores at 24 h postoperatively than PBO group ($P = 0.0119$)	No statistically significant difference between groups
Pinar et al, 2017; spinal surgery[36]	RCT in ASA physical status I or II subjects aged 18–65 y	Preoperative ibuprofen 800 mg IV (n = 21)	PBO (n = 21)	Pregabalin 150 mg po; PCA morphine 1 mg bolus, 10-min lockout, 30 mg/4 h maximum	Significantly less morphine consumption in ibuprofen group at 2, 4, 8, 12, and 48 h postoperatively ($P < 0.05$)	Significantly lower pain scores in ibuprofen group at 0, 1, 2, 36, and 48 h postoperatively ($P < 0.05$)	No difference between groups for sedation, nausea, vomiting, dizziness, and visual disturbances
Singla et al, 2010; orthopedic surgery[28]	RCT in subjects aged 18–80 y	Ibuprofen 800 mg IV q6h (n = 99) for 7 d	PBO (n = 86)	PCA morphine 1–2 mg bolus; 5-min lockout	Ibuprofen group used 31% less morphine than PBO group ($P < 0.001$)	Ibuprofen group had significantly lower pain scores than PBO group ($P < 0.001$)	No significant difference in AEs
Southworth et al, 2009; orthopedic or abdominal surgery[32]	RCT in subjects aged 18–70 y	Ibuprofen 800 mg IV q6h (n = 138); ibuprofen 400 mg IV q6h (n = 134) up to 5 d	PBO (n = 134)	PCA morphine 1–2 mg every 5 min	Ibuprofen 800 mg group used 22% less morphine than PBO group in first 24 h ($P = 0.03$)	Ibuprofen 800 mg group had significantly lower pain scores than PBO group in 1–24, 6–24, and 12–24 h time periods ($P \leq 0.001$ for each time period vs PBO); ibuprofen 400 mg group had significantly lower pain scores than PBO group in 6–24 h and 12–24 h time periods ($P < 0.05$ for each comparison)	Both doses of ibuprofen associated with fewer cases of pyrexia, nausea, and GI AEs ($P < 0.05$); ibuprofen 800 mg associated with more dizziness ($P = 0.011$)
White et al, 2011; ambulatory surgery[15]	RCT in subjects scheduled for superficial surgical procedures; mean age, 48.7 y	Ibuprofen 1200 mg/d (n = 60); celecoxib 400 mg/d (n = 60) for 4 d	PBO (n = 60)	Hydrocodone 5 mg/ acetaminophen 500 mg PO as rescue medication	Ibuprofen group used fewer rescue medication pills at 48 and 72 h than PBO group ($P < 0.05$)	Lower overall pain scores (0–72 h) in ibuprofen group than in PBO group ($P < 0.05$)	Postoperative constipation higher in PBO group ($P < 0.05$); no unusual bleeding, wound, or cardiovascular AEs

AEs = adverse events; ASA = American Society of Anesthesiologists (I, normal healthy patient; and II, patient with mild systemic disease); GI = gastrointestinal; PBO = placebo; PCA = patient-controlled anesthesia; RCT = randomized, controlled trial.

Table IV. Opioid-sparing studies of ketoprofen and dexketoprofen.

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Ketoprofen							
Hanna et al, 2003; orthopedic surgery[27]	RCT in ASA physical status I or II subjects aged 18–75 y	Ketoprofen 2 × 100 mg IM (n = 56) dexketoprofen trometamol 2 × 50 mg IM (n = 58); first dose of both administered immediately postoperatively and second administered 12 h later	PBO (n = 54)	PCA morphine 1 mg bolus, 5-min lockout	Statistically significant decrease in morphine use by 36% in ketoprofen group vs PBO	Significantly lower pain scores in ketoprofen group than in PBO group at the 1–6 h time period ($P = 0.0001$) but not between hours 9–12 or 13–24	PONV more frequent in PBO group (47%) than in ketoprofen group (34%); 1 incident of GI bleeding in ketoprofen group, none in PBO
Oberhofer et al, 2005; major abdominal surgery[17]	RCT in subjects undergoing major abdominal surgery; mean age, 64.5 y	Ketoprofen 100 mg IV postoperatively (n = 21) at 1 and 9 h postoperatively	PBO (n = 22)	Tramadol 200 mg IV + metamizole 5 g IV; tramadol 25 mg bolus (rescue)	Tramadol consumption was 18% lower in ketoprofen group ($P < 0.001$)	Pain scores were significantly lower in ketoprofen group at 12 h postoperatively; no difference at 24 h	PONV more frequent in PBO group (n = 7) than ketoprofen group (n = 4); no excessive bleeding in ketoprofen group
Rao et al, 2000; abdominal surgery[42]	RCT in subjects aged 18–60 y	Ketoprofen 100 mg IV (n = 20) given 0.5 h before end of surgery and 12 h later	PBO (n = 19)	PCA morphine 1 mg bolus, 5-min lockout	Significantly less morphine consumption in ketoprofen group in the recovery room (55% reduction; $P = 0.013$) and significantly less at 8, 12, and 24 h postoperatively ($P < 0.05$ for each time point)	No statistically significant difference between groups	4 cases of PONV in ketoprofen group vs 6 cases in PBO group; 1 patient with transient oliguric renal failure in the ketoprofen group
Silvanto et al, 2002; knee arthroplasty[11]	RCT in ASA physical status I–III adults; mean age, 65.4 y	Ketoprofen 100 mg IV + 100 mg PO TID (n = 24); diclofenac 75 mg IV + 50 mg PO TID (n = 24) until the third postoperative day	PBO (n = 16)	PCA oxycodone 30 μg/kg bolus, 12-min lockout	The ketoprofen groups used 34% and 66% less oxycodone than the PBO group 13–24 h and 61–72 h postoperatively, respectively ($P < 0.05$)	Pain scores were significantly lower in ketoprofen group than PBO controls 2 d postoperatively ($P < 0.05$)	Significantly more irritation at injection site in ketoprofen group vs PBO ($P < 0.01$)
Dexketoprofen							
Hanna et al, 2003; orthopedic surgery[27]	RCT in ASA physical status I or II subjects aged 18–75 y	Dexketoprofen trometamol 2 × 50 mg IM (n = 58); ketoprofen 2 × 100 mg IM (n = 56); first dose of both administered immediately postoperatively and second administered 12 h later	PBO (n = 54)	PCA morphine 1 mg bolus, 5-min lockout	Statistically significant decrease in morphine use by 39% in dexketoprofen group vs PBO	Significantly lower pain scores in dexketoprofen group compared with placebo group across 3 time periods (1–6, 9–12, and 13–24 h; $P < 0.05$)	PONV more frequent in PBO group (47%) than in dexketoprofen group (21%); 2 incidents of GI bleeding in dexketoprofen group, none in PBO group

Kesimci et al, 2011; laminectomy[35]	Prospective RCT in ASA physical status I or II subjects aged 18–65 y	Single preoperative dose dexketoprofen 25 mg PO (n = 25) or acetaminophen 500 mg PO (n = 25)	PBO (n = 25)	PCA morphine 1 mg bolus, 15-min lockout, 0.3 mg/h background infusion	24-h morphine consumption in dexketoprofen group was 36% lower than in the PBO group ($P < 0.006$) and 31% lower than in the acetaminophen group	Mean pain scores were not different between groups	No significant difference in AEs
Sivrikoz et al, 2014; major orthopedic surgery[29]	RCT in ASA physical status I–III subjects; mean age, 61 y	Dexketoprofen 50 mg IV BID the day of surgery (n = 40); lornoxicam 8 mg IV BID the day of surgery (n = 40)	PBO (n = 40)	PCA morphine 0.01 mg/kg bolus, 10-min lockout	Dexketoprofen group used 50% less morphine than PBO ($P < 0.001$)	Dexketoprofen group had significantly lower pain scores at rest at 1, 2, 4, 8, 12, and 24 h postoperatively vs PBO group (P value between 0.01 and 0.001 for each time point listed)	NR

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease; III: patient with severe systemic disease); BID = twice daily; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NR = not reported; PBO = placebo; PCA = patient-controlled anesthesia; po = orally; PONV = postoperative nausea and vomiting; RCT = randomized, controlled trial; TID = 3 times daily.

Table V. Opioid-sparing studies of other NSAIDs.

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Anwari et al, 2008; abdominal hysterectomy[24]	RCT in ASA physical status I or II women aged 25–60 y	Single dose meloxicam 15 mg PR (n = 23); diclofenac 100 mg PR (n = 24)	PBO (n = 23)	PCA morphine 1.5 mg bolus, 10-min lockout, basal infusion of 1 mg/h	Meloxicam 24-h morphine use not different from diclofenac or PBO groups	No statistically significant difference between groups	No statistically significant difference between groups in sedation or PONV
De Decker et al, 2001; spinal surgery[34]	RCT in ASA physical status I–III subjects aged 20–70 y	Piroxicam 40 mg IM (n = 15) preoperatively; tenoxicam 40 mg IV (n = 15) preoperatively; tenoxicam 40 mg IM preoperatively (n = 15)	PBO (n = 15)	PCA morphine 3 mg loading dose; 1 mg bolus, 5-min lockout; 1-h limit of 5 mg	During the entire 24-h study, the tenoxicam IV group used 41% less morphine ($P < 0.05$); tenoxicam treatment groups were no different than PBO	At 24 h, all 3 treatment groups had significantly lower resting pain scores than PBO group	Urinary retention observed frequently, tenoxicam IV group had significantly fewer events requiring catheterization than PBO group ($P = 0.037$)
Kotsovolis et al, 2015; laparoscopic cholecystectomy[43]	RCT in adults aged 18–70 y	A) Lornoxicam 8 mg IV + ketamine 0.3 mg/kg IV + gabapentin 600 mg PO pre- and postoperatively + ropivacaine 0.75% local infiltration; (B) gabapentin only; (C) ketamine only; (D) lornoxicam only; (E) ropivacaine only (n = 28 for each group); all up to 24 h	PBO (n = 28)	PCA morphine 1 mg bolus, 10-min lockout	24-h morphine consumption was 68% lower in the combination group ($P < 0.001$), 53% lower in the gabapentin group ($P = 0.01$), and 54% lower in the lornoxicam group ($P = 0.008$) than PBO	No statistically significant difference between groups	Combination group had significantly fewer incidents of nausea than PBO group ($P = 0.018$); no other differences in AEs
Sivrikoz et al, 2014; major orthopedic surgery[29]	RCT in ASA physical status I–III subjects; mean age, 61 y	Lornoxicam 8 mg IV BID the day of surgery (n = 40); dexketoprofen 50 mg IV BID the day of surgery (n = 40); PBO (n = 40)	PBO (n = 40)	PCA morphine 0.01 mg/kg bolus, 10-min lockout	Lornoxicam group used 36% less morphine than PBO group ($P < 0.001$)	Lornoxicam group had lower pain scores than PBO group at 24 h ($P < 0.001$); dexketoprofen group had lower pain scores than lornoxicam group through 4 h ($P < 0.01$)	NR
Yamashita et al, 2006; spinal surgery[37]	RCT in ASA physical status I or II subjects scheduled for spinal fusion surgery; mean age, 61.7 y	Preoperative flurbiprofen axetil 1 mg/kg IV (n = 12); postoperative flurbiprofen 1 mg/kg IV (n = 12)	PBO (n = 12)	PCA morphine 0.1 mg/kg bolus, 3 mL dose, 30-min lockout	Morphine consumption was roughly 50% lower with presurgical flurbiprofen than with PBO or postoperative flurbiprofen ($P < 0.05$)	Pain scores were significantly lower with presurgical flurbiprofen than with PBO through 24 h ($P < 0.05$)	No AEs reported in flurbiprofen treatment groups

Yeh et al, 2005; cesarean delivery[22]	Prospective RCT in ASA physical status I or II women; mean age, 31.2 y	Tenoxicam 20 mg IV perioperatively: primiparous (n = 20); multiparous (n = 20)	PBO: primiparous (n = 20); multiparous (n = 20)	PCA morphine 2 mg bolus, 10-min lockout	Tenoxicam reduced morphine use in primiparous women compared with PBO (38%; $P < 0.05$), but not in multiparous women	Tenoxicam reduced pain from uterine cramping in primiparous women ($P < 0.05$), but not in multiparous women	No statistically significant difference between groups

AEs = adverse events; ASA = American Society of Anesthesiologists (I, normal healthy patient; II, patient with mild systemic disease; and III, patient with severe systemic disease); NR = not reported; PBO = placebo; PCA = patient-controlled analgesia; po = orally; PONV = postoperative nausea and vomiting; PR = per rectum; RCT = randomized, controlled trial.

dexketoprofen provided significant pain control for 24 h versus placebo, while ketoprofen did so for the first 6 h only.[27] Intravenous ibuprofen was opioid sparing,[28,30,32,36] as was oral ibuprofen at a dose of 1200 mg/d.[15] If over-the-counter strength analgesics are useful in providing consistently effective postoperative pain relief, substantial health care cost-savings could be realized by shifting these costs to the patient. In general, studies show that a reduction in opioid use was accomplished without a compromise in pain control (vs opioid alone), in addition to a reduction in opioid-related side effects such as nausea, vomiting, sedation, and pruritus.

Across the studies reviewed, NSAIDs were well-tolerated components of multimodal analgesia. The rates of AEs reported in patients receiving NSAIDs were generally similar to those reported by patients receiving placebo, and there were fewer AEs associated with NSAID use than with conventional morphine analgesia. For instance, several studies in this review reported a lower prevalence of PONV when NSAIDs were used with PCA opioids, a finding that is likely related to a diminished opioid requirement in patients using NSAIDs. Recently, Zhao-Fleming et al[44] reviewed potential complications associated with perioperative NSAID use. They found the strongest level of evidence for delayed healing of nonunion bone fractures and recommended judicious use of NSAIDs in the perioperative period in this context. For other potential complications reviewed (eg, anastomotic leak, negative effects on wound healing or wound infections, and postoperative bleeding), more research is required. NSAID-associated AEs reported in these studies included injection site irritation (ketoprofen, n = 12 and diclofenac, n = 6 vs placebo, n = 0; both, $P < 0.01$),[11] dizziness (ibuprofen 800 mg, n = 12 vs placebo, n = 2; $P = 0.011$),[32] gastrointestinal bleeding (diclofenac[38] and ketoprofen[27] [1 incident each], and dexketoprofen[27] [2 incidents]), bladder perforation (diclofenac [1 incident]),[26] and transient oliguric renal failure (ketoprofen [1 incident]).[42] Interestingly, although there is a theoretical risk for bleeding associated with NSAIDs due to their mechanism of action,[9] none of the trials reviewed herein found that NSAIDs were associated with increased postoperative bleeding.

Several limitations must be considered when interpreting the findings of this review. Foremost is the variability in terms of study design among the

studies cited here, including the timing of NSAID administration (eg, preoperatively vs postoperatively), dosing regimens used, routes of administration, follow-up times, and outcome assessments. In addition, opioid consumption outcomes were measured in several different ways, including reductions in PCA, rescue, or titrated analgesia requirements, and these differences make comparisons among agents difficult. Finally, the included studies may be skewed toward findings of positive efficacy since articles reporting a positive result are broadly over-represented in the scientific literature.[45]

CONCLUSIONS

NSAIDs have the potential to play an important role in reducing postoperative opioid requirements. Reducing the amount of opioids used perioperatively could be expected to reduce opioid-related side effects and may contribute to reversing the opioid epidemic by decreasing the risk for opioid-use disorder. As the use of NSAIDs as part of a multimodal analgesic strategy becomes more commonplace, more data on the advantages and disadvantages will become apparent to inform such use.

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Address correspondence to: Luc Martinez, MD, 30, Rue du stade, La Rochelle, France 17000. E-mail: luc.martinez@orange.fr