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NSAIDs in the Treatment of Postoperative Pain

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Abstract
Purpose of Review Postoperative pain results in multiple undesirable physiologic and psychological outcomes, and it should be managed in a multimodal approach. This article reviews the latest scientific literature of NSAIDs in the treatment of postoperative pain. The goal is to answer the following questions: (1) Are NSAIDs effective in the postoperative period? (2) Are NSAIDs safe in all surgical patients? and (3) Are adverse effects of NSAIDs increased or diminished in the acute postoperative period?
Recent Findings NSAIDs are safe and effective in the treatment of postoperative pain, and they should be administered to all postoperative surgical patients unless contraindicated.
Summary Based on literature, NSAIDs have been shown to increase patient satisfaction and decrease opioid requirements, minimizing opiate-induced adverse events. They have no increased incidence of adverse effects during the acute postoperative period. NSAIDs and COX-2 inhibitors, however, should be used with caution in colorectal surgery as they are proven to increase the risk of anastomotic leak.

Keywords NSAIDs in postoperative pain · Postoperative pain · Multimodal NSAIDs · NSAIDs acute pain · Postoperative analgesics · NSAID adverse effects

This article is part of the Topical Collection on *Other Pain*

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Introduction

The most recent practice guidelines released by the American Society of Anesthesiologists (ASA) Task Force in 2012 stated that undertreatment of postoperative pain results in multiple undesirable physiologic and psychological outcomes including pulmonary complications, extended hospital or intensive care unit stay, unplanned readmission, and the development of chronic pain [1]. The prevalence of acute postoperative pain is about 80 %, of which 86 % report moderate to severe pain [2].

Postoperative pain is a physiological result of stimulation of both the somatic and visceral pain pathways. Specialized nociceptors are stimulated by noxious stimuli released after tissue damage such as inflammatory mediators including bradykinin, serotonin, prostaglandins, and cytokines. These signals are then transmitted to the CNS via primary afferent A-delta and C nerve fibers that synapse with secondary afferent neurons within the dorsal horn of the spinal cord and ascend via the spinothalamic or spinoreticular tracts into the cerebral cortex. Persistent postoperative pain, a chronic pain state where symptoms continue beyond 2 months past the expected postsurgical healing, is prolonged through inflammatory, ischemic, and neuropathic causes [2].

As a result, inflammatory mediators are major players in acute postoperative pain, and management needs to be approached in a multimodal fashion by including agents capable of inhibiting the perception of pain peripherally and centrally in combination with other synergistic analgesics [1, 2]. Opioids have been the mainstream treatment for postoperative pain. However, they mainly act within the central nervous system to provide analgesia; they do not interrupt the inflammatory component of pain. Addressing the inflammatory response may reduce the overall need for opioid analgesics and improve recovery after surgical procedures.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a well-established class of drugs that have long been used for the blockage of pain and inflammation in both acute and chronic pain. They can maintain a constant level of prostaglandin inhibition over the course of a prolonged surgery and during the postoperative period. They have no risk of abuse; therefore, postoperative use of NSAIDs helps reduce growing concerns of opioid abuse and the potential over-prescription of opiate [3]. In the USA, over 244 million prescriptions were issued for narcotics in 2010, with an estimated cost of over $8.4 billion [4]. NSAID use helps mitigate that cost.

NSAIDs have been shown to function both peripherally and centrally in nociception. In the ascending pain pathway, NSAIDs would act at the peripheral nociceptors by blocking the cyclooxygenase (COX) enzyme that inhibits the conversion of arachidonic acid to prostaglandins, thereby preventing the sensitization of pain receptors in response to injury. Centrally, NSAIDs act in the spinal dorsal horn to inhibit prostaglandin E2 (PGE2) production via COX-2 and in the brain by activating medullary and cortical regions involved in the descending inhibitory pain cascade, resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue.

The ASA notes that, unless contraindicated, patients should receive an around-the-clock regimen of NSAIDs, COX inhibitors, or acetaminophen as part of a postoperative multimodal pain management regimen [2]. This article will review scientific evidence for the efficacy and adverse effects of NSAIDs in the treatment of postoperative pain. The goal is to answer the following questions: (1) Are NSAIDs effective in the postoperative period? (2) Are NSAIDs safe in all surgical patients or are there some postsurgical contraindication? and (3) Are NSAID adverse effects increased or diminished in the acute postoperative period? This review is primarily based on data from systematic reviews; meta-analyses; and randomized clinical trials, cohort studies, and retrospective studies from literature search on NSAIDS in postoperative pain and multimodal NSAIDs using MEDLINE databases. Reference lists of relevant articles were checked to identify additional studies (please see Table 1 for a detailed summary of reviewed studies).

Analgesic Efficacy of NSAIDs

Overall, NSAIDs and COX-2 inhibitors are to be considered for all surgical procedures as they decreased opioid requirements, therefore minimizing opioid-induced adverse events such as nausea, vomiting, and sedation; they improve patient satisfaction, decrease PACU recovery times, and decrease morbidity in the postoperative period [7, 8]. Current available NSAID therapies are either reversible competitive inhibitors (except aspirin), variably blocking both COX-1 and COX-2 isoforms (ibuprofen, diclofenac, ketorolac, ketoprofen, mefenamic acid, piroxicam, meloxicam, lornoxicam, indomethacin) or selective inhibitors of COX-2 (celecoxib, rofecoxib) [2]. All available data suggest similar efficacy of nonselective NSAIDs and selective COX-2 inhibitors, although the latter have less adverse effects in the short-term perioperative period. When it comes to drug selection, in general NSAIDs with longer half-life have a slower onset and, at higher doses, have faster onset with higher peak effect and longer durations. Therefore, it is more beneficial for the patient to be started on a high dose of a short-life drug, such as ibuprofen, and then adjust the dose when analgesic efficacy has been achieved to facilitate patient compliance.

NSAIDs have been proven specifically useful in the ambulatory setting. Rana et al. (2016) recently conducted a review of the multimodal approach for pain management in the ambulatory surgery setting and found that NSAIDs are more effective than acetaminophen with much lower numbers needed to treat [9]. Viscusi et al. (2012) were able to prove that perioperative use of etoricoxib reduces pain and opioid side effects in total abdominal hysterectomy by approximately 30 % compared to placebo ($p < 0.001$), which led to more rapid bowel recovery in the active treatment groups by 10 h vs. placebo. Also, a greater proportion of patients on etoricoxib achieved mild levels of pain with movement [10].

NSAIDs also have been shown to be effective in orthopedic surgery; they decrease pain and inflammation, therefore allowing patients to have an increased knee range of motion, leading to a shorter period of physical therapy. According to Buvanendran et al. (2003), patients treated with rofecoxib had an overall decrease in pain scores by 40 % ($p < .05$), increased knee range of motion, and decrease in sleep disturbance compared with the placebo [11]. In addition, Takada et al. (2007) showed that flurbiprofen suppresses local production of PGE2 during tourniquet ischemia, resulting in reduced early postoperative pain in patients undergoing knee surgery [12], and in 2009, they conducted a randomized study in which patients who received flurbiprofen before arthroscopic rotator cuff repair had greater analgesic effect and early postoperative recovery [13].

NSAIDs and COX-2 inhibitors have been found to be safe and effective in reducing pain scores and decreasing opioid consumption in neurosurgery patients including laminectomy or discectomy [14]. A double-blind randomized control trial by Srivastava et al. (2012) on patients undergoing single-level lumbar discectomy showed reductions in pain scores at rest and on movement with patients who received 120 mg of etoricoxib postoperatively compared to the control ($p < 0.05$) [15]. Also, patients in the etoricoxib group had a better sleep at night ($p = 0.0004$), therefore concluding that single preoperative oral dose of clinical benefit of NSAIDs extends beyond

Table 1 Summary of studies

References	Title	Journal	Type of Study	Summary	Result/conclusion	Comments
Nir et al. 2016 [5••]	Preoperative preemptive drug administration for acute postoperative pain: a systematic review and meta-analysis	Eur J Pain	Review	Data from randomized placebo-controlled trials were analyzed with the primary outcome measure which was reduction in postoperative analgesic consumption during 24 h postsurgery.	A significant reduction in postoperative analgesic consumption was observed using preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs; 95 % CI, −0.61 to −0.14; 31 comparisons), chiefly by the COX-2 inhibitor class (95 % CI, −0.95 to −0.33; 13 comparisons).	
Pogatzki-Zahn et al. 2014 [18]	Nonopioid analgesics for postoperative pain management	Curr Opin Anaesthesiol.	Review	A review that examines the most recent findings on nonopioid analgesics and how these translate into clinical practice	Data found that the efficacy of tylenol is inferior to NSAIDs, and the authors believe that the risk of adverse events might have been underestimated. There are significant data supporting similar efficacy of nonselective and COX-2 inhibitors, although the latter have less adverse effects in the short-term perioperative period.	Metamizol (dipyrone) is a very effective nonopioid analgesic that is not currently available worldwide.
Gritsenko et al. 2014 [7]	Multimodal therapy in perioperative analgesia	Clin Anaesthesia	Review	A review of the current literature of multimodal analgesic regimens for common surgical procedures	NSAIDs and COX-2 inhibitors are to be considered for all surgical procedures as they decreased narcotic requirements, improved patient satisfaction, decreased PACU recovery times, and decreased morbidity in the postoperative period	
De Baerdemaeker et al. 2016 [17]	Best anesthetic drug strategy for morbidly obese patients	Curr Opin Anaesthesiol.	Review	Review of currently anesthetic therapies in morbidly obese patients	NSAIDs are encouraged to be used in these patients unless contraindicated. The authors state the data that ketorolac may increase the risk of postoperative hemorrhage after laparoscopic Roux-en-Y gastric by-pass. Bypass depends more on the type of procedure and the patient's compliance to avoid nicotine, alcohol, and chronic use of NSAIDS.	
Michelet et al. 2012 [16]	A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain	Anesth Analg	Meta-analysis	27 randomized controlled trials were analyzed, and outcomes measured were opioid consumption, pain intensity, postoperative nausea and vomiting (PONV), and urinary retention during PACU stay and the first 24 postoperative hours	Perioperative administration of NSAIDs decreased postoperative opioid requirement (both in the PACU and during the first 24 postoperative hours), pain intensity in the PACU, and PONV during the first postoperative day	
Mathiesen O et al. 2013 [8]	A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery	Eur Spine J	Case-control study	Investigated a multimodal postoperative pain protocol in treatment of pain and postoperative nausea and vomiting (PONV) in 41 patients undergoing multilevel spinal surgery	Addition of NSAIDs in the postoperative multimodal pain treatment decreases opioid use, therefore decreasing opioid side effects.	
Rana et al. 2016 [9]	Perioperative pain control in the ambulatory setting	Curr Pain Headache Rep	Review	Reviews the multimodal approach for pain management in the ambulatory surgery setting.	NSAIDs are more effective than acetaminophen with much lower numbers needed to treat. They are recommended to be a component of any multimodal regimen in the ambulatory setting when not contraindicated by patient medical conditions.	
Jung et al. 2004 [22]	Onset of analgesia and analgesic efficacy of tramadol/acetaminophen and codeine/acetaminophen/ibuprofen in acute postoperative pain: a single-center, single-dose, randomized, active-controlled, parallel-group study in a dental surgery pain model	Clin Ther	Randomized controlled trial	Compares onset of analgesia and efficacy of single-dose tramadol/acetaminophen 75/650 mg (Tr/Ac) and codeine/acetaminophen/ibuprofen 20/500/400 mg (Co/Ac/Ib) in 128 healthy subjects undergoing surgical extraction of >1 which impacted third molar requiring bone removal. Time to onset of analgesia was measured 6 h after dosing.	The Co/Ac/Ib group had significantly greater postoperative pain control compared to the Tr/Ac group ($p < 0.05$). However, Tr/Ac did provide rapid and effective analgesia for acute postoperative dental pain	

Table 1 (continued)

References	Title	Journal	Type of Study	Summary	Result/conclusion	Comments
Takada et al. 2007 [12]	Preadministration of flurbiprofen suppresses prostaglandin production and postoperative pain in orthopedic patients undergoing tourniquet inflation	J Clin Anesth	Randomized, controlled, double-blind study	32 patients scheduled for total knee arthroplasty or open anterior cruciate ligament reconstructions were randomly assigned to two groups. Group A ($n = 16$) received placebo (intralipid, 1 ml/kg) 5 min before tourniquet inflation (350 mmHg), and group B ($n = 16$) received flurbiprofen 1 mg/kg IV 5 min before tourniquet inflation (350 mmHg). Catheters were placed in the ipsilateral femoral vein for collection of local blood and in a cubital vein for sampling of systemic blood.	Group A, PGE2 in femoral vein increased significantly compared to group B which showed no change, therefore concluding that flurbiprofen suppresses local production of PGE2 during tourniquet ischemia, resulting in reduced early postoperative pain in patients undergoing knee surgery	
Takada et al. 2009 [13]	Postoperative analgesic effect of preoperative intravenous flurbiprofen in arthroscopic rotator cuff repair	J Anesth	Randomized double-blind study	44 patients who underwent an elective arthroscopic rotator cuff repair were divided into two groups. Group A ($n = 22$) received lipid emulsion as a placebo, and group B ($n = 22$) received flurbiprofen before the surgery. Postoperative analgesia was supplied with IV buprenorphine according to the patient's demand.	VAS scores for group B were significantly ($p < 0.01$) lower than those in group A during the first 6 h postoperatively. The amount of buprenorphine consumption in group B was also significantly ($p < 0.01$) less than that in group A within the first 2 h postoperatively, and time to first analgesic request in group B was significantly ($p < 0.01$) longer than that in group A, therefore concluding that preoperative intravenous flurbiprofen facilitates the analgesic effect in the early postoperative period after arthroscopic rotator cuff repair.	
Kesimci et al. 2011 [21]	Comparison of efficacy of dexketoprofen versus paracetamol on postoperative pain and morphine consumption in laminectomy patients	Ağrı	Randomized, double-blind study	75 patients scheduled for single-level lumbar disc surgery were randomly divided into three equal groups. Group D received oral dexketoprofen 25 mg, group P received 500 mg paracetamol, and group C received placebo tablets 30 min before induction of standard anesthesia	The cumulative (SD) 24-h morphine consumption was 28.1, 40.6, and 43.6 mg for groups D, P, and C, respectively. The amount of morphine use at 2, 6, and 24 h was significantly lower in group D ($p < 0.006$). Sedation and side effects did not differ among the groups ($p > 0.05$), concluding that preemptive dexketoprofen trometamol 25 mg is associated with a decrease of up to 35 % in morphine consumption following lumbar disc surgery which was not observed with paracetamol.	
Srivastava et al. 2012 [15]	Effects of preoperative single dose etoricoxib on postoperative pain and sleep after lumbar diskectomy: prospective randomized double blind controlled study	Middle East J Anaesthesiol	Randomized, double-blind, controlled study	44 patients who were undergoing single-level lumbar discectomy were given either placebo or etoricoxib 120 mg orally 1 h before surgery. Postoperatively, fentanyl intravenous (IV) PCA pump was started. Visual analog score (VAS) was assessed at 0, 6, 12, 18, and 24 h at rest and on movement	Reductions in VAS at rest and on movement were observed in the etoricoxib group when compared with the control group at all the intervals till 24 h postoperatively ($p < 0.05$). Total fentanyl consumption is higher in the control group ($p = 0.007$). Patients in the etoricoxib group had better sleep at night than did the control group ($p = 0.0004$), therefore concluding that single preoperative oral dose (120 mg) of etoricoxib has significantly reduced postoperative pain in patients undergoing single level discectomy with great patient satisfaction and no notable effects	Clinical benefit extends to minimizing psychological distress, sleep disturbances, and the need for further analgesics with the associated adverse effects
Rivkin et al. 2014 [14]	Perioperative nonopioid agents for pain control in spinal surgery	Am J Health Syst Pharm.	Review	A review of frequently used nonopioid analgesic agents incorporated into multimodal perioperative pain management protocols	For patients undergoing laminectomy or discectomy, NSAIDs appear to be safe and effective in reducing pain scores and decreasing opioid consumption	

Table 1 (continued)

References	Title	Journal	Type of Study	Summary	Result/conclusion	Comments
Huang et al. 2008 [53]	Perioperative celecoxib administration for pain management after total knee arthroplasty—a randomized, controlled study	BMC Musculoskelet Disord	Randomized, controlled study	80 patients who underwent total knee arthroplasty were randomized into two groups. Treatment group received a single 400 mg dose of celecoxib, 1 h before surgery and 200 mg of celecoxib every 12 h for 5 days, along with patient-controlled analgesic (PCA) morphine. The control group received only PCA morphine for postoperative pain management.	Treatment group reported significantly decreased in pain, increased active range of motion (ROM) during the first three postoperative days, and decreased total opioid use by 40 %. There were no significant differences in postoperative nausea/vomiting and blood loss (intraoperative and postoperative) between the groups.	
Buvanendran et al. 2003 [11]	Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial	JAMA	Randomized controlled trial	70 patients randomly assigned to receive 50 mg of oral rofecoxib at 24 h and at 1 to 2 h before TKA, 50 mg daily for 5 days postoperatively, and 25 mg daily for another 8 days, or matching placebo at the same times.	Rofecoxib administered resulted in significant decrease in opioid consumption ($p < .05$), overall VAS pain scores, and opioid side effects including postoperative vomiting. Treatment group also had an increased knee range of motion over 1 month, as well as a decrease in sleep disturbance compared with the placebo group	Extrapolation of these results also demonstrated improved patient satisfaction and a shorter period of physical therapy to achieve an adequate range of motion
Beaussier et al. 2005 [20]	A comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patient	Anesth Analg	Randomized double-blind trial	182 patients scheduled for initial inguinal hernia repair were randomly assigned to receive a single injection of 40 mg parecoxib or 2 injections of 2 g of propacetamol within the first 12 h after surgery.	Total morphine consumption did not differ between the two groups; however, pain was less intense in the parecoxib group at rest ($p = 0.035$) and parecoxib group had significant patient satisfaction (87 vs. 70 % in the propacetamol group, $p = 0.001$). Side effects were similar.	
Smirnov et al. 2008 [31]	Etoricoxib for pain management during thyroid surgery: a prospective, placebo-controlled study	Otolaryngol Head Neck Surg	Randomized, double-blind, controlled trial	69 patients who underwent thyroid surgery were randomized to receive etoricoxib 120 mg ($n = 34$) or placebo ($n = 35$) 60 min before surgery	Etoricoxib 120 mg reduced pain and less opioid use in the 7 to 24 postsurgical time period, a 24 % difference compared to placebo. However, there was no opioid-sparing effect during the first 6 h after surgery	Etoricoxib is not currently approved in the USA but is approved in Europe. Advantage of etoricoxib is the duration of action of 24 h; thus, only one dose per day is required and may increase compliance
Rawal et al. 2013 [32]	Evaluation of etoricoxib in patients undergoing total knee replacement surgery in a double-blind, randomized controlled trial	BMC Musculoskelet Disord	Double-blind, randomized trial	776 patients undergoing knee replacement receive placebo ($N = 98$), etoricoxib 90 mg ($N = 224$) or 120 mg ($N = 230$), or ibuprofen 1800 mg ($N = 224$) daily for 7 days postoperatively	Etoricoxib 90 and 120 mg was found to be both superior to placebo and equivalent to ibuprofen in reducing pain at rest and also reduces opioid consumption. Pain reduction of etoricoxib 90 and 120 mg was similar, and no significant adverse events were noted.	
Daniels et al. 2011 [33]	Evaluation of the dose range of etoricoxib in an acute pain setting using the postoperative dental pain model	Clin J Pain	Double-blind, randomized trial	588 patients randomized to placebo, etoricoxib (90 mg, etoricoxib 120 mg, ibuprofen 2400 mg, and acetaminophen (600 mg/codeine	In dental procedure postoperative pain, control etoricoxib (90, 120 mg) was significantly greater than placebo ($p \leq 0.001$) and not inferior to ibuprofen; no discernible difference was observed between etoricoxib 90 and 120 mg. Both etoricoxib doses were superior to acetaminophen mg/codeine ($p \leq 0.001$), which was associated with significantly more adverse events including nausea and vomiting. Etoricoxib and ibuprofen were well tolerated and had a similar incidence of adverse events	
Viscusi et al. 2012 [10]	Perioperative use of etoricoxib reduces pain and opioid side-effects total abdominal hysterectomy: a double-blind, randomized, after placebo controlled phase III study	Curr Med Res Opin	Double-blind, randomized, controlled phase III study	Patients were randomly assigned to receive either placebo ($n = 144$), etoricoxib 90 mg/day ($n = 142$), or etoricoxib 120 mg/day ($n = 144$).	Patients on etoricoxib 90 and 120 mg required ~30 % less morphine per day than those on placebo ($p < 0.001$), which led to more rapid bowel recovery in the active treatment groups by ~10 h vs. placebo. A greater proportion of patients on etoricoxib (10–30 % greater than	Parecoxib can in patients without renal risk factors replace IV paracetamol because of its greater efficacy.

Table 1 (continued)

References	Title	Journal	Type of Study	Summary	Result/conclusion	Comments
					placebo) achieved mild levels of pain with movement, defined as pain ≤3/10	
Derry et al. 2009 [25]	Single dose oral diclofenac for acute postoperative pain in adults	Cochrane Database Syst Rev	Review	This review updates an earlier review published in The Cochrane Database of Systematic Reviews (Issue 2, 2004) on "Single-dose oral diclofenac for postoperative pain."	Fifteen studies were reviewed, and overall, 50 to 60 % of participants experienced at least 50 % pain relief over 4 to 6 h at any dose with diclofenac, compared to 10 to 20 % with placebo, giving NNTs of about 2.5 for doses of 25 to 100 mg; no dose response was demonstrated. NNTs for diclofenac potassium were significantly lower (better) than for diclofenac sodium. Adverse events were reported at a similar rate to placebo, with no serious events.	
Derry et al. 2015 [26]	Single dose oral diclofenac for acute postoperative pain in adults	Cochrane Database Syst Rev	Review	This review updates an earlier review published in the Cochrane Database of Systematic Reviews (Issue 2, 2009) entitled "Single dose oral diclofenac for acute postoperative pain in adults."	Diclofenac potassium provides good pain relief at 25-, 50-, and 100-mg doses. Diclofenac sodium has limited efficacy and should probably not be used in acute pain	
Argoff et al. 2016 [29]	SoluMatrix(R) diclofenac: sustained opioid-sparing effects in a phase 3 study in patients with postoperative pain	Pain Med	Multicenter, randomized, double-blind study	428 patients following bunionectomy surgery were randomized to receive low-dose SoluMatrix diclofenac 35 or 18-mg capsules three times daily, celecoxib 400 mg loading dose followed by 200-mg capsules twice daily, or placebo capsules postoperatively	Significantly fewer patients receiving SoluMatrix diclofenac or celecoxib (400 mg loading, 200 mg twice daily) required rescue medication during 0–24 h and >24–48 h following bunionectomy compared with placebo. No serious adverse events were reported among patients who received SoluMatrix diclofenac.	
Mowafi et al. 2011 [35]	Preoperative lornoxicam for pain prevention after tonsillectomy in adults	J Clin Anesth	Prospective, randomized, double-blinded study	40 patients posttonsillectomy were randomly allocated to receive either lornoxicam 16 mg or saline as control preoperatively	Pain scores were significantly lower in the lornoxicam group compared to placebo. Similarly, pain scores on swallowing were lower in the lornoxicam group during the first 4 postoperative hours. No significant differences were noted for intraoperative bleeding. The frequency of postoperative nausea and vomiting was similar in both groups.	Preoperative 16-mg lornoxicam was effective for immediate postoperative pain relief after tonsillectomy in adults.
Hillstrom et al. 2013 [34]	Lornoxicam: pharmacology and usefulness to treat acute postoperative and musculoskeletal pain a narrative review	Expert Opin Pharmacother	Review	A review of clinical studies documenting lornoxicam effectiveness in short-term treatment of acute postoperative pain following various surgical procedures	Lornoxicam was found to be effective in acute postoperative pain management and has been shown to be superior to paracetamol with similar effects to other NSAIDs and standard opioids. Adverse effects are equivalent to other NSAIDs.	
Inan et al. 2007 [36]	Efficacy of lornoxicam in postoperative analgesia after total knee replacement surgery	Agri	Double-blind, randomized, controlled study	46 elderly patients were randomized in two groups: group L who received morphine with PCA and lornoxicam 16 mg intravenously 15 min before surgery and 8 mg at postoperative 12th and 24th hours, and group M who received only morphine PCA postoperatively.	Morphine consumption in group L was significantly lower than in group M at 2, 3, 6, 8, 24, 36, and 48 h postoperatively ($p < 0.05$). Incidence of side effects in group M was 60 and 25 % in group L ($p < 0.05$). In group M, 8 patients (40 %) experienced nausea and 3 (15 %) patients experienced itching whereas in group L, 3 patients (15 %) experienced nausea, 1 patient (5 %) itching, and 1 patient (5 %) dry mouth.	During the first 48 h after the arthroplasty, opioid consumption was significantly lower in the patients receiving lornoxicam. The patients in the control group also exhibited a trend toward a higher rate of opioid-related side effects.
Kurukahvecioglu et al. 2007 [37]	Effect of meloxicam on postoperative pain relief after inguinal hernia repair with local anaesthesia	J West Indian Med	Randomized Trial	Fifty patients who underwent inguinal hernia repair were randomized to two groups regarding administration and nonadministration of preemptive meloxicam. The postoperative visual analogue pain scale (VAS) values at 4, 8,	Postoperative pain severity and analgesic requirement were significantly decreased in the patients who received meloxicam preemptively. Single-dose preemptive meloxicam seems to be an effective analgesic therapy for patients undergoing inguinal	

Table 1 (continued)

References	Title	Journal	Type of Study	Summary	Result/conclusion	Comments
				12, and 24 h and analgesic needs of the patients were recorded.	hernia repair under local anesthesia. It thereby improves patient comfort and should be considered for use in outpatient surgery.	
Aghadavoudi et al. 2015 [38]	Comparison of pre-emptive effect of meloxicam and celecoxcib on postoperative analgesia: a double-blind, randomized clinical trial	Middle East J Anaesthesiol	Double-blind, randomized clinical trial	70 patients, undergoing lower-extremity surgery, were randomized to two groups. Meloxicam (15 mg) was administered orally to one group and celecoxib (400 mg) to the other group, 2 h before the surgery.	At 1 and 2 h postsurgery, pain severity was significantly higher in the celecoxib group. However, 6 h following surgery, mean pain severity was higher with meloxicam administration. Pain severity was not significantly different in the two groups, 12 and 24 h following surgery, therefore concluding that the analgesic effect of celecoxib seems to cover a longer duration than meloxicam; but meloxicam appears to be a stronger analgesic in a shorter time interval.	
Chang et al. 2013 [39]	Effect on pain relief and inflammatory response following addition of tenoxicam to intravenous patient-controlled morphine analgesia: a double-blind, randomized, controlled study in patients undergoing spine fusion surgery	Pain Med	Double-blind, randomized, controlled study	Ninety-four patients were randomized to one of three groups: the M group (PCA regimen with morphine), the TM group (PCA regimen with tenoxicam and morphine), or the T + TM group (20 mg tenoxicam administered 30 min before wound closure in addition to the tenoxicam and morphine regimen)	Tenoxicam showed, in combination with IV PCA after spinal fusion no improvement in postoperative pain control, but opioid sparing and suppression of local inflammation at the surgical site	
Nonaka et al. 2016 [19]	Comparison of the analgesic effect of intravenous acetaminophen with that of flurbiprofen axetil on post-breast surgery pain: a randomized controlled trial.	J. ANESTH	Randomized Controlled Trial	40 patients who were scheduled for partial mastectomies were randomly divided into two groups: an acetaminophen (1000 mg × 3) group (group A) and a flurbiprofen (50 mg × 3) group (group F). Each drug was administered 15 min before the end of surgery and at 6 and 12 h after the operation.	Eighteen of 20 patients in group A and 20 of 20 patients in group F expressed a satisfaction rating of greater than good, therefore concluding that acetaminophen produces an equivalent analgesic effect to flurbiprofen in postpartial mastectomy patients.	
Southworth et al. 2009 [6]	A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 h in the management of postoperative pain	Clin Ther	Randomized, double-blind, controlled trial	406 patients scheduled to undergo elective, single-site orthopedic or abdominal surgery were randomly assigned in a 1:1:1 ratio to receive ibuprofen 400 mg iv, ibuprofen 800 mg IV, or inactive placebo.	Ibuprofen IV q6h was associated with significant reductions in morphine use and pain at rest and with movement compared with placebo. Ibuprofen was not associated with significant increases in adverse events compared with placebo, with the exception of dizziness with the 800-mg dose.	
Lloyd et al. 2009 [30]	Intravenous or intramuscular parecoxib for acute postoperative pain in adults	Cochrane Database Syst Rev	Review	Seven randomized, double-blind, placebo-controlled clinical trials of parecoxib compared with placebo for relief of acute postoperative pain in adults were included.	A single dose of parecoxib 20 or 40 mg provided effective analgesia for 50 to 60 % of those treated compared to about 15 % with placebo, and was well tolerated. Duration of analgesia was longer, and significantly fewer participants required rescue medication over 24 h with the higher dose. Adverse events were generally mild to moderate and did not differ in frequency between groups. No serious adverse events were reported with parecoxib or placebo.	

postoperative pain control; it improves psychological condition of patients by minimizing distress and sleep disturbances [15].

In a special population such as the elderly, morbidly obese patients, and pediatric patients, NSAIDs are encouraged to be used unless contraindicated. NSAIDs allow a balanced analgesia and provide opioid-sparing effects in these population. A meta-analysis of 27 randomized controlled trials were conducted to analyze the use of NSAIDs in pediatric postoperative pain by Michelet et al.(2012), and outcomes measured were opioid consumption, pain intensity, postoperative nausea and vomiting (PONV), and urinary retention during PACU stay and the first 24 postoperative hours [16]. They found that perioperative administration of NSAIDs decreased postoperative opioid requirement (both in the PACU and during the first 24 postoperative hours), pain intensity in the PACU, and PONV during the first postoperative day [16]. Opioid-sparing effects of NSAIDs in children and infants make NSAIDs ideal for balanced postoperative analgesics in these patients.

Regarding morbidly obese patients, NSAIDs were believed to increase the risk of postoperative hemorrhage after laparoscopic Roux-en-Y gastric bypass; however, De Baerdemaeker et al. (2016) state that NSAIDs are encouraged to be used in this patient population and that previous data depended more on the type of procedure and the patient's compliance to avoid nicotine, alcohol, and chronic use of NSAIDS than acute postoperative use of these drugs [17].

Comparison of the Efficacy of NSAIDs with Other Analgesics

There is a misconception that acetaminophen is as effective as NSAIDs in acute pain management. However, there are numerous data contradicting this theory. Many studies have in fact proven NSAIDs to be more efficacious [18, 19]. Results from Pogatzki-Zahn et al. (2014) and Nonaka et al. (2016) showed acetaminophen to be inferior to NSAIDs in postoperative pain, and the authors believe that the risk of acetaminophen adverse events might have been underestimated [18, 19]. Beaussier et al. (2005) found patients treated with parecoxib after an inguinal hernia repair to have greater satisfaction, less pain score compared to acetaminophen, and a decrease in opioid consumption up to 35 % [20, 21].

Jung et al. (2004) compared onset of analgesia and efficacy of single-dose tramadol/acetaminophen 75/650 mg (Tr/Ac) and codeine/acetaminophen/ibuprofen 20/500/400 mg (Co/Ac/Ib) in 128 healthy subjects undergoing surgical extraction of >1 which impacted third molar requiring bone removal. They uncovered that the Co/Ac/Ib group had significantly greater postoperative pain control compared to the Tr/Ac group ($p < 0.05$) [22].

Effects of Formulation on the Analgesic Activity of NSAIDs

NSAID formulation is another factor that affects the efficacy. For example, ibuprofen lysine 400 mg produces faster onset and higher peak analgesia than a conventional tablet of ibuprofen acid 400 mg in dental pain [23]. Solubilized liquid gel ibuprofen 400 mg had a more rapid onset than acetaminophen 1000 mg and had a longer duration of action than either acetaminophen 1000 mg or ketoprofen 25 mg [24].

Diclofenac is a phenylacetic acid which inhibits both COX-1 and COX-2 enzymes and is the most widely used NSAID worldwide. In contrast to other traditional NSAIDS, it shows a higher selectivity for the COX-2 enzyme compared to the COX-1 enzyme. Derry et al. (2009 and 2015) completed an intensive review on diclofenac which showed that patients had a 50 % pain relief over 4 to 6 h at any dose with diclofenac compared to placebo, making the number needed to treat (NNT) to be 2.5 for doses of 25 to 100 mg; no dose-response was demonstrated [25, 26]. Diclofenac comes in two formularies, diclofenac potassium and diclofenac sodium. NNTs for diclofenac potassium were significantly lower than for diclofenac sodium [25, 26]. Derry et al. believe that diclofenac sodium has limited efficacy and should not be used in acute pain management [26]. There were no serious adverse effects in both drugs.

Solumatrix diclofenac (Zorvolex™) was manufactured to address concerns of NSAID adverse events. It has a much-improved side effect profile compared to other NSAIDs [27]. Solumatrix diclofenac consists of submicron unionized particles of the diclofenac molecule combined with proprietary excipients, therefore providing analgesia at reduced doses when compared to other diclofenac-containing preparations, and allows faster systemic absorption [27, 28]. To demonstrate the effectiveness of solumatrix diclofenac, Argoff et al. (2016) completed a multicenter, randomized, double-blind study of 428 patients following bunionectomy surgery [29]. Patients were selected to receive low-dose SoluMatrix diclofenac 35- or 18-mg capsules three times daily, celecoxib 400 mg loading dose followed by 200-mg capsules twice daily, or placebo capsules postoperatively [29]. Results showed that fewer patients receiving solumatrix diclofenac or celecoxib (400 mg loading, 200 mg twice daily) required rescue medication during 0–24 and >24–48 h compared to placebo [29]. No serious adverse events were reported among patients who received SoluMatrix diclofenac [29].

Use of COX-2 Inhibitors

COX-2-selective inhibitors (COXIB) have the advantage over nonselective COX inhibitors by not increasing the risk of platelet inhibition, therefore decreasing the risk of bleeding and GI ulceration. However, they have an increased risk of

myocardial infarction and cardiovascular derangements along with thromboembolic phenomenon.

Parecoxib is an intravenously injectable COXIB with a safe cardiovascular profile. A review of controlled clinical trials of parecoxib showed that a single dose of parecoxib 20 or 40 mg provided effective analgesia in 50 to 60 % of those treated, compared to about 15 % with placebo [30]. Duration of analgesia was longer, and fewer participants required rescue medication over 24 h with higher doses. Adverse events were generally mild to moderate and did not differ in frequency between the two doses. No serious adverse events were reported with parecoxib [30].

Etoricoxib is another COXIB with a long half-life effect that is not currently approved in the USA but is approved in Europe. The advantage of etoricoxib is its duration of 24 h [31]. Thus, only one dose per day is required and therefore it has high patient compliance [31]. Etoricoxib 120 mg reduced pain and opioid use 24 % compared to placebo [31]. Etoricoxib is not dose dependent, and pain reduction of etoricoxib 90 and 120 mg was equivalent, and no significant adverse events were noted between the two groups [32]. Both etoricoxib doses are also superior to acetaminophen mg/codeine ($p \leq 0.001$), which was associated with significantly more adverse events including nausea and vomiting, and were equivalent to ibuprofen [33].

Use of Oxicams

Oxicams are a class of NSAIDs that are nonselective inhibitors of the COX enzymes. Lornoxicam is a member of this group that has been shown to be effective in short-term treatment of acute postoperative pain following various surgical procedures [34]. It has been shown to be superior to acetaminophen and is similarly effective to standard opioids and other NSAIDs with equivalent adverse events [34]. Mowafi et al. (2011) conducted a prospective, randomized, double-blinded study of 40 posttonsillectomy patients who received lornoxicam 16 mg or saline as control preoperatively [35]. Pain scores were significantly lower in the lornoxicam group compared to placebo up to 4 h postoperation [35]. No significant differences were noted for intraoperative bleeding, and the frequency of PONV was similar in both groups [35]. Inan et al. (2007) additionally found during the first 48 h after arthroplasty that opioid consumption was significantly lower in patients receiving lornoxicam; therefore, these patients had lower opioid-related side effects [36].

Meloxicam is another oxicam found to be an effective analgesic therapy for postoperative pain relief after inguinal hernia repair [37]. Aghadavoudi et al. (2015) compared the effect of meloxicam and celecoxib and found that pain severity was significantly higher in the celecoxib group initially, but 6 h following surgery, the pain severity was higher with meloxicam, therefore concluding that the analgesic effect of celecoxib seems to cover a longer duration than meloxicam [38]. However, meloxicam appears to be a stronger analgesic in a shorter time interval [38].

Not all oxicam members showed analgesic effects in postoperative pain control. For example, Chang et al. (2013) showed that tenoxicam in combination with IV PCA after spinal fusion had only suppression of local inflammation at the surgical site with no improved postoperative pain control [39].

Adverse Effects of NSAIDs

Despite proven efficacy in postoperative pain management, there are still growing concerns of NSAID adverse events (AEs) which limit their use particularly with high-risk patients, such as the elderly or patients with preexisting renal insufficiency. NSAIDs are well known to be associated with gastrointestinal, renal, and cardiovascular side effects [40]. Because of the concerns about cardiovascular risks, manufacturers in the USA are now required to include warnings about potential cardiovascular risks in all product labeling [40]. NSAID AEs are proven to be dose dependent and a result of chronic use. There are limited data supporting an increase in AEs with acute postoperative use of NSAIDs. Mathiesen et al. (2014) completed a review of NSAID adverse effects postoperatively and found that data were inconclusive regarding NSAID association of mortality, cardiovascular events, surgical bleeding, and renal impairment [41].

NSAID AEs are a result of the actual mechanism of the drug. Inhibition of the synthesis of PGE2, which is cytoprotective in the GI tract leads to the gastric mucosa being predisposed to irritation and ulcer formation resulting in gastrointestinal bleeding. Prostaglandins also regulate renal blood flow; therefore, its inhibition can impair renal function and result in chronic kidney disease. Please see Table 2 for a summary of adverse events of specific studies.

Cardiovascular Risks of NSAIDS

Inhibition of the COX-2 enzyme results in an imbalanced metabolism of overproduction of harmful by-products that may damage the arterial wall and induce arterial blood clotting [44]. Also, inhibition of COX-2 results in decrease in prostaglandin synthesis and more thromboxane A2 (TXA2) production, leading to an increase in vasoconstriction and risk for cardiovascular adverse events. Gan et al. (2016) recently completed a cardiovascular safety of hydroxypropyl-beta-cyclodextrin-diclofenac (HPβCD-diclofenac) and ketorolac in 608 surgical patients who underwent abdominal/pelvic and orthopedic surgery [45•]. They found that there was no increase in cardiovascular incidence in either group [45•]. A data analysis of short-term use (approximately 7–10 days) of parecoxib and

Table 2 NSAID adverse effects

References	Title	Journal	Type of study	Summary	Result/conclusion
Klein et al. 2012 [50••]	Postoperative use of nonsteroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data	BMJ	Cohort study	Study evaluating 2756 patients undergoing elective operation for colorectal cancer with colonic or rectal resection and primary anastomosis. Anastomotic leakage was significantly increased among patients receiving diclofenac and ibuprofen treatment, compared with controls (12.8 and 8.2 vs. 5.1 %).	Diclofenac treatment results in an increased proportion of patients with anastomotic leakage after colorectal surgery and recommends that COX-2 be used with caution.
Southworth et al. 2009 [6]	Severe complications with diclofenac after colonic resection	Dis Colon Rectum	Cohort study	Study evaluated 152 patients who underwent colonic resections with primary anastomosis.	The anastomotic leakage rate for colonic resections was significantly increased from 3.9 to 20.5 % after diclofenac treatment and decreased to 1.3 % once diclofenac was discontinued
Holte et al. 2009 [47]	Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery	Br J Surg	Cohort study	502 patients having colonic anastomoses performed were evaluated.	Study found that anastomosis leakage rate increased from 3.3 to 15.1 % after patients received celecoxib postoperatively.
Klein et al. 2009 [49]	Increased risk of anastomotic leakage with diclofenac treatment after laparoscopic colorectal surgery	Dig Surg	Retrospective, case-control study	75 patients undergoing laparoscopic colorectal resection with primary anastomosis. Two time intervals measured. In period 1, patients received diclofenac 150 mg/day. In period 2, diclofenac was withdrawn and the patients received an opioid analgesic	Increased number of clinically significant anastomotic leakages in patients receiving oral diclofenac for postoperative analgesia
Aveline et al. 2009 [42]	Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study	Circulation	Cohort study	83,677 patients ≥30 years of age were admitted with first-time MI during 1997 to 2006; 42.3 % were identified to have used NSAIDs from nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark.	They found that NSAID treatment was significantly associated with an increased risk of death/recurrent MI (hazard ratio, 1.45; 95 % confidence interval, 1.29 to 1.62) at the beginning of the treatment, and the risk persisted throughout the treatment course (hazard ratio, 1.55; 95 % confidence interval, 1.46 to 1.64 after 90 days). Diclofenac was associated with the highest risk (hazard ratio, 3.26; 95 % confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatments
Gan et al. 2016 [45•]	Cardiovascular safety of hydroxypropyl-beta-cyclodextrin-diclofenac in the management of acute postsurgical pain: a pooled analysis of 2 randomized, double-blind, placebo- and active comparator-controlled phase III clinical trials	J Clin Anesth	Randomized, double-blind, controlled phase III clinical trials	Phase III clinical trials examining the efficacy and safety of intravenous (IV) HPβCD-diclofenac vs. placebo and ketorolac. A total of 608 surgical patients who underwent abdominal/pelvic and orthopedic surgery were selected for this study.	IV HPβCD-diclofenac was found to not be associated with increase of cardiovascular (CV) incidence vs. placebo (11.6 vs. 12.2 %; relative risk, 0.96 [95 % confidence interval, 0.56–1.62]) at emergence and follow-up period, with CV occurring in 1.3, 0, and 1.4 % of patients in the HPβCD-diclofenac, ketorolac, and placebo groups, respectively. Authors stated there were no reports of myocardial infarction or cerebrovascular accident.
Schjerning Olsen et al. 2011 [43]	Vascular and upper gastrointestinal effects of nonsteroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials	Lancet	Meta-analysis	Analysis of 280 trials of NSAIDs vs. placebo and 474 trials of NSAID vs. another NSAID with main outcomes measured were major vascular events (nonfatal	Long-term NSAID use increases vascular and gastrointestinal risks; however, there is no data available for short-term NSAIDs used. High-dose naproxen is found to be

Table 2 (continued)

References	Title	Journal	Type of study	Summary	Result/conclusion
				myocardial infarction, nonfatal stroke, or vascular death); major coronary events (nonfatal myocardial infarction or coronary death); stroke; mortality; heart failure; and upper gastrointestinal complications (perforation, obstruction, or bleeding).	associated with less vascular risk than other NSAIDs
Schug et al. 2009 [46]	Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: an analysis of integrated data	Anesth Analg	Meta-analysis	17 controlled trials of parecoxib for noncardiac studies and 15 studies of valdecoxib were analyzed.	Short-term use (approximately 7–10 days) of parecoxib and valdecoxib after surgery does not increase the cardiovascular risk in noncardiac surgical patients.
Mathiesen et al. 2014 [8]	Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review	Acta Anaesthesiol Scand.	Review	Review was based on data from systematic reviews with meta-analyses of analgesic efficacy and/or adverse effects of perioperative nonopioid analgesics and randomised trials and cohort/retrospective studies.	Data were inconclusive regarding NSAID association of mortality, cardiovascular events, surgical bleeding, and renal impairment. However, there was increased anastomotic leakage with NSAID usage.
Kelley et al. 2016 [51••]	Ibuprofen may not increase bleeding risk in plastic surgery: a systematic review and meta-analysis	Plast Reconstr Surg.	Review/meta-analysis	881 publications were reviewed and 4 randomized controlled trials were selected for full analysis. Data related to pain assessment, postoperative recovery, and complications were reviewed.	Ibuprofen provides equivalent pain control to narcotics. Importantly, ibuprofen was not associated with an increased risk of bleeding and is a safe postoperative analgesic in patients undergoing common plastic surgery soft-tissue procedures.
Gobble et al. 2014 [52]	Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials	Plast Reconstr Surg	Meta-analysis	Analysis of 27 studies randomized controlled trials. Postoperative bleeding occurred in 33 of 1304 patients (2.5 %) in the ketorolac group compared with 21 of 1010 (2.1 %) in the control group. Other adverse events were similar in the groups, 31.7 % in the control group and 27.9 % percent in the ketorolac group.	Pain control with ketorolac was found to be safe and superior to controls and equivalent to opioids in the perioperative period.

valdecoxib by Schug et al. (2009) also supported that there was no increase in the cardiovascular risk in acute settings [46]. The duration of NSAID treatment was the significant factor impacting the increase of AEs in these drugs.

Anastomotic Leakage with NSAIDs

There have been numerous data published supporting that anastomotic leak rate is increased in colonic resections with the use of postoperative NSAIDs and COX-2 inhibitors [47]. Rosenberg et al. (2007) and Klein et al. (2009) found the leakage rate to increase from 3.9 to 20.5 % with postoperative NSAID use and decrease to 1.3 % once NSAIDs were discontinued [48, 49]. Klein et al. 2012 went further and completed a large-scale study evaluating 2756 patients undergoing an elective operation for colorectal cancer with colonic or rectal resection and primary anastomosis [50••]. Anastomotic leakage was significantly increased among patients receiving diclofenac and ibuprofen treatment, compared with controls (12.8 and 8.2 vs. 5.1 %). They recommend NSAIDs and COX-2 inhibitors to be used with caution in colorectal surgery [50••].

Bleeding Risks with NSAIDs

The risk of bleeding with NSAIDs is due to inhibition of TXA2 which is involved in platelet aggregation as well as stimulation of new platelet activation. Despite the temporary effect of NSAIDs on platelet function, there is no evidence that there is an increased risk of operative bleeding or postoperative hematoma [51••]. Complete platelet functional recovery has been demonstrated within 8 to 24 h from the last dose of NSAIDs in healthy subjects [51••]. Gobble et al. (2014) went on to prove that ketorolac resulted in postoperative bleeding of 33 out of 1304 patients (2.5 %) compared with 21 out of 1010 (2.1 %) in the control group, therefore concluding ketorolac to be safe in the postoperative period [52]. In addition, Huang et al. (2008) conducted a randomized, controlled trial of 80 patients who underwent total knee arthroplasty and found that there were no significant differences in blood loss intraoperative and postoperative between the celecoxib treatment group who received 200 mg of celecoxib every 12 h for 5 days and placebo [53].

Alternative Analgesics

Metamizole or dipyrone is a nonspecific COX inhibitor with spasmolytic effects and very little gastrointestinal, cardiovascular, and renal system adverse effects. It is a very potent analgesic but is only limitedly available in European countries due to an ongoing debate on its risk of agranulocytosis [54]. Further studies need to be completed to evaluate effectiveness and safety of metamizole in acute postoperative pain management.

Conclusion

From the data reviewed, it can be concluded that NSAIDs are safe and effective in the treatment of postoperative pain [55–57]. They should be administered as part of a multimodal approach to all postoperative surgical patients unless contraindicated. NSAIDs and COX-2 inhibitors should be used with caution in colorectal surgery as they are proven to increase anastomotic leakage risk [58–60]. NSAIDs have no increased adverse effects during the acute postoperative period; in fact, there were minimal AEs observed in all the studies including the risk of postoperative bleeding, cardiovascular events, and bone healing [61]. Finally, NSAIDs and COX-2 inhibitors decreased opioid requirements, minimized opioid-induced adverse events, and have been proven to increase patient satisfaction.

Compliance with Ethical Standards

Conflict of Interest Anita Gupta and Maimouna Bah declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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