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Immune Modulatory Effects of Nonsteroidal Anti-inflammatory Drugs in the Perioperative Period and Their Consequence on Postoperative Outcome

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ABSTRACT

Nonsteroidal anti-inflammatory drugs are among the most commonly administered drugs in the perioperative period due to their prominent role in pain management. However, they potentially have perioperative consequences due to immune-modulating effects through the inhibition of prostanoid synthesis, thereby affecting the levels of various cytokines. These effects may have a direct impact on the postoperative outcome of patients since the immune system aims to restore homeostasis and plays an indispensable role in regeneration and repair. By affecting the immune response, consequences can be expected on various organ systems. This narrative review aims to highlight these potential immune system–related consequences, which include systemic inflammatory response syndrome, acute respiratory distress syndrome, immediate and persistent postoperative pain, effects on oncological and neurologic outcome, and wound, anastomotic, and bone healing.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and are known for their analgesic, antipyretic, and immune–modulating properties. Their mechanism of action is though inhibition of cyclooxygenase, also known as prostaglandin–endoperoxide synthase, the key enzyme involved in prostaglandin synthesis. Cyclooxygenases (COX-1 and COX-2) catalyze the formation of prostaglandin (PS) H_2 (PGH_2) from arachidonic acid, upon which PGH_2 is metabolized by tissue–specific isomerases to other prostanoids such as prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$), prostacycline (PGI_2), and thromboxane. Prostanoids are a subgroup of eicosanoids with distinct functions in health and disease. Their most important general and immunologic effects are summarized in table 1 and shown in figure 1.

Both cyclooxygenase isoenzymes have a similar molecular weight, a 65% amino acid sequence homology, and nearly identical catalytic sites, but differ in function, pattern, and location of expression.[17] COX-1 has predominantly homeostatic functions, such as maintaining normal gastric mucosa, regulating renal blood flow, and regulating coagulation by abetting platelet aggregation. It is present in most cells and is constitutively expressed, and various studies have shown that its messenger RNA and protein expression does not change upon inflammation.[18] In contrast, COX-2 is less widely expressed, but its expression is induced upon activation by proinflammatory mediators, like interleukin 1, tumor necrosis factor α, lipopolysaccharides, and tumor promotors.[19] Although it is generally stated that COX-1 is not involved upon immune activation, its role in inflammation should not be underestimated. Studies in animal models have shown that COX-1 serves an important role in the development of inflammatory sequelae like edema.[20,21] Nevertheless, COX-2–derived metabolites are considered to be responsible for mediating pain and inflammation. To minimize side effects, while maintaining their function, selective COX-2 inhibitors were developed and have been available since 2000 (fig. 2).

A specific category of NSAIDs, aspirin, not only inhibits cyclooxygenase but also stimulates the production of anti–inflammatory and proresolving mediators. These mediators are endogenous bioactive metabolites that are involved in the regulation and resolution of an effective innate immune response. Proresolving mediators stop the recruitment of leukocytes in inflamed

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Table 1. Short Outline of General and Immune Effects of Prostanoids

Prostanoids	Receptor	Function	Immunologic Effect
PGD$_2$	DP$_{1-2}$	• Platelet aggregation • Allergic reactions • Contraction of bronchial airway • Sensation of pain • Sleep–wake cycle	• Involved in type 2 immune responses, including T helper 2 cells, type 2 innate lymphoid cells, and eosinophils with a subsequent effect on asthmatic airways inflammation through increased inflammatory cell chemotaxis/cytokines and enhanced immunoglobulin E class switching in B cells.[1] • Elevated level of PGD$_2$ resulted in a defect in virus-specific T-cell responses due to impaired respiratory dendritic cells migration.[2] • PGD$_2$ also has anti-inflammatory effects upon multiple spontaneous dehydrations and conversion into 15-deoxy-Δ-prostaglandin J2, which in turn inhibits the activation of nuclear factor κB system resulting in reduction of interleukins 6, 1β, and 12 and tumor necrosis factor α from macrophages and decreases the production of inducible nitric oxide synthase.[3]
PGE$_2$	EP$_{1-4}$	• Contraction and relaxation of smooth muscle • Control of blood pressure • Sensation of pain • Proinflammatory response	• Serves as an important proinflammatory mediator, involved in development of all physical signs of inflammation such as rubor, tumor, and dolor. • Also has anti-inflammatory properties that are context-dependent; downregulation of interleukin 2 by T cells and phagocytosis by macrophages.[4] • Promotes dendritic cells migration and upregulates costimulatory molecule expression to promote T cell activation.[5] • Promotes T helper 2 cell response by impairing the ability of dendritic cells to produce interleukin 12 and shifts the balance away from a cellular T helper 1 cell to a humoral T helper 2 cell response with a decreased T helper 1/T helper 2 ratio.[6] • Involved in the activation of the T helper 17 cell responses that characterized by the production of the proinflammatory cytokine interleukin 17.[7] • Promotes the development and function of regulatory T cells.[8] • Inhibits the cytolytic function of natural killer cells and therefore reduces target cell lysis.[9] • Suppresses proliferation and induce apoptosis of immature B cells and enhances immunoglobulin class switching in mature B cells.[10,11]
PGI$_2$	P	• Platelet aggregation • Vasodilatation • Renin release	• Decreases the production of proinflammatory cytokines (tumor necrosis factor α and interleukins 12, 1β, and 6) and chemokines (MIP-1α and MCP-1) and increases the production of the anti-inflammatory cytokine interleukin 10 by bone marrow dendritic cells.[12] • Inhibits the ability of dendritic cells to stimulate antigen-specific T-cell proliferation.[12] • Inhibits T helper 1 cell and T helper 2 cell activation, differentiation, and cytokine production, while enhancing T helper 17 cell immune responses and interleukin 17 production.[13]
PGF$_2$α	FP$_{A-B}$	• Stimulates the contraction of uterine and bronchial smooth muscle • Produces vasoconstriction	• Involved in cellular infiltration and early recruitment of neutrophils.[14]
Thromboxane	TPα,β	• Platelet aggregation • Vasoconstriction • Bronchoconstriction	• Acts as a general suppressor of a low-avidity interaction between dendritic cells and T cells and inhibits T cell activation.[15,16]

PG, prostaglandin.

tissue and increase the removal of apoptotic polymorphonuclear neutrophils. Polymorphonuclear neutrophils enhance microbial killing and clearance and are considered organ-protective.[22] This unique feature of aspirin involves acetylation rather than inhibition of the active site of COX-2 in endothelial or epithelial cells, which results in the conversion of arachidonic acid to proresolving mediators. Examples of proresolving mediators activated by aspirin, termed aspirin-triggered specialized proresolving mediators, are aspirin-triggered resolvins and lipoxins.[23] Lipoxins are known to regulate leukocyte traffic, interfere with the chemokine-cytokine axis, reduce edema, and block pain signals.

The immune-modulatory consequences of NSAIDs are considered to be relevant in the perioperative period, since surgical injury elicits an inflammatory response associated with postoperative outcome.[24] Several reviews and meta-analyses have focused on the adverse effects of NSAIDs

on multiple organ systems like the kidney and heart, which are beyond the scope of this review, whereas the immune-modulating effects of NSAIDs are poorly described.[25–29] Therefore, the aim of this narrative review is to describe the immunologic effects of NSAIDs in the perioperative period and their consequence on different postoperative outcomes. When possible, a distinction will be made between selective and nonselective cyclooxygenase inhibitors.

Beneficial Immune-modulating Effects of NSAIDs

Effects on the Surgical Stress Response

Surgical injury activates the immune system in a direct manner by the binding of danger-associated molecular patterns to pattern recognition receptors of the innate immune system and indirectly *via* surgical injury induced activation of the neuroendocrine system, through the hypothalamic–pituitary–adrenal axis. Activation then involves the release of
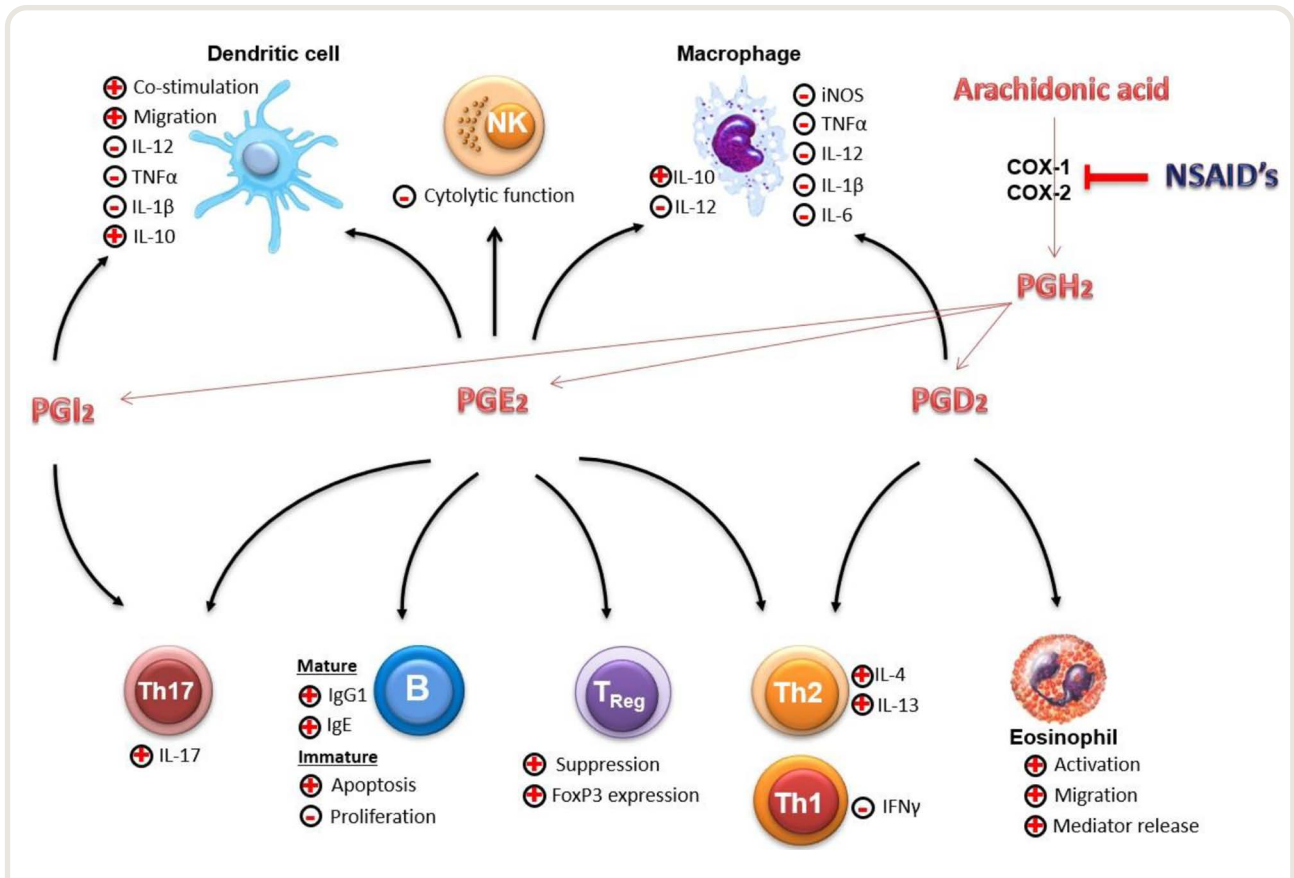
Fig. 1. Effects of the most important immune active prostanoids: prostaglandin (PG) I$_2$, PGE$_2$, and PGD$_2$. PGI$_2$ increases the level of anti-inflammatory cytokines, while the proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and interleukin 12 decrease *in vitro*. Depending on the stage of inflammation, PGE$_2$ has a profound effect on the production of cytokines by T cells. Particularly at later stages of immune responses, PGE$_2$ has immune suppressive properties, resulting in the inhibition of T helper (Th) 1 cell cytokines (interferon γ [IFN-γ] and IL-2), which results in the suppression of Th1 cell–dependent antimetastatic immunity. Furthermore, PGE$_2$ is a potent inhibitor of the cytolytic effector function of natural killer cells and therefore reduces target cell lysis. In contrast, PGE$_2$ promotes the production of cytokines produced by Th2 (IL-4, IL-5, IL-10, and IL-13), although these cytokines can also be mediated indirectly by PGE$_2$ through cyclic adenosine monophosphate (cAMP). Thus, PGE$_2$ promotes Th2 cell differentiation and shifts the balance away from a cellular Th1 cell to a humeral Th2 cell response, with a decreased Th1/Th2 ratio. PGD$_2$ is a prostaglandin produced mainly by mast cells but also by other leukocytes, including dendritic cells and Th2 cells. Production of PGD$_2$ by mast cells is an important initiator of immunoglobulin E (IgE) mediated type 1 acute allergic reactions. PGD$_2$ has anti-inflammatory effects through inhibition of the production of inducible nitric oxide synthase (iNOS), TNF-α, and IL-1β by mouse and human macrophages.

hormones, cytokines, chemokines, and prostanoids, which are essential to restore homeostasis and are involved in tissue repair and the host's response against invading pathogens.[24] An exaggerated surgical stress response may lead to a systemic inflammatory response syndrome, is associated with postoperative morbidity and a higher risk of infections and organ failure, and may be detrimental to long-term survival after oncological surgery.[30] In response to surgical injury, the T helper 1/T helper 2 balance (between T helper 1 cells and T helper 2 cells) shifts toward T helper 2 cells, suggesting that cell-mediated immunity is downregulated and antibody/humoral-mediated immunity is upregulated.[31] This also affects the cytolytic function of natural killer cells, which is enhanced by a T helper 1 cell response. In a study examining the immunologic effects of parecoxib (a selective COX-2

inhibitor) in adults undergoing laparoscopic cholecystectomy, the balance between T helper 1 cells, T helper 2 cells, T helper 17 cells, and regulatory T cell cytokines was restored after administration of parecoxib, suggesting an important role for prostanoids in the polarization of T helper cells.[32]

In two randomized controlled trials, the effect of intravenous ibuprofen on the surgical stress response during cholecystectomy was assessed.[33,34] Although administration strategies were different (500 mg ibuprofen, 12 and 2 h before surgery and every 8 h until the third postoperative day *vs.* a single preoperative dose of 800 mg ibuprofen), a reduced endocrine response and cytokine release were observed in both studies in patients receiving ibuprofen. Both trials, however, observed increased intraoperative levels of tumor necrosis factor α, which the authors
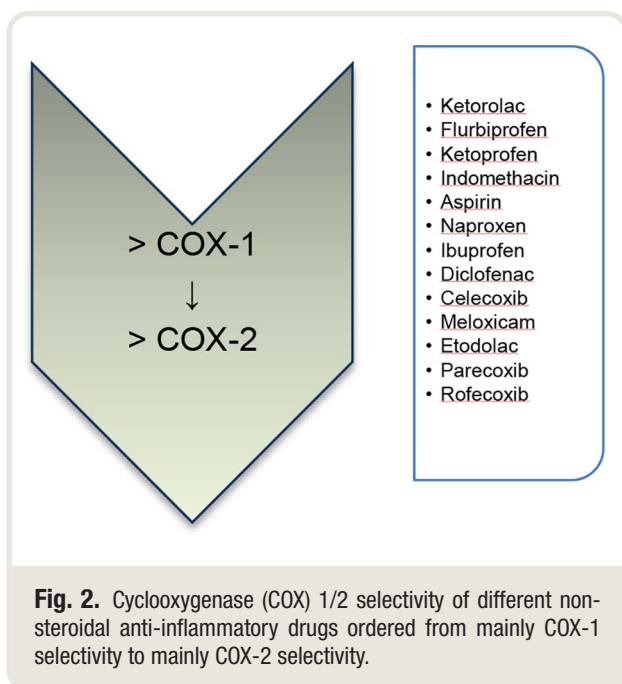
Fig. 2. Cyclooxygenase (COX) 1/2 selectivity of different non-steroidal anti-inflammatory drugs ordered from mainly COX-1 selectivity to mainly COX-2 selectivity.

ascribe to the direct stimulation of mononuclear cells and the release of tumor necrosis factor α by NSAIDs, thereby causing a subsequent short–term intraoperative increase.[34] Ibuprofen attenuated postoperative anti-inflammatory interleukin 10 release, suggesting a reduction of the proinflammatory response, requiring less interleukin 10 modulation.[18] Although the study of Le *et al.*[34] could not demonstrate a difference in perioperative interleukin 6 levels, several other studies, administering ibuprofen, diclofenac, and parecoxib perioperatively, demonstrated an association between the use of NSAIDs and lower interleukin 6 levels.[33,35,36] Moreover, high perioperative levels of interleukin 6 are associated with postoperative complications in different types of surgery.[37,38] According to clinicaltrials.gov (accessed January 2, 2021), there are no current randomized controlled trials assessing the effect of NSAIDs on the surgical stress response.

The effects of NSAIDs in septic patients undergoing surgery has not been investigated. In (animal) sepsis models, however, aspirin and other NSAIDs are associated with improved hemodynamic parameters, organ function, and survival.[39,40] There are several hypotheses about the potential beneficial effect of NSAIDs or aspirin in systemic inflammatory response syndrome/sepsis patients. The immune response in systemic inflammatory response syndrome/sepsis is a dynamic process and differs between an immune–activated state and a paralyzed state. Effects will therefore depend on the time of administration and the current immunologic state of the patient. During an exaggerated immune response, one could hypothesize that it might be beneficial to have NSAIDs mitigating this response. The positive effect of aspirin might be explained by the ability of aspirin to stimulate the production of anti–inflammatory and proresolving

mediators, a feature that is not shared by other NSAIDs. On the other hand, aspirin has been shown to potentiate leukocytic cytokine production in human endotoxemia trials.[41,42] This proinflammatory response might be beneficial in a sepsis–induced immunoparalysis and could contribute to the improved survival found in a meta-analysis that included 17,065 patients from observational studies: aspirin use before the onset of sepsis resulted in a 7% decrease in mortality.[43] In a recent double-blind, placebo-controlled follow-up study, in which 16,703 patients aged above 70 yr were randomized to receive either 100 mg aspirin or placebo, these beneficial effects could not be confirmed. After follow-up with a median of 4.6 yr, a total of 203 deaths were considered to be associated with sepsis, with no differences between the two groups.[44] These studies, however, have a different design (meta-analysis of observational studies *vs.* randomized controlled trial), which may explain the difference in outcome. In a randomized, double-blind, placebo-controlled trial that included 455 septic patients, treatment with ibuprofen (10 mg/kg given every 6 h for eight doses) decreased fever, tachycardia, oxygen consumption, and lactic acidosis but was not associated with improved survival or development of shock.[45] With a maximum of eight doses of ibuprofen, longer-lasting therapy might have produced different results. Comparing these studies is difficult due to major methodologic differences such as duration and start of treatment and type of NSAID. Administration of NSAIDs might even have negative consequences, since the use of NSAIDs in patients with septic shock led to a delayed administration of antibiotic therapy by masking the signs of sepsis.[46] Moreover, various case reports have suggested that NSAIDs in septic patients might increase the severity of infection, which might be due to the immune suppression seen in these patients.[47,48] According to clinicaltrials.gov (accessed January 2, 2021), there is currently one randomized controlled trial (NCT01784159) in septic patients assessing the effect of aspirin on the reduction of intensity of organ dysfunction, measured by the variation of the Sequential Organ Failure Assessment score, starting from the day of admission to day 7.

Taken together, there is no beneficial effect of NSAIDs in patients with sepsis and in those with an exaggerated surgical stress response. These responses are highly dynamic, not only changing over time but also differing between subjects. In addition, prostaglandins possess pro- and anti–inflammatory properties, again dependent on type, time of release, and context (table 1). The ultimate effect, tempering or enhancing the immune response, therefore, most likely depends on the cause of sepsis, patient characteristics (immune status, comorbidity), type of NSAID (COX-1 and/or COX-2, aspirin), dosage, and time point of administration (studies are summarized in table 2).

Acute Respiratory Distress Syndrome

Aspirin and, to a lesser extent, other NSAIDs might have beneficial effects on patients with acute respiratory distress

Table 2. Overview of Described Literature and Their Conclusions about the Effect of Nonsteroidal Anti-inflammatory Drugs on Different Postoperative Outcomes

Outcome	Randomized Controlled Trial	(Systemic) Review	Meta-analysis
Immune response			
Surgical stress response	• Decreased[33–36]		
Systemic inflammatory distress syndrome/sepsis	• Improved[45]		• Improved[43]
	• No effect[44]		
Pulmonary effects			
ARDS	• No effect[49]	• Unknown[50]	• Improved (animal)[51]
Aspirin-exacerbated respiratory disease	• No effect (COX-2)[52]	• No effect (COX-2)[53]	
Inflammation and pain			
Preemptive		• Moderate effect[54]	• Improved (COX-2)[55,56]
Perioperative		• Improved[57]	• Improved[58,59]
Persistent pain	• No effect[60–63]		• No effect[64]
Oncology			
Outcome	• Improved[65]	• Unknown[66]	• Improved (animal studies)[67]
Neurology			
Postoperative cognitive dysfunction			• Improved[68]
Aneurysmal subarachnoid hemorrhage	• No effect[69]		
Healing processes			
Wound healing	• No effect[70]		
Anastomotic healing	• Impaired (animal study)[71]		• Impaired[72–74]
			• No effect[75]
Bone healing	• No effect[76]	• No effect[77]	• Impaired[78]
			• No effect in high-quality studies[79]

ARDS, acute respiratory distress syndrome; COX, cyclooxygenase.

syndrome (ARDS) due to their effect on platelet activation and anti-inflammatory properties. Aspirin covalently and irreversibly binds to platelet cyclooxygenase, whereas other NSAIDs reversibly inhibit platelet cyclooxygenase. Platelets are activated in the presence of lipopolysaccharides and thrombin, both sepsis mediators, resulting in pulmonary microcirculatory thrombosis, increasing pulmonary vascular dead space, ventilation perfusion mismatch, and worse outcomes in patients with ARDS.[80] The interaction between activated platelets and leukocytes results in production of proinflammatory cytokines (interleukins 1β and 8 and tumor necrosis factor α) and pulmonary edema.[81] Aspirin has the ability to modify these pathways and might be used both preventively and therapeutically. Furthermore, aspirin-triggered specialized proresolving mediators can potentially contribute to regulation of the immune response during ARDS. These effects are further enhanced by the fact that aspirin has the ability to regulate leukocyte traffic by aspirin-triggered lipoxins.[82] In different *in vitro*, animal, and observational studies, the administration of aspirin was related to the prevention of or an improvement in patients with ARDS.[50] In a review of preclinical models and a meta-analysis of clinical studies, the authors concluded that the administration of aspirin in animal studies was associated with improved survival and attenuated inflammation and pulmonary edema. In clinical trials, there was an association with a reduced incidence of ARDS.[51] The differences between preclinical and clinical studies may be explained by differences in dosage and timing of administration. In preclinical studies, higher doses of aspirin have generally been administered compared to clinical

studies in which lower doses were used. A higher dose provides a greater COX-2 blockade, while a lower dose provides a greater COX-1 blockade. A 2015 review by Toner *et al.*[50] concluded that ongoing randomized controlled trials would elucidate the role of aspirin in treating ARDS. Afterward, a multicenter double-blind, placebo-controlled, randomized controlled trial including 390 patients at risk of ARDS was performed: in contrast to former research, the use of aspirin compared with placebo did not reduce the risk of ARDS at 7 days, nor were there any differences in secondary outcomes or adverse events.[49] Patients in this study were administered a loading dose of 325 mg aspirin, followed by 81 mg/day for up to 7 days after admission. Although, or perhaps because, patients were enrolled in the emergency department, the incidence of ARDS was lower than expected (9.5% *vs.* 18%), resulting in an insufficient power. Another randomized controlled trial (NCT02326350), investigating the effect of 75 mg aspirin on oxygenation index at day 7 in patients diagnosed with ARDS, was terminated prematurely due to slow recruitment (clinicaltrials.gov). Recently, Chow *et al.*[83] examined the relationship between aspirin and clinical outcomes in patients with ARDS due to COVID-19. In this retrospective study of 412 patients, patients who received aspirin (N = 98) were less likely to need mechanical ventilation (35.7% *vs.* 48.4%) and intensive care unit admission (38.8% *vs.* 41.0%), despite a higher rate of comorbidities in the aspirin group. These results, however, should be interpreted with caution, since COVID-19 patients display a hypercoagulatory state, the study only concerns a small number of patients, and the differences are

small, making the clinical relevance minimal. Currently, the Effect of Aspirin on REducing iNflammation in Human *in vivo* Model of Acute Lung Injury (ARENA) trial is including patients (according to clinicaltrials.gov accessed January 2, 2021; 33 patients after 8 yr of inclusion) and examines the effect of aspirin on inflammation in acute lung injury (NCT01659307). In conclusion, despite a pathophysiologic explanation for a beneficial effect of aspirin or other NSAIDs in patients with ARDS, the only performed randomized controlled trial does not show a protective effect (the studies are summarized in table 2).

Inflammation and Pain

Surgical injury leads to activation and sensitization of the nociceptive system through the release of different mediators, like bradykinin, prostanoids, and cytokines. Activated prostanoids, in particular PGE_2 and PGI_2, are involved in peripheral and central sensitization and in (neuro)inflammatory pain. PGE_2 serves as an important proinflammatory mediator and is involved in development of all physical signs of inflammation. Peripheral sensitization by PGE_2 involves the activation of E-prostanoid receptors (EP1, EP2, and EP4), which mediate pain responses from noxious and innocuous stimuli.[84] These receptors are also found in the spinal cord, highlighting the central sensitization activity of PGE_2, where it is considered the dominant prostaglandin in the spinal nociceptive system.[85] PGI_2 causes hyperalgesia by activating the prostacyclin (IP) receptor, which acts directly on the peripheral afferent nociceptors.[85] In addition, PGE_2 and PGI_2 also have sensitizing properties through other mechanisms. For instance, PGE_2 enhances the sensitization of nociceptors by lowering the threshold of the tetrodoxin-resistant sodium channels (found in the cell bodies of many peripheral nervous systems).[84] Second, the transient receptor potential vanilloid 1 channel, which is involved in heat sensation, is potentiated severalfold by PGE_2 and PGI_2 in afferent neurons.[84] Finally, PGE_2 sensitizes afferent neurons to produce bradykinin, which is involved in lowering the heat threshold of bradykinin 2 receptors and is therefore responsible for long-lasting pain associated with inflammation.[84] In addition to activated prostanoids, proinflammatory cytokines, like tumor necrosis factor α and interleukins 1β, 6, and 17, secreted at and recruited to the site of injury, have the ability to activate and to increase the sensitivity to pain stimuli.[86] Receptors for these specific cytokines are located on the nociceptive neurons and, together with other noxious stimuli, stimulate the primary afferent A-delta and C-nerve fibers and synapse with neurons in the dorsal horn of the spinal cord.[87] Neutralization of these cytokines results in a quick reduction of pain. In addition, these cytokines not only play a role in mechanical pain stimulation but also are involved in the development of neuropathic pain.[84]

NSAIDs as Preemptive Analgesics

NSAIDs are widely used in the treatment of acute (perioperative) or chronic pain but are also used as a preemptive analgesic agent. NSAIDs might be ideal for this purpose due to their anti-inflammatory effects and by preventing the establishment of peripheral and central sensitization in nociceptive pathways. In a systematic review, the authors concluded that some aspects of postoperative pain control were improved by preemptive treatment in 4 of the 20 randomized controlled trials, but overall, the effect was moderate.[54] Moreover, there was no analgesic benefit to preemptive administration of NSAIDs compared with postincisional administration. Despite including only randomized controlled trials, the studies displayed a wide heterogeneity, ranging from abdominal to orthopedic surgery, and many different NSAIDs (for example, ibuprofen, diclofenac, ketorolac, naproxen, and flurbiprofen) were used. In a more recent systemic review and meta-analysis, the authors examined the effect of preemptive drug administration on postoperative analgesic consumption during the 24 h postsurgery. A significant reduction of postoperative analgesic consumption was observed using COX-2 inhibitors but not for nonselective NSAIDs.[55] Comparable results were found in a meta-analysis that examined the efficiency of selective COX-2 inhibitors in patients undergoing total knee arthroplasty. The authors found a beneficial effect on the visual analog scale score (24 and 72 h postoperatively) and a decreased opioid consumption.[56] The clinical relevance, however, of both meta-analyses is not clear, since there were no statements about the reduction in the visual analog scale or opioid consumption. Based on the included studies in these meta-analyses, it is also unclear whether preemptive administration has advantages over postincisional administration. This question, however, is not about the efficacy of NSAIDs but about the most ideal time to administer them. This most likely will remain difficult to answer due to small differences in direct clinical outcome measures and many different covariates. Furthermore, interpretation of current literature is hampered by a high degree of heterogeneity with differences in dose and timing, type of postoperative rescue analgesic, postoperative analgesia therapy, type of surgery, and reported outcomes.

NSAIDs in Multimodal Management of Acute Postoperative Pain

While it is uncertain whether preemptive administration of NSAIDs is beneficial over postincisional administration, these drugs have been given an important role in the multimodal management of acute postoperative pain. The American Society of Anesthesiologists (ASA; Schaumburg, Illinois) recommend administration, unless contraindicated, of multimodal pain management consisting of acetaminophen combined with an NSAID or selective COX-2 inhibitor during the perioperative period.[88] In contrast to opioids, which mainly act in the central nervous system, NSAIDs alleviate pain by reducing the inflammatory response caused by tissue damage and by preventing peripheral and central sensitization. The effects of NSAIDs are predictable and suitable for most surgical procedures and have, in contrast to

opioids, no risk of addiction. Moreover, the administration of NSAIDs leads to a shorter recovery period, higher patient satisfaction, and a reduction in postoperative morbidity.[89]

Several meta-analyses have been performed to demonstrate the efficiency of NSAIDs or COX-2 inhibitors. In a meta-analysis from 2005, four conclusions emerge regarding the perioperative use of NSAIDs: nonopioid analgesics are opioid-sparing, the visual analog scale score is significantly decreased, and their use is associated with a reduction of opioid-related adverse effects.[58] However, there was also an increased risk of rare but important adverse effects related to the use of nonselective NSAIDs/selective COX-2 inhibitors, such as renal failure in cardiac patients (odds ratio, 4.86; 95% CI, 1.01 to 23.4; nonselective NSAIDs/COX-2 inhibitors) and increased surgical bleeding (odds ratio, 4.54; 95% CI, 1.54 to 13.42; nonselective NSAIDs). To determine which class of nonopioid analgesic is the most effective in reducing morphine consumption and morphine-related adverse effects, a systematic review was conducted by Maund *et al.*[57] The authors concluded that, in combination with a patient-controlled analgesia with morphine, NSAIDs (mean difference, −10.18 mg) and COX-2 inhibitors (mean difference, −10.92 mg) were related to a reduced morphine consumption. Furthermore, nausea and postoperative vomiting were significantly reduced by adding NSAIDs to a multimodal management.[57] In another meta-analysis, the authors focused on the effect of NSAIDs on opioid-related adverse effects. They observed a reduction in nausea (12%), vomiting (32%), and sedation (29%).[59] There was no reduction in pruritus, urinary retention, and respiratory depression. The authors tried to limit the degree of heterogeneity as much as possible but still included different NSAIDs and type of surgeries. In addition, their primary endpoints were scored differently throughout the included studies. In conclusion, these meta-analyses demonstrate a reduction in the visual analog scale score, opioid consumption, and various opioid-related adverse effects when administered in a multimodal regimen. It is, however, important to realize that studies investigating the effect of multimodal analgesic regiments all suffer from the same weakness: namely, if something changes in the model, it is nearly impossible to conclude whether this is due to one drug *versus* another drug, which makes it difficult to draw firm conclusions.

NSAIDs in Preventing Chronic Pain after Surgery

Persistent postoperative pain is a major problem and affects health-related quality of life. The exact pathophysiology is not fully understood but has recently been discussed in several reviews.[90–92] In summary, it is a multifactorial disorder involving (neuro)inflammation, which is characterized by the activation of glial cells and results in the release of cytokines and chemokines, and peripheral and central sensitization due to persistent noxious signaling, leading to nociceptive and neuropathic pain. Under normal circumstances, the immune response, elicited by surgical injury, resolves after several days,

resulting in baseline nociceptive receptor sensitivity. In patients with persistent postoperative pain, these receptors remain overstimulated. Prolonged augmented action potentials will lead to central sensitization and results in allodynia and hyperalgesia. In addition, proinflammatory cytokines and chemokines in the central nervous system, released by glial cells, also play a role in the development of central sensitization. Moreover, this neuroinflammatory condition will contribute to allodynia, hyperalgesia, and widespread pain throughout the body.[92] The importance of prostaglandins in persistent pain has been confirmed in a mouse model in which hyperalgesic doses of PGE_2 induced long-lasting sensitization of afferent nociceptors.[93] Since NSAIDs interfere with these processes, there is a theoretical basis for a beneficial effect in preventing chronic pain after surgery. Nevertheless, studies examining the long-lasting effects of perioperative NSAID administration could not demonstrate a positive effect on persistent postoperative pain.[60–63] In a recent meta-analysis and systematic review, the effects of various perioperative pharmacologic strategies to prevent chronic pain after surgery were assessed. The included studies differed in type of NSAID, duration of administration, type of surgery, but also outcome measures such as reported time endpoints to score the prevalence of pain ranged from 3 to 12 months.[64] The authors concluded that none of the examined pharmacologic interventions could be recommended to prevent chronic pain after surgery.

Tumor Growth and Metastasis

In various epidemiologic studies, it has been shown that the long-term use of aspirin or other NSAIDs is associated with a reduction in the incidence of cancer.[94,95] In a large systemic review of epidemiologic studies, the relative risk was decreased by 43% for colon cancer, 25% for breast cancer, 28% for lung cancer, and 27% for prostate cancer.[96] Of the two cyclooxygenase isoforms, COX-2 expression is dysregulated in many types of cancer and is associated with carcinogenesis, invasiveness, and angiogenesis.[97] With elevated levels of COX-2, the metastatic potential also seems to increase. Of the prostanoids, PGE_2 seems to be the most important prooncogenic prostanoid.[97] PGE_2 is involved in tumor angiogenesis, cell migration or invasion, and inhibition of apoptosis.[97] In addition to its effect on prostanoids, aspirin activates aspirin-triggered specialized proresolving mediators, including resolvins and lipoxins. These anti-inflammatory mediators inhibit primary tumor growth and metastasis by enhancing endogenous macrophage clearance and cytokine response.[23] In addition to the long-term protective properties of NSAIDs against certain cancer types, these drugs also interfere with the immune response against circulating tumor cells during the surgical resection of a solid tumor. The likelihood of circulating tumor cells is dependent on several factors, including the immune response of the patient. Local inflammation increases the level of circulating tumor cells in the bloodstream, and an adequate functioning

immune response is pivotal for the first-line defense against circulating tumor cells.[98] The elimination of cancer cells takes place through natural killer cells, cytotoxic T cells, and dendritic cells. Their activity is inhibited by PGE_2, which is over-expressed by many tumors, such as colorectal, breast, cervical, bladder, and ovarian.[99] In addition, surgical injury increases a number of proinflammatory cytokines such as interleukins 1β and 6 and tumor necrosis factor α, which also suppress the activity of immune cells necessary for the elimination of circulating tumor cells.[100] Theoretically, NSAIDs have the ability to reduce these effects. The inhibition of PGE_2 synthesis in tumor cells leads directly to an impaired capacity to survive and proliferate and leads indirectly to an increased cytotoxic activity of natural killer and T cells.[101] Brunda et al.[102] showed that in vivo administration of indomethacin or aspirin resulted in a marked restoration of natural killer activity in tumor-bearing animals. In a meta-analysis of animal studies, the authors concluded that treatment with analgesics significantly decreased the number and risk of metastases, which was mainly the consequence of NSAIDs.[67]

Recently, five randomized controlled trials (NCT00888797, NCT02141139, NCT00502684, NCT01806259, and NCT03172988; clinicaltrials.gov) were conducted to assess the effect of perioperative NSAIDs on cancer recurrence. These trials differed in the type of cancer, the duration of NSAID administration, whether administration started preoperatively, the coadministration of a β-adrenergic antagonist, and the NSAID type (COX-1 and/or COX-2). The status of four of these randomized controlled trials (NCT00888797, NCT02141139, NCT01806259, and NCT03172988) is either unknown or lacking in sufficient power due to early termination, protocol violation, or a lower recurrence rate than anticipated.[103] The positive effect of NSAIDs in the perioperative period was shown in a randomized controlled trial (NCT00502684) that combined a COX-2 inhibitor with a β-adrenergic antagonist (propranolol), using study outcome points of cellular and molecular responses related to metastasis and disease recurrence.[65] Cata et al.[66] conducted a systemic review and found mainly observational and retrospective studies, all dealing with a high degree of heterogeneity, and concluded that the current evidence was equivocal regarding the effects of short-term NSAIDs on cancer recurrence after major cancer surgery. However, these observational and retrospective studies claim a reduced recurrence rate, longer disease-free survival, or overall survival due to the effects of perioperative NSAIDs.[104–112] In conclusion, despite the positive effect of NSAIDs in epidemiologic studies, immune-based perioperative antitumor effects, and positive observational and retrospective studies, there is insufficient or inconclusive evidence from high-quality clinical studies to support the experimental data (studies are summarized in table 2).

Neurologic Effects

Neuroinflammation is an important underlying mechanism in several neurologic disorders. Affecting this pathophysiologic process through the anti-inflammatory effects of NSAIDs is of general interest. Regarding the perioperative period, postoperative cognitive dysfunction is a common complication, particularly affecting the elderly population. Postoperative elevated levels of proinflammatory cytokines are associated with the development of postoperative cognitive dysfunction in both animal and human studies.[113–120] The hypothesis is that proinflammatory cytokines disrupt the blood–brain barrier via upregulation of COX-2 and matrix metalloproteinases, upon which these cytokines can enter the central nervous system.[121] After surgical injury, increased inflammatory activity was found in plasma and in human cerebrospinal fluid.[122] In a study by Peng et al.,[123] administration of parecoxib, a selective COX-2 inhibitor thought to have good central nervous system distribution, resulted in reduced surgery-induced levels of interleukin 1β and tumor necrosis factor α in the hippocampus in aged rats. Improvements in memory function in mice were demonstrated by Kamer et al.,[124] who administered meloxicam 24 h after surgical splenectomy. A recent meta-analysis included eight randomized controlled trials assessing the effect of parecoxib on the incidence of postoperative cognitive dysfunction in geriatric patients undergoing orthopedic surgery.[68] The authors concluded that perioperative administration of parecoxib was effective in reducing the incidence of postoperative cognitive dysfunction and improving the score on the Mini-Mental State Examination. The methodologic quality of the included studies was assessed as moderate to good. Nevertheless, only one of the eight randomized controlled trials was sufficiently powered, parecoxib was administered pre- or postoperatively, and postoperative cognitive dysfunction definitions were different between studies. Furthermore, it is unclear whether these results can be extrapolated to other surgical interventions.

NSAIDs are also associated with reduced cerebral ischemic injury in patients with aneurysmal subarachnoid hemorrhage.[125,126] Encouraging results of NSAIDs were found in animal models of aneurysmal subarachnoid hemorrhage, which showed an overall better control of cerebral vasospasm.[127–132] After propensity score matching of 178 patients, positive effects were observed by Nassiri et al.,[133] who concluded that administration of NSAIDs after aneurysmal subarachnoid hemorrhage was associated with reduced mortality and improved functional outcome. In this study, no distinction was made between the different types of NSAIDs, nor is it clear how long NSAIDs were administered. An important limitation, however, concerns the indication for administration of NSAIDs. Patients with a better neurologic status are more likely to report pain and therefore receive more NSAIDs than patients with a poorer neurologic status. A randomized controlled trial by Ghodsi et al.,[69] however, could not demonstrate significant differences in cerebral vasospasm, hospital stay, or mortality after administration of meloxicam (7.5 mg for 7 days) in patients

with subarachnoid hemorrhage. This study may have been underpowered (N = 81), since no sample size calculation was made. Regarding the safety of NSAIDs, several studies have shown that there is no association with higher rates of rebleed in aneurysmal subarachnoid hemorrhage patients.[125]

Neuroinflammation is an important underlying mechanism in the pathophysiology of various neurologic disorders. NSAIDs might have additional value in the multimodal treatment approach in patients at risk of postoperative cognitive dysfunction, but well-designed clinical trials are needed to determine whether these effects are clinically relevant. Encouraging results of NSAIDs in patients with aneurysmal subarachnoid hemorrhage are not yet sufficiently substantiated to justify any advice (studies are summarized in table 2).

Unfavorable Immune-modulating Effects of NSAIDs

Wound, Anastomotic, and Bone Healing

Wound Healing

NSAIDs might have immune-modifying properties that are detrimental in the process of normal wound healing. There are a number of crucial steps in the process of normal wound healing, including the acute phase response, proliferation, and remodeling of tissue. The acute phase is characterized by homeostasis and inflammation. Neutrophils are involved at an early stage and stimulate the migration of fibroblasts, epithelial cells, and vascular endothelial cells.[134] In a later stage, macrophages become the predominant cells and form an important barrier against bacteria.[134] In response to cytokines, released upon (surgical) injury, nitric oxide is produced, which is essential for angiogenesis and mediation of inflammation.[135] In an animal study in which nitric oxide was bound to ibuprofen, wound contraction increased, and epithelialization improved; the authors concluded that the results indicated that the esterification of ibuprofen with nitric oxide reverses the healing-suppressant effect of ibuprofen.[136] During the proliferation step, fibroblasts are the most important cells and are involved in wound contraction, collagen synthesis, and angiogenesis.[137] NSAIDs might impair the acute and proliferation phase of wound healing by their inhibitory effects on PGE_2.[138–140] Inhibition of PGE_2 is related to impaired wound healing; therefore, the use of NSAIDs in the proliferative phase of wound healing may result in increased scar formation.[140] PGE_2 has shown to be essential for neutrophil removal *via* the promotion of reverse migration.[141] Although the negative effects of NSAIDs on wound healing are well documented in animal studies, large clinical trials describing the effects of NSAIDs in wound healing are lacking. During a phase 3 randomized, placebo-controlled trial to evaluate the safety of intravenous meloxicam (30 mg) after major surgery, no differences were observed regarding wound healing.[70] The authors, however, pointed out the relatively healthy study population, in which patients with a history of cardiovascular, renal, hepatic, and bleeding events were excluded.

Anastomotic Healing

The hypothesis of impaired wound healing also applies to an intraabdominal bowel anastomosis, in which NSAIDs may increase the risk of anastomotic leakage. COX-2 is essential for gastrointestinal homeostasis, and the subsequent prostaglandin PGE_2 is involved in mucosal repair.[142,143] Moreover, anastomotic healing benefits from a proinflammatory response, leading to proliferation, angiogenesis, and granulation.[144] Reduced prostaglandin expression has been shown to reduce measured hydroxyproline levels and collagen repair in fresh anastomosis.[145] However, no information has been provided about the subtype of collagen, and therefore, the quality of the collagen cannot be determined.[144] An association between the perioperative use of NSAIDs and an increased risk of anastomotic leakage is demonstrated in various animal experiments and human clinical trials.[143,146] A randomized controlled trial in 24 rats assessed the effect of parecoxib on abdominal wound healing, both clinically and histologically.[71] There were no differences in clinical outcome; however, histological differences, on which the study was powered, were observed, such as decreased epithelization and increased necrosis in the parecoxib group.[71] The results, however, are not generalizable to humans, as the authors chose an intraperitoneal route of administration. Interestingly, the risk of anastomotic leakage caused by NSAIDs seemed to be location-dependent, with a higher risk in small bowel anastomosis compared to colon anastomosis.[147–149] Three meta-analyses, one published in 2018, 2019, and 2020, all concluded that caution must be taken when prescribing NSAIDs after gastrointestinal anastomosis.[72–74] A subgroup analysis in the meta-analysis of Jamjittrong *et al.*[72] showed that nonselective NSAIDs, but not selective COX-2 inhibitors, were significantly associated with anastomotic leakage. However, according to the authors, the safety of selective COX-2 inhibitors was inconclusive. In another subgroup analysis of randomized controlled trials by the same authors, no significant association was observed.[72] Finally, a fourth meta-analysis has recently been published, in which the authors pointed to important methodologic concerns regarding the previous meta-analyses, such as the inclusion of different types of gastrointestinal anastomoses and the underlying surgical pathology.[75] In this latest meta-analysis, only patients with colorectal cancer were included (N = 10,868). The authors concluded that perioperative NSAID administration does not increase the overall anastomotic leakage rate and that these findings were consistent throughout subgroup analyses for low anterior resections and both NSAID classes. Nevertheless, this latest meta-analysis also has important

methodologic limitations: like most studies, there are no data on dosage and duration of administration. In addition, it is unclear when administration was started, as later dosing during the postoperative phase is associated with a lower risk of anastomotic leakage. There are currently no registered studies (accessed January 2, 2021, clinicaltrials. gov) examining the effects of NSAIDs on anastomotic leakage.

Bone Healing

In addition to the potential negative effects on wound and anastomotic healing, the use of NSAIDs perioperative might also affect bone healing, since inflammation is an essential part of the early stage of bone fracture healing. Although the contribution of NSAIDs is controversial with respect to other risk factors (comorbidities, medications, oncology interventions, and lifestyle habits), the inhibition of COX–1 and COX–2 might result in an impaired bone turnover.[150] COX–2 is involved in the differentiation of mesenchymal cells into osteoblasts.[151] In COX–2 knockout animals, bone density was significantly decreased, whereas parathyroid hormone levels were increased, implicating a compensatory mechanism for the lack of COX–2 expression.[152] In a meta-analysis from 2010, the authors reviewed all available evidence regarding the effect of NSAIDs exposure on bone healing.[79] Lower-quality reports showed a significant association between NSAID exposure and nonunion, while this association disappeared when only higher-quality studies were included in the analysis.[79] A more recent meta-analysis from 2019, however, observed a negative effect of NSAIDs on bone healing, which may be dose- and/or duration-dependent, since low dose or short duration was not associated with nonunion.[78] Low dose or short duration was, however, not defined in this study and could only be analyzed in 4 of 16 evaluable studies, of which 2 found no effect and 2 found an increased risk. Moreover, it should be noted that no randomized studies were included in either meta-analysis. A systematic review including 3 randomized controlled trials and 13 retrospective studies concluded that there was no strong evidence that NSAIDs led to an increased rate of nonunion.[77] In all of these analyses, the authors had to deal with heterogeneity and conflicting data among the included studies. Important differences between long bones and vertebral bones, with variation in reported nonunion rates between both, and lifestyle habits, such as smoking, should be taken into account. Furthermore, there was a significant difference in the definition of nonunion between studies, ranging from a radiographic score to the need for reoperation. Finally, these studies also showed a large variation in dosage, type of NSAID, and duration of administration. A recent randomized trial examined the effect of different ibuprofen regimens (3 × 600 mg ibuprofen for 7 days *vs.* 3 × 600 mg ibuprofen for 4 days *vs.* placebo) on bone healing in Colles' fracture patients.[76] The authors

concluded that there were no differences in bone mineral density, histomorphometric estimations, and changes in bone biomarkers between the treatment groups.[76] Although confounding variables were equally distributed between groups, the start of treatment could differ substantially between patients. According to clinicaltrials.gov, this study was initially registered under NCT01606540, with a power calculation of 192 participants. The final study is registered under NCT01567072, with the same power calculation, but only 95 patients were included. A forthcoming randomized controlled trial (NCT03880981) will study the effect of NSAIDs on the healing of tibia fractures and Achilles tendon ruptures (accessed January 2, 2021).

In conclusion, based on histological and animal studies, there appears to be an association between NSAIDs, in particular COX–2 inhibition, and impaired wound, anastomotic, and bone healing after surgery. However, high-quality clinical trials are lacking, and many questions are unanswered, such as the duration of use, type of NSAID, and, for anastomotic healing, whether underlying pathology and the location of the anastomosis influences the outcome. The potentially negative consequences that have emerged in histological and animal studies have therefore not been sufficiently substantiated in clinical studies. Administration must be individually weighed against the other known risk factors and benefits of NSAIDs (studies are summarized in table 2).

Aspirin-exacerbated Respiratory Disease

The pulmonary effects of NSAIDs in the perioperative period are considered to be minimal. Nevertheless, the administration of NSAIDs should be carefully considered in specific circumstances, and detrimental effects may occur in patients with a history of asthma. In 2% of patients with mild asthma up to 25% of patients with severe asthma, the inhibition of COX–1 may trigger aspirin-exacerbated respiratory disease, a condition characterized by eosinophilic rhinosinusitis with humoral T helper 2 cell inflammation, bronchospasm, and acute asthma exacerbation.[153] Bronchospasm can be severe and life-threatening, developing within 1 to 3 h of administration.[153] The underlying pathophysiologic mechanism is related to inhibition of the cyclooxygenase pathway, resulting in activated lipoxygenase, which leads to increased leukotriene synthesis. Leukotriene provokes the constriction of smooth muscle and the stimulation of airway mucus production.[154] The prostanoids PGD_2 and PGE_2 also have pulmonary effects, but their role in the development of aspirin-exacerbated respiratory disease is not fully understood. PGE_2 causes bronchodilation, while PGD_2 causes bronchoconstriction.[155] It is generally assumed that all nonselective cyclooxygenase inhibitors pose a risk for patients with a history of asthma and that highly selective COX–2 inhibitors are safe. This assumption is based on previous data suggesting that the release of both prostanoids (PGD_2 and PGE_2) is

only COX-1–dependent. Although two cases of aspirin-exacerbated respiratory disease were described in a case report after administration of a highly selective COX-2 inhibitor, this observation was not supported by a randomized crossover study in which 16 subjects with mild asthma received etoricoxib, and none developed pulmonary symptoms.[52,156] These results are consistent with a meta-analysis performed by Morales *et al.*,[53] who concluded that acute exposure to COX-2 inhibitors is safe in patients with stable mild-to-moderate asthma with aspirin-exacerbated respiratory disease. In conclusion, nonselective NSAIDs should be avoided during the perioperative period in patients with a history of asthma. Highly selective COX-2 inhibitors are most likely safe.

Conclusions

In this narrative review, we have summarized the immune-modulating effects of NSAIDs in the perioperative period and their effect on various postoperative outcomes. The body's response to surgical injury, and the accompanying release of subsequent cytokines, chemokines, and prostanoids, affects the postoperative course in various organ systems and regeneration processes. NSAIDs interfere with this response through the inhibition of cyclooxygenase, leading to a reduction in the synthesis of several of the prostanoids involved. Aspirin also stimulates the production of anti-inflammatory and proresolving mediators, but the consequences of this additional effect, to date, are unclear in clinical practice.

NSAIDs have been shown to have immune modulatory effects in cellular and animal models and significantly affect various outcome in these models. In randomized clinical studies, however, the immune-modulatory effects are much less evident, potentially due to a high degree of heterogeneity, genetic variances among patients, the use of various comedications, and the presence of several comorbidities. The risks and benefits of NSAID administration should be weighed individually, taking into account that the dosage and duration of administration often play important roles. To date, there is insufficient or inconclusive evidence from high-quality clinical studies to support the administration of NSAIDs to control the surgical stress response or sepsis, to prevent or improve ARDS, to improve postoperative neurologic outcome, or to minimize the risk of metastatic disease after oncological surgery. On the other hand, there is also insufficient evidence that NSAIDs are related to an impaired wound healing, increased risk of anastomotic leakage, and impaired bone regeneration. Their role in the multimodal treatment of acute pain has been sufficiently demonstrated and is associated with an opioid-sparing effect. It is not yet sufficiently clear whether preemptive administration of NSAIDs also has beneficial effects on postoperative pain perception. There does not, however, appear to be a beneficial effect on the development of chronic pain after surgery.

Search Strategy

We searched PubMed, Google, and clinical guidelines and screened the reference lists of studies retrieved by the searches. Most up-to-date studies and/or those with high impact were selected. Thereafter, a selection was made based on randomized controlled trials, reviews, and systematic reviews, or meta-analyses. We used the following terms: "nonsteroidal anti-inflammatory drugs" OR "NSAID" OR "aspirin" AND:

- "surgical stress response" OR "cytokine" OR "SIRS" OR "sepsis"
- "ARDS" OR "acute respiratory distress syndrome"
- "AERD" OR "aspirin-exacerbated respiratory disease"
- "surgery" AND "preemptive" OR "preoperative"
- "surgery" AND "perioperative"
- "surgery" AND "chronic pain" OR "persistent pain"
- "surgery" AND "oncology"
- "surgery AND "postoperative cognitive dysfunction" OR "POCD"
- "aneurysmal subarachnoid hemorrhage" OR "aSAH"
- "surgery" AND "wound healing" OR "tissue healing"
- "surgery" AND "anastomotic leakage" OR "anastomotic dehiscence"
- "surgery" AND "bone healing" OR "nonunion"

Competing Interests

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