Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs, and Cyclooxygenase-2 Selective Inhibitors: An Update

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Summary: Plastic and cosmetic surgery is often performed as an ambulatory procedure, and pain is often mild to moderate. Good pain relief is central to patient comfort and satisfaction. Analgesics used should ensure rapid onset and adequate pain relief lasting a sufficiently long duration with minimal or no side effects. Acetaminophen is well tolerated by patients, efficacious, and associated with only minor side effects, when used in the minimal effective doses. Nonsteroidal anti-inflammatory drugs (NSAIDs) are more efficacious, having lower numbers needed to treat compared with acetaminophen, but have several side effects and contraindications. However, when used in the correct doses in healthy patients, NSAIDs are excellent for pain management with one caveat that there is an increased risk for oozing or bleeding. In contrast, cyclooxygenase inhibitors (Coxibs) are equally efficacious as NSAIDs but have the added advantage that they have minimal or no effect on platelet function, and therefore, the risk for bleeding complications is minimal. However, there has been some concern about the risk of vascular events in patients with ischemic heart disease, specifically when using Coxibs, but even some NSAIDs, for example, diclofenac. In conclusion, acetaminophen should be given postoperatively to all patients undergoing plastic surgical procedures. For patients undergoing moderately invasive surgery, the addition of Coxibs to acetaminophen would be an advantage except in the patient with ischemic heart disease where NSAIDs could have a place in management of pain. Side effects and contraindications of NSAIDs, however, restrict their use to the healthy patient with mild comorbidities. (*Plast. Reconstr. Surg.* 134: 24S, 2014.)

The advent and subsequent expansion of ambulatory surgery has increased the demands on postdischarge pain management considerably. Not only do patients have to be awake, alert, and able to ambulate within a short period of time but they also need to be eating, analgesic, and not amnesic from the residual effects of anesthetics. These essential requirements for home readiness have resulted in new strategies and innovative ideas to reduce hospital costs while maintaining the highest standards of safety. It is likely that in the future, healthcare costs and constraints will put even greater pressure on physicians to mobilize, discharge, and return patients to their work environment in even shorter periods of time.

Among other requirements, good postoperative analgesia is a fundamental need for both early home discharge and patient satisfaction. Although opiates have been used satisfactorily in the past for pain management following major surgery, their side effects limit their use in ambulatory surgical procedures. Additionally, most plastic and reconstructive procedures are on body surfaces not

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Received for publication March 18, 2014; accepted July 15, 2014.

DOI: 10.1097/PRS.0000000000000672

Disclosure: *Dr. Jakobsson has received unrestricted research grants from Baxter, Abbott, Pfizer, and MSD; has been part of advisory board and company-sponsored symposium for Baxter, Merck Sharp & Dohme, Abbott, Maque, and Linde; and has a consult agreement with Linde. Dr. Gupta has no financial interests to disclose.*

involving major muscle groups, and therefore, pain management can be adequately fulfilled using nonopiate medications, including, but not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or tramadol in combination with local anesthetics. The introduction of cyclooxygenase (COX)-2 selective inhibitors has also added a new dimension in pain management, and even drugs, such as gabapentin/pregabalin, clonidine, and low-dose ketamine, are perfectly viable options during ambulatory surgery.

In this review, we focus on the advantages and disadvantages of acetaminophen, NSAIDs, and more selective NSAIDs with predominant COX-2 selective inhibitory effects, hereinafter called cyclooxygenase inhibitors (Coxibs). We shall try to provide current evidence for the use of these drugs in different perioperative scenarios and discuss common side effects and complications. When possible, evidence is presented from studies on patients undergoing plastic and reconstructive surgery. It is important to state that good pain management requires a multidisciplinary approach that includes surgeons, anesthesiologists, nurses, and patients, in achieving satisfactory outcomes. No profession or person can achieve this alone and a team attitude should be central in achieving the objectives laid out both in hospital and individual or group practice.

CLINICAL PHARMACOLOGY

Acetaminophen

Acetaminophen (paracetamol) is the most commonly prescribed analgesic for the treatment of acute pain. Acetaminophen is a weaker analgesic than NSAIDs or Coxibs but is often preferred because of its better tolerance.

Graham et al[1] have recently updated the pharmacology of acetaminophen. Despite its similarities to NSAIDs, the precise mechanism of action of acetaminophen remains unclear even today. However, it is believed primarily to act via inhibition of COX-1 and COX-2 enzymes through metabolism by the peroxidase function of these isoenzymes centrally in the central nervous system. However, even peripheral effects may be involved by inhibiting isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin synthesis and thereby increasing the pain threshold.[2] The pharmacological properties of different oral and intravenous (IV) formulations of acetaminophen are shown in Table 1. Acetaminophen is today available in different formulations for oral, rectal, and IV administration. The bioavailability following oral administration is variable.[3,4] Plasma concentration increases with dose, and the therapeutic plasma concentration following a single oral dose of 2 g is reached within less than 1 hour. However, considerable variation exists between individuals. Acetaminophen is both analgesic and antipyretic in therapeutic doses. The analgesic efficacy is dose dependent, but the maximum recommended daily dose in adults without liver or renal disease is 4 g. However, dose reduction is recommended in patients with liver insufficiency.

Table 1. NNT for 50% Pain Reduction (95% Confidence Interval) for the Different NSAID and COX-2 Inhibitors

	NNT	95% Confidence Interval
Acetaminophen 650 mg	5.3	4.1–7.2
Acetaminophen 1000 mg	3.8	3.4–4.4
NSAIDs		
Indomethacin 400 mg	2.7	2.5–3.0
Indomethacin 600 mg	2.4	1.9–3.3
Diclofenac 50 mg	2.3	2.0–2.7
Ketorolac 10 mg IV	2.6	2.3–3.1
COX-2 inhibitors		
Celecoxib 200 mg	3.5	2.9–4.4
Celecoxib 400 mg	2.1	1.8–2.5
Etoricoxib	1.9	1.7–2.1
Parecoxib 20 mg IV	3.0	2.3–4.1
Parecoxib 40 mg IV	2.2	1.8–2.7

Information was obtained from different sources.

Toms et al[5] published a meta-analysis on the analgesic efficacy of acetaminophen and found that about half of the patients treated with standard doses of acetaminophen achieved at least 50% pain relief over 4–6 hours, compared with about 20% treated with placebo. The numbers needed to treat (NNT) (95% confidence interval) for >50% pain relief following a single dose of acetaminophen is as follows: 500 mg, NNT 3.5 (2.7–4.8); 600–650 mg, NNT 4.6 (3.9–5.5); and 975–1000 mg, NNT 3.6 (3.4–4.0) (Table 1). The authors' conclusion was that there was no clear dose-response relationship and lower doses are equally efficacious compared with higher doses.

IV acetaminophen gives a rapid and predictable plasma concentration, whereas rectal administration has a low and variable uptake.[6,7] IV acetaminophen is recommended as a first-line agent for the treatment of pain and fever in adults and children when oral administration is not possible. In double-blind clinical trials, the analgesic efficacy of a single dose or multiple doses of IV acetaminophen 1 g was significantly greater than placebo treatment in adult patients who had undergone dental, orthopedic, or gynecological surgery. McNicol et al[8] recently published

Table 2. Pharmacokinetic Data Are Presented as Average Values (Data Obtained from Different Sources)

	Bioavailability	Peak Plasma Concentration	Plasma Half-Life	Duration of Action
Acetaminophen oral (1 g)	85–95%	10–90 min	2–3 h	4–6 h
Acetaminophen IV (1 g)	100%	5–10 min	2.7 h	4–6 h
NSAID				
Indomethacin (50 mg)	90%	1 h	4.5 h	4–6 h
Ibuprofen (400 mg)	?	1–2 h	2 h	4–6 h
Diclofenac (50 mg)	60–70%	15–30 min	1.2–2 h	4–8 h
Ketorolac IV (30 mg)	100%	10–15 min	4–9 h	11 h
COX-2 inhibitors				
Etoricoxib (120 mg)	100%	1 h	22 h	20 h
Parecoxib IV (40 mg)	100%	10–15 min	8 h	15 h

Parecoxib is a prodrug and is converted to the active form valdecoxib rapidly in the liver.

a systematic review and meta-analysis comparing single-dose IV acetaminophen or propacetamol for prevention or treatment of postoperative pain. The proportion of patients in propacetamol or IV acetaminophen groups experiencing at least 50% pain relief diminished over 6 hours. However, this did not translate into a reduction in opioid-associated adverse events. Tzortzopoulou et al[9] also found similar results, and Hahn et al[10] found that increasing the IV dose had limited benefit. In contrast, Korpela et al[11] found that children undergoing ambulatory surgery showed a dose-response effect for analgesic efficacy. They also found that increasing the dose of acetaminophen reduced the need for rescue morphine medication.

Side Effects and Contraindications

Acetaminophen is a relatively safe drug when used in therapeutic doses. Acetaminophen in clinical doses is associated with few and mild side effects. Unlike morphine analogues, there are no effects on respiration. Additionally, acetaminophen does not cause sedation, nausea, and vomiting and reduced gastrointestinal (GI) motility. The effects of acetaminophen on platelets and hemostasis in clinical doses are minor, if any, in patients without a history of coagulopathy.[12] The most serious side effect is liver damage when administered in high doses, for chronic use or when given concomitantly with alcohol or other drugs that are also hepatotoxic. The Food and Drug Administration has recently recommended the use of the lowest effective dose, 325 mg (see http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm381650.htm). Acetaminophen has no significant side effects on the cardiovascular, respiratory, or renal systems. A recent study[13] from Denmark suggests a possible relation between acetaminophen use during pregnancy and risk for neurobehavioral defects in the child. This observation, however, requires further confirmation.[14] Blood dyscrasia (eg, thrombocytopenia), methemoglobinemia, and hemolytic anemia are very rare side effects of acetaminophen.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs have been used extensively for the management of acute and chronic pain over several decades, and many of these drugs are today available over the counter due to their relatively safe profile when used correctly. They act primarily by inhibiting the activity of both COX-1 and COX-2 enzymes and thereby the synthesis of prostaglandins and thromboxanes. They have analgesic, antipyretic, and anti-inflammatory effects. They are also used in neonates to promote closure of a patent ductus arteriosus via inhibiting of prostaglandin synthesis. Leung et al[15] have recently reviewed the clinical pharmacology of NSAIDs. NSAIDs are available for oral, rectal, topical (dermal cream), and IV administration. The bioavailability, onset of action, duration of effect, and half-life of different NSAIDs are shown in Table 2, whereas the selectivity of action on COX-1 or COX-2 is shown in Table 3.

In general, NSAIDs are efficacious in the management of pain and have a low NNT when used in adequate doses but have several side effects

Table 3. The Selectivity of Different NSAID and COX-2 Inhibitors on the COX-2 and COX-1 Isoenzymes

	COX-2/COX-1 Ratio	COX-1/COX-2 Ratio
Aspirin	167	3.1
Naproxen	0.6	1.7
Ketorolac	2.0	0.5
Diclofenac	2.2	1.4
Indomethacin	30	0.02
Ibuprofen	15	0.07
Piroxicam	33	0.04
Tenoxicam	15	0.62
Meloxicam	0.33	3
Etoricoxib	0.02	344
Celecoxib	0.03	30
Rofecoxib	0.003	272

Information was obtained from different sources.

(see below). There are overwhelming data from the use of NSAIDs for acute pain management following a variety of ambulatory surgical procedures including plastic and cosmetic surgery. The Cochrane group has conducted a series of meta-analysis documenting the analgesic efficacy of single-dose NSAIDs, for example, ketoprofen[16] and lornoxicam,[17] and found good evidence for effective and safe analgesia. A recent Cochrane review also found more rapid uptake and subsequent pain relief from a new formulation of ibuprofen.[18] Fast-acting formulations of ibuprofen demonstrated more rapid absorption, faster initial pain reduction, better overall analgesia at the same dose, and probably even longer-lasting analgesia without higher incidence of adverse events. Ibuprofen is available for IV administration in some countries and has been shown to be safe and effective for the treatment of posttonsillectomy pain in a recent study by Moss et al[19] It was found to reduce pain and need for rescue analgesia. There was no increase in blood loss, and postoperative bleeding was not observed.

Side Effects and Contraindications

The spectrum of side effects is largely related to the dominance of COX-1 or COX-2 inhibition (Table 4). NSAID hypersensitivity with cross-reactivity between different drugs has been reported, and caution should also be taken in patients with history of sensitivity to acetyl salicylic acid. The Coxibs may be a safer alternative, but avoidance of hypersensitivity in those allergic to NSAIDs is not guaranteed.[20] NSAIDs are known to cause GI irritation and may also cause GI bleeding. NSAIDs affect platelet function negatively and may therefore cause impaired hemostasis. Furthermore, because of prostaglandin inhibition, there is a potential risk of NSAID exacerbated asthma and risk for renal insufficiency. The latter occurs specifically in the presence of hypovolemia as following major perioperative bleeding or dehydration. Cardiovascular side effects include myocardial infarction, specifically in the presence of ischemic heart disease (IHD), but this seems to differ between the drugs, being greatest in case of diclofenac and possibly none with naproxen (Table 2). However, some reports suggest that ketorolac can be protective in patients with IHD, having a positive effect during ischemia reperfusion.[21] NSAIDs increase the risk for heart failure and are therefore contraindicated in this condition and should be used with caution in patients taking angiotensin-converting enzyme inhibitors due to a potential risk for interaction. In summary, contraindications (relative or absolute) for the use of NSAIDs are long, and care needs to be taken in patients with comorbid conditions. However, NSAIDs are efficacious and should be used routinely for the management of postoperative pain and whenever there is no contraindication. The minor risk of bleeding or hematoma formation during cosmetic procedures may, however, preclude their routine use.

COX-2 Receptor Inhibitors

The selective COX-2 inhibitors were developed with the aim of reducing the GI side effects and bleeding associated with the use of NSAIDs. It has been shown that the Coxibs reduce but not eliminate the risk for a GI bleed.[22] Like NSAIDs, Coxibs also have relative selectivity for COX-2 inhibition (Table 3). Thus, rofecoxib is much more selective on COX-2 isoenzyme compared with celecoxib. The selectivity of COX-2 does not seem to prevent other side effects of NSAIDs, such as an increased risk of renal failure and probably an increase in the risk for myocardial infarction, deep vein thrombosis, and stroke due to an increase in thromboxane activity that is not balanced by prostacyclin. The latter is inhibited by COX-2 inhibition. Coxibs are also efficacious in the management of postoperative pain and have a low NNT (Table 1). However, their analgesic superiority as compared with traditional NSAIDs has not been proven.[23] One major benefit when using Coxibs during surgery is that they have only

Table 4. Incidence of Cardiovascular Events in Patients Taking NSAIDs and COX-2 Inhibitors

	Incidence of Event in Experimental Group (%)	Incidence of Event in Placebo Group (%)	*p* (Experimental Group versus Placebo)
Rofecoxib 50 mg			
Hypertension	14.3	7.3	<0.05
Thromboembolic event	4.5	2.0	0.008
Celecoxib 400 mg			
Major adverse cardiovascular events	2.8	0.8	0.01
Naproxen			
Myocardial infarct	1.28	0.95	0.5
Stroke	1.70	0.76	0.06

Events are in patients on long-term treatment with NSAID/COX-2 inhibitors. Information was obtained from different sources.

minor (if any) effect on platelet function, and thus, the risk for any significant bleeding, oozing, or hematoma formation, as during plastic surgery, is negligible.[24] Coxibs are available in an injectable form, parecoxib (Dynastat), which can be administered intravenously and has a short onset of action but a sufficiently long duration of effect to provide good pain relief well into the postoperative period (Table 1). However, unlike the injectable formulation of NSAID, ketorolac, parecoxib is a parenteral prodrug and therefore needs to be converted into its active form (valdecoxib) in the liver and has no local effects when injected intra- or periarticularly.

It has been shown that a single dose of oral etoricoxib[25] provides good pain relief after surgery and that the incidence of adverse events is not very different from placebo. The analgesic efficacy of celecoxib[26] 400 mg is probably similar to ibuprofen 400 mg. Assareh et al[27] compared preoperative versus early postoperative Coxib for pain management following shoulder arthroscopy and found no differences suggesting that time of administration is probably unimportant. Postoperative oral analgesia is probably an effective and adequate alternative when local anesthetics or peripheral nerve blocks are used during surgery, and these provide adequate pain control during the early phase of recovery until the onset of therapeutic effects of the oral medication.

Side Effects and Contraindications

The potential risk for cardiovascular and thromboembolic events associated with long-term use of Coxibs is well known today, which is the reason why rofecoxib (Vioxx) was withdrawn from the market. In general, because of the real risk of perioperative myocardial infarction, Coxibs should be avoided in patients with IHD, even for shorter periods of time. No differences in the incidence of renal side effects have been found between NSAIDs and Coxibs, but the latter are probably safer in patients with mild asthma. Coxibs do have a lower risk for bleeding complications because of minor effects on platelet function and a lower risk of GI ulcers and GI bleeding compared with NSAIDs.

COMPARATIVE STUDIES OF ANALGESICS

There are several studies comparing acetaminophen and NSAIDs and their combination.

Hein et al[28] found more pronounced analgesia using a standard dose of NSAID compared with 1 g oral acetaminophen. Iorno et al[29] studied the addition of acetaminophen to a single-dose 30 mg ketorolac IV for pain relief and showed additive effects of the combination. Derry et al[30] published a meta-analysis in 2013 and concluded that the combination of ibuprofen and acetaminophen provided better analgesia than either drug alone (at the same dose), with a lesser need for additional analgesia during approximately 8 hours postoperatively and with a smaller risk of experiencing an adverse event.

White et al[31] studied 180 patients undergoing outpatient surgery in a prospective randomized 3-armed clinical trial. Patients were randomized to celecoxib 400 mg daily, ibuprofen 400 mg 3 times daily, or placebo control for the first 3 postoperative days. Compared with placebo, both celecoxib and ibuprofen significantly decreased the need for rescue analgesic medication after discharge. The incidence of postoperative constipation was significantly higher in the control group (28%) compared with the celecoxib (5%) and ibuprofen (7%) groups, respectively. Both active treatments were well tolerated in the postdischarge period. However, the time to resumption of normal activities of daily living was similar amongst the 3 groups. Thus, no difference was seen between a 3-day NSAID compared with Coxib protocol following ambulatory surgery. However, both active groups had superior pain relief and a more rapid recovery. Thus, no clinical difference between a traditional and a selective NSAID was found. Jacobson et al[32] also compared traditional NSAID and a Coxib for pain management during the first 4 days after knee arthroscopy. They found no differences between a selective and a traditional NSAID. Brattwall et al[33] conducted a prospective study in 100 women in the American Society of Anesthesiology Physical Status 1–2 who were randomized to oral etoricoxib 120 mg or sustained release oral tramadol. Overall, pain was well controlled, but the mean visual analog pain score was significantly lower among patients in etoricoxib group evaluated during the entire 7-day period and satisfaction with pain medication was higher in those receiving etoricoxib. Patients receiving tramadol reported significantly more side effects.

It seems reasonable to conclude that acetaminophen, NSAIDs, and selective Coxibs are safe and efficacious analgesics for pain management after ambulatory surgical procedures. They reduce pain and improve recovery without major side effects. They seem to have lower GI side effects as compared with opioid analgesics, thus facilitating resumption of activities of daily living earlier. The risk for bleeding complication seems

to be minimal, even when Coxibs are administered before cosmetic surgical procedures. IV acetaminophen is safe and effective, and rectal acetaminophen is less reliable probably because of its variable absorption. It seems, however, reasonable to suggest that the NSAIDs are more effective as compared with acetaminophen as a sole agent. However, the combination has superior analgesic efficacy compared with either drug given alone. Whether there is any clear clinical difference in analgesic efficacy between the different NSAIDs and Coxibs is debatable.

RISK VERSUS BENEFIT OF ANALGESIC DRUGS

There are several potential side effects associated with the protracted use of NSAIDs.

The commonest and most discussed in the literature include GI bleeding, risk for cardiovascular and cerebral events, and the effects of NSAIDs on tissue and bone healing. Although the risk for major GI side effects associated with the short-term use (2–3 days) of these drugs in the postoperative setting seems to be small, patients with a history of GI bleed should be treated with caution, even for short-term use.

No studies are available on the short-term use of NSAIDs/Coxibs and the risk for cardiovascular events. However, in consideration of the potential harm caused by Coxibs when used for longer periods and the increased risk of cardiovascular events when parecoxib was administered for up to 14 days after coronary bypass surgery would suggest that this class of drugs should preferably be avoided in the patient at risk. On the contrary, ketorolac has been used postoperatively for pain management in the patient with IHD without any significant events. Having said this, there is a small but definite risk even when using NSAIDs in the patient with cardiac disease. Naproxen has been shown to have the lowest risk for cardiovascular events and should be considered in the patients at risk.[34] There is little evidence to support the proposition that an imbalance of thromboxane and prostacyclin resulting from COX-2-specific inhibition increases the risk of cardiovascular events and that this is a class effect. Therefore, it seems wise to consider an alternative approach than NSAIDs/Coxibs in high-risk patients.[35] The combination of 0.1 mg/kg dexamethasone with Coxibs not only results in antiemetic effects but even additive analgesic effects.[36–38] The benefit of short-term use of NSAIDs for postoperative pain management following ambulatory surgery seems, however, significant.

There has been an intensive debate on the potential impact of NSAIDs and Coxibs on wound and bone healing. Specifically orthopedic surgeons, but possibly even plastic surgeons, are concerned about tissue healing and scar formation. There are a number of experimental studies in animals on the potential impact of Coxibs and NSAIDs on bone healing and fracture repair. A recent study by Moreschi et al[39] in rabbits did not find any clinically significant negative effects of Coxibs on bone graft repair. NSAIDs have been used for more than a decade around hip and knee joints using a technique called local infiltration analgesia without any adverse effects. Despite the extensive evidence from studies in elective surgical patients, many orthopedic surgeons remain concerned about using these drugs in patients undergoing fracture surgery.

PLASTIC SURGERY–SPECIFIC SITUATIONS

Reconstructive surgery demands minimal risk for perioperative bleeding, oozing, and hematoma formation that may jeopardize the results. Acetaminophen has minimal effect on bleeding and can thus be used safely and without any such risk, and it can be administered intravenously providing safe and effective analgesia and reducing the need for opioid analgesics. Beer et al[40] suggest that a preventive analgesic strategy is superior to on-demand administration. Pain-induced stress response with consequent increase in blood pressure may worsen bleeding or oozing. Parsa et al[41] studied 695 patients undergoing subpectoral breast augmentation. The patients were randomized to receive 400 mg celecoxib or placebo 30 minutes before surgery. Patients who received 400 mg of celecoxib 30 minutes before surgery required significantly fewer opioid analgesics after the operation than those given placebo. Side effects were, however, not reported. Sun et al[42] performed a prospective randomized study in 120 healthy patients who underwent plastic surgery. Patients were randomized into 3 groups of 40 patients each. Two groups received 400 mg celecoxib before or after surgery, and 1 group received placebo. Study medications were administered until day 3 after surgery, and the patients were followed up for 1 week. Compared with the control group, the celecoxib groups had significantly lower postoperative pain and need for opioid analgesics during the first 3 postoperative days. Recovery of bowel function and normal activities occurred earlier in the celecoxib groups.

In addition, patient satisfaction with pain management and quality of recovery were significantly better in the celecoxib (versus control) groups. There was no increase in bleeding, and there were no significant differences between the Coxib groups. Pain management with a combination of acetaminophen 1 g and ibuprofen 400 mg orally after the end of surgery has been shown to be superior compared with acetaminophen-codeine combination following skin procedures, such as Mohs micrographic surgery and reconstruction.[43] Forget et al[44,45] recently published a study with retrospectively collected data, suggesting that the intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. There are ongoing studies looking at a new generation of Coxibs with nitric oxide–releasing capacity that may improve cardiovascular safety.[46]

CONCLUSIONS

Acetaminophen and NSAIDs/Coxibs are effective components of a multimodal pain management strategy. Acetaminophen in standard recommended dose of 1 g 4 times daily is a safe and cost-effective. The Food and Drug Administration safety alert on the dose of acetaminophen needs to be taken into account and the benefit versus risk assessed on an individual basis. NSAIDs/Coxibs are potent analgesics and have an additive effect when combined with acetaminophen. NSAIDs are contraindicated in patients with several comorbidities, and they have many side effects. However, in otherwise healthy patients undergoing ambulatory surgery, including those having plastic surgery and other cosmetic procedures, the risks are likely to be low and the analgesic benefits are significant. In contrast, Coxibs have a minimal risk for bleeding, oozing, and hematoma formation; have a lower risk for GI side effects; and are better tolerated by patients with mild asthma. However, the risk for thromboembolic side effects, including major adverse cardiac events, prevents their use in patients with IHD or a history of thrombotic stroke/transient ischemic attack. Acetaminophen and NSAID/Coxib started before or early during the postoperative period are today well established and proven to be safe in clinical practice. These drugs in combination with other nonopioid analgesics could prove to be beneficial and improve pain management following plastic and reconstructive surgery. These can be combined with nonopioid adjuncts, thus improving pain management.

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