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Cyclooxygenase-2 Inhibitors in Postoperative Pain Management

Current Evidence and Future Directions

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NONSTEROIDAL antiinflammatory drugs (NSAIDs) have been shown to reduce pain and opioid consumption and often accelerate recovery after surgery. However, perioperative inhibition of prostaglandin synthesis by NSAIDs may cause complications, including renal injury, gastric ulceration, and bleeding. Recent molecular studies distinguishing between constitutive cyclooxygenase-1 (COX-1) and inflammation-inducible cyclooxygenase-2 (COX-2) enzymes have led to the exciting hypothesis that the therapeutic and adverse effects of NSAIDs could be uncoupled. The purpose of this article is to review the mechanistic differences between nonselective NSAIDs and selective COX-2 inhibitors (COX-2Is) and to examine currently available COX-2I clinical trials to consider the role of these drugs in postoperative pain management.

Safety and Analgesic Efficacy of NSAIDs

The administration of NSAIDs is one of the most common nonopioid analgesic techniques currently used for postoperative pain management.[1] The efficacy of NSAIDs for postoperative pain has been repeatedly demonstrated in many analgesic clinical trials.[2,3] The efficacy of traditional NSAIDs can be summarized by results from recent meta-analyses of postoperative single-dose trials showing numbers needed to treat (to obtain one patient with at least 50% pain relief) of 2.6 for 10 mg oral ketorolac,[4] 2.4 for 1,200 mg oral acetylsalicylic acid,[5] and 2.4 for 400 mg oral ibuprofen.[6] Unlike opioids, which preferentially reduce *spontaneous* postoperative pain,[7,8] NSAIDs have comparable efficacy for both spontaneous *and* movement-evoked pain,[9–11] the latter of which may be more important in causing postoperative physiologic impairment.[12,13] Furthermore, NSAIDs have been shown to reduce postoperative opioid consumption[14,15] and accelerate postoperative recovery[16,17] after certain types of surgery and are thus thought to be an important component of balanced postoperative analgesic regimens.[18]

The majority of data about adverse effects of NSAIDs come from the setting of chronic use for arthritis.[19,20] However, perioperative inhibition of cyclooxygenase (also called prostaglandin H synthase) by NSAIDs may also cause serious complications, including renal injury, gastric ulceration, and excessive bleeding.[21] Brief perioperative NSAID use in healthy adults does not seem to cause important renal dysfunction,[22] but clinicians continue to be cautioned by occasional but recurring reports of perioperative NSAID-related renal failure.[23–28] Similarly, cases of gastrointestinal ulceration or bleeding have been reported after brief NSAID use,[29–33] making this an important risk to consider when using NSAIDs for postoperative pain. Finally, the potential for excessive, and infrequently catastrophic, perioperative blood loss due to NSAID use has been well documented as yet another hazard of these drugs.[34–38] Careful patient screening for renal dysfunction, gastritis, gastric ulcers, or bleeding diathesis and judicious administration of NSAIDs may largely prevent these major complications. Rare NSAID-related problems, which are also thought to be due to cyclooxygenase inhibition, include hepatocellular injury,[39] asthma exacerbation, anaphylactoid reactions, tinnitus, and urticaria.[40]

Mechanisms of Analgesia and NSAID-related Adverse Effects

Traditional NSAIDs comprise a chemically diverse[41] group of compounds (*e.g.*, salicylates, benzothiazines, and indoleacetic, pyrrolacetic, and propionic acids)

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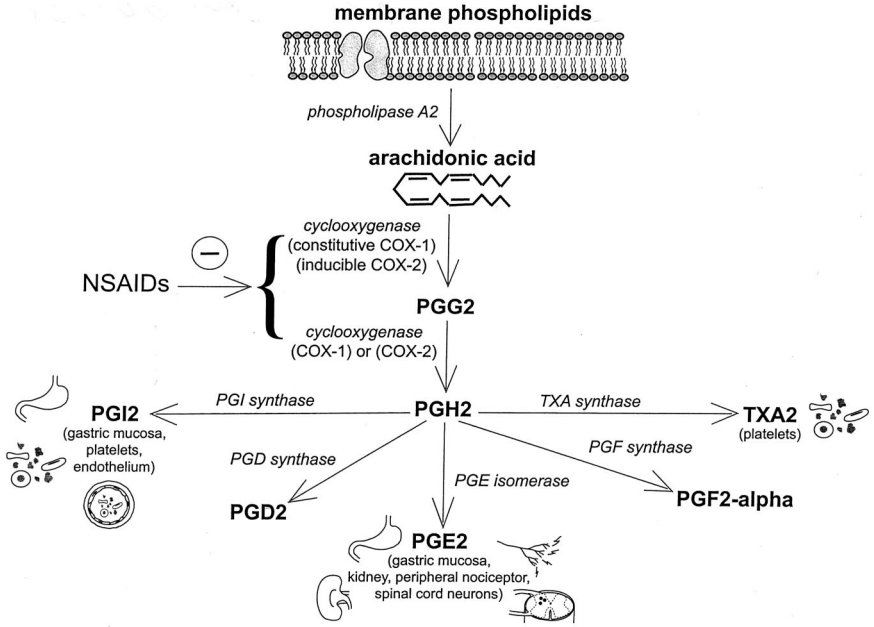

Fig. 1. The role of cyclooxygenase (COX) in prostaglandin (PG) synthesis. Prostaglandins (PGD_2, PGE_2, PGF_2-α, and PGI_2) and thromboxanes (TXA_2), which are important in inflammation and homeostasis, are products of a biochemical cascade by which membrane phospholipids are converted to arachidonic acid, then to intermediate prostaglandins (PGG_2 and PGH_2) by cyclooxygenase, and to their final products by a series of synthases. NSAID = nonsteroidal antiinflammatory drug. Adapted from Myoshi.[41]

which, among other actions, inhibit prostaglandin synthesis[42] by competing with arachidonic acid for binding to the cyclooxygenase active site.[43] Until recently, NSAIDs have been thought mainly to suppress the peripheral nociceptive manifestations of postinjury inflammation.[44] After the conversion of membrane phospholipids to arachidonic acid by phospholipase A_2 in the periphery, cyclooxygenase converts arachidonic acid to the cyclic endoperoxide prostaglandin G_2 (fig. 1) and then acts as a peroxidase to reduce prostaglandin G_2 to the cyclic endoperoxide prostaglandin H_2.[41] Several synthases then convert prostaglandin H_2 to other prostaglandins (*e.g.*, prostaglandin D_2, prostaglandin E_2, prostaglandin F_2-alpha, prostaglandin I_2) and to thromboxane A_2.[45] It has been observed that cyclooxygenase inhibition results in shunting of arachidonic acid to lipoxygenase pathways, resulting in increased leukotriene synthesis, a putative mechanism of NSAID-induced bronchospasm.[41] NSAIDs are thought to reduce postoperative pain by suppressing cyclooxygenase-mediated production of prostaglandin E_2, which is thought to be the primary inflammatory prostaglandin that directly activates and also up-regulates the sensitivity of peripheral nociceptors to cause pain.[41] Prostaglandins have also been shown to play a role in spinal nociception,[46–48] thus contributing to a growing body of evidence supporting a spinal analgesic mechanism of NSAIDs.[49] NSAID-mediated suppression of prostaglandins and thromboxanes, which play a homeostatic role in the stomach (prostaglandin E_2 and prostaglandin I_2),[50] kidney (prostaglandin E_2),[51] and platelets (prostaglandin I_2 and thromboxane A_2),[52] is also thought to be the primary mechanism by which NSAIDs cause some of the adverse effects described above. In addition to these three major complications, inhibition of prostaglandin synthesis by NSAIDs is also thought to be the primary mechanism underlying NSAID-induced asthma[53] and the suppression of heterotopic bone formation.[54]

COX-1 and COX-2 Isoforms of Cyclooxygenase

Subsequent to cloning the gene that encodes for cyclooxygenase in 1988,[55] several studies yielded the discovery of a second form of cyclooxygenase and distinguished between the constitutive COX-1 and the inducible COX-2 isoforms of cyclooxygenase.[56,57] The advent of new selective COX-2Is has allowed the investigation of differential inhibition of COX-1 *versus* COX-2[58] such that NSAIDs, new and old, can be evaluated[59–61] with respect to their COX-1/COX-2 inhibitory profile (table 1). The data shown in table 1 indicate that all NSAIDs have at least some effect on both COX-1 and COX-2 isoenzymes and that there are, as yet, no specific values that define a drug as a purely selective COX-2 inhibitor. COX-1 is active and present at a constant concentration in most tissues, particularly in the kidney, stomach, and platelets, where it plays a homeostatic and protective role through the production of prostaglandin E_2 and prostaglandin I_2.[62] COX-2, however, is normally present in only very low concentrations but is induced peripherally under conditions of inflammation.[63] This functional distinction has led to the exciting hypothesis that selective COX-2Is could uncouple the therapeutic and adverse effects of traditional NSAIDs. However, it is important to note that some exceptions do exist, *i.e.*, COX-2 plays a homeostatic role in the renal medulla, and COX-1 may produce some prostaglandins that contribute to inflammation.[41] Also of great interest in pain management, recent work has shown that COX-2 is constitutively expressed in

Table 1. COX-1 *versus* COX-2 Selectivity of Various NSAIDs

Drug	COX-1 IC_{50}, μM	COX-2 IC_{50}, μM	COX-2/COX-1 IC_{50} Ratio	Assay Model
Nonselective NSAIDs				
Piroxicam[59]	0.0005	0.3	600	Cultured animal cells
Aspirin[59]	1.67	278	166	Cultured animal cells
Indomethacin[59]	0.028	1.68	60	Cultured animal cells
Ketorolac[124]	0.00001	0.00007	7	Purified COX *in vitro*
Ibuprofen[125]	12	80	6.7	Human monocytes
Diclofenac[59]	1.57	1.1	0.7	Cultured animal cells
COX-2 inhibitors				
Meloxicam[60]	4.8	0.43	0.09	Human whole blood
Nimesulide[60]	9.2	0.52	0.06	Human whole blood
Celecoxib[61]	6.3	0.96	0.15	Human whole blood
Rofecoxib[61]	18.8	0.53	0.028	Human whole blood

COX = cyclooxygenase; IC_{50} = drug concentrations that inhibit COX-1 or COX-2 activity by 50%; NSAID = nonsteroidal antiinflammatory drug. Modified from Vane *et al.*[62]

brain and spinal cord and is further up-regulated after persistent noxious inputs such that spinal COX-2 inhibition may be an important mechanism for reducing postinjury hyperalgesia.[49] Finally, COX-2 inhibition results in selective suppression of prostaglandin I_2 without affecting thromboxane A_2,[41] and this imbalance may explain the potential for cardiovascular toxicity discussed in the section entitled "Safety of Selective COX-2 Inhibitors in the Treatment of Chronic Arthritis."

Evidence Suggesting Potential Advantages of COX-2 Inhibitors

Administration of aspirin to arthritis patients resulted in decreased platelet aggregation, whereas the COX-2I celecoxib failed to inhibit platelet aggregation.[64] Consistent with animal studies showing that COX-1 inhibition but not COX-2 inhibition leads to gastric ulceration,[65,66] multicenter arthritis trials have reported decreased incidences of gastrointestinal ulceration with COX-2Is in comparison with nonselective NSAIDs.[67,68] Although these data do not come from the postoperative setting, they do provide further support for the theoretical advantages of COX-2Is.

Safety of Selective COX-2 Inhibitors in the Treatment of Chronic Arthritis

The majority of postmarketing data about COX-2Is comes from experience with celecoxib and rofecoxib, which were approved in the United States in 1998 and 1999, respectively.[69] Other COX-2Is available in Europe include meloxicam and nimesulide.[41] The COX-2Is nimesulide and meloxicam were marketed in Europe long before the discovery of COX-2 and have since been used as molecular precursors for the development of newer COX-2Is.[62] Currently, the major indication of chronic COX-2I use is for the treatment of arthritic pain, although early studies may suggest promise for the prevention of colorectal cancer[70] and Alzheimer disease.[71] Evidence gathered to date suggests that COX-2Is are safer than traditional NSAIDs with respect to gastrointestinal ulceration and bleeding but not renal dysfunction, and furthermore, COX-2Is may confer increased risk for cardiovascular events (*e.g.*, cerebrovascular accident, angina, or myocardial infarction).[69] Preclinical studies demonstrating the role of COX-2 in the kidney have been echoed by human data indicating that COX-2Is can cause sodium retention and decreased glomerular filtration rate and thus warrant similar precautions that are followed for traditional NSAIDs.[72] Gastrointestinal safety data comes largely from two studies, the Vioxx Gastrointestinal Outcomes Research trial (VIGOR)[67] and the Celecoxib Long-term Arthritis Safety Study (CLASS).[68] In the VIGOR trial, rofecoxib was shown to cause a significantly lower incidence of upper gastrointestinal perforation, ulceration and bleeding as compared to naproxen.[67] In the CLASS study, there was no difference in gastrointestinal toxicity between celecoxib and traditional NSAIDs across patients who were also taking low-dose aspirin; however, in patients not taking aspirin, celecoxib did demonstrate a lower incidence of symptomatic ulcers and ulcer complications compared to traditional NSAIDs.[68] It was suggested that aspirin's gastrointestinal risks eliminated celecoxib's benefits.[68] Important recent reports have suggested that COX-2Is cause an increased risk of thrombotic cardiovascular events.[67,69] It has been postulated that COX-2Is may unfavorably alter the thromboxane-prostacyclin balance by inhibiting the vasoprotective prostacyclin (prostaglandin I_2) but not the procoagulant thromboxane (thromboxane A_2).[69] In the VIGOR trial, rofecoxib caused a fourfold increase in the incidence of myocardial infarction compared to naproxen,[67] whereas no increase in risk was observed for celecoxib in the CLASS trial.[68] However, in the CLASS study, 22% of patients were taking low-dose aspirin for cardioprotection, and this trial did not include patients with rheumatoid arthritis,

who have an increased risk of cardiovascular complications.[68] This remains a critical issue that requires further investigation, and until resolved, the potential for cardiovascular toxicity should be considered when using COX-2Is in patients at risk for coronary artery disease. Using the example that even brief perioperative β blockade may significantly reduce mortality,[73] the potential for postoperative COX-2I administration, however brief, to cause cardiovascular complications must be addressed. Further concerns regarding potential cardiovascular effects of COX-2Is are raised by a recent study in hypertensive osteoarthritis patients demonstrating that the COX-2I rofecoxib but not the NSAID namebutone increased nocturnal blood pressure.[74]

Selective COX-2 Inhibitors and Postoperative Pain

In contrast to chronic treatment of arthritis, routine perioperative pain management generally occurs over a period of less than 4 weeks. However, surgery is associated with a set of special situations and problems, including blood loss, fluid shifts, risks of infection and thrombosis, and concomitant administration of anesthetic, analgesic, anticoagulant, and antibiotic drugs. For these reasons, the study and implementation of COX-2Is in the setting of perioperative pain require a unique perspective.

Perioperative Clinical Trials of COX-2Is

Literature searches of perioperative analgesic clinical trials of COX-2Is were conducted using the Cochrane Controlled Trials Register (third quarter 2002) and MEDLINE Database (1966 to February 2003). The database search strategy involved a Boolean search of [celecoxib OR etoricoxib OR flosulide OR meloxicam OR nimesulide OR parecoxib OR rofecoxib OR valdecoxib] AND [postoperative pain OR surgery OR surgical] AND [randomized controlled trials]. Trials reported in abstract form at recent scientific congresses were not included, given their preliminary nature and sometimes limited peer review. It has been well recognized that the use of a placebo control in analgesic trials serves to minimize the risk of false-positive and false-negative results.[75,76] Only double-blind, randomized, placebo-controlled trials were evaluated in this review for these reasons. For differing measures of analgesic efficacy and side effects across these trials, statistically significant differences ($P < 0.05$) between treatments (*e.g.*, COX-2I, NSAID comparator, placebo) were reported in this review. Most studies use multiple analgesic efficacy measures (*e.g.*, analgesic use, pain intensity, pain relief). Only the outcome measure that demonstrated a difference was reported on in studies showing significant differences between treatment groups.

The above database search yielded a total of 27 publications of COX-2I trials, one of which described 6 trials, for a total of 32 controlled trials reported (table 2). These included 25 single-dose and 7 multidose trials (number of trials/drug) of rofecoxib (19), celecoxib (6), parecoxib (5), valdecoxib (3), nimesulide (1), and meloxicam (1). Some trials included more than one COX-2I among their treatment arms. Surgical procedures studied in these trials included minor oral surgery, gynecologic surgery, prostatectomy, lumbar discectomy, spinal fusion, and major joint arthroplasty. Reported efficacy measures also varied across studies and included pain intensity, pain relief, and consumption of other analgesics (table 3).

Analgesic Efficacy

Of the 19 rofecoxib trials, 17 demonstrated superior efficacy of rofecoxib to placebo,[77–88] whereas two trials showed no difference.[89,90] Five of the six celecoxib trials showed superiority to placebo,[81,85,91–93] and one showed no difference.[94] Parecoxib (the parenteral prodrug of valdecoxib),[95–99] valdecoxib,[80,100,101] nimesulide,[102] and meloxicam[103] were found to be superior to placebo in all reported trials. A recent meta-analysis of five rofecoxib trials that investigated 1,118 patients (of whom 211 received placebo and 464 received 50 mg rofecoxib) reported a number needed to treat of 2.3.[104] Of 23 trial comparisons with nonselective NSAIDs (17), acetaminophen (3), or opioids (3), 13 NSAID[81–83,92,97,99,102] and 1 opioid[91] comparator were no different than the studied COX-2I (table 4). The studied COX-2I was observed to be more efficacious than the comparator NSAID[79] or opioid[78,91,97] in four comparative trials and less efficacious in two trials.[81,93] It should be noted that the reported comparative studies are mostly single-dose trials that do not necessarily address relative potency of the drugs being compared. Thus, although one drug may be more potent than another, that drug can only be said to be more efficacious if optimal doses of each drug are being compared. Three trials compared COX-2Is to each other, two of which showed that rofecoxib is more efficacious than celecoxib,[81,85] and the third of which demonstrated that valdecoxib is more efficacious than rofecoxib.[80] One orthopedic trial by Reuben *et al.*[86] showed that 50 mg rofecoxib given 1 h preoperatively was more effective at reducing postoperative pain than the same dose given 15 min postoperatively, suggesting that, as with traditional NSAIDs, COX-2Is may have preemptive analgesic effects.

Postoperative Analgesic Dose–Response Studies

The analgesic dose–response relation of COX-2Is has been studied in trials of rofecoxib,[83,84] parecoxib,[95–99] valdecoxib,[100,101] and nimesulide[102] (table 5). Rofecoxib was studied at 7.5, 12.5, 25, 50, 100, and 200 mg orally

Table 2. Double-blind, Randomized, Placebo-controlled Postoperative COX-2 Inhibitor Trials

Drug/Reference	Study Drug, Dose, No. of Patients	Comparators, Dose, No. of Patients	Surgery	Duration/Timing of Dose	Analgesic Efficacy Results
Rofecoxib (oral)					
77	R, 50 mg, 31	PLC, 30	Lumbar disc	Hours before surgery + 30 min before surgery (2 doses)	R > PLC
78	R, 50 mg, 182	PLC, 31 COD, 60 mg + A, 600 mg, 180	Oral surgery	Postoperatively as soon as moderate to severe pain (1 dose)	R > COD + A > PLC
79	R, 50 mg, 121	PLC, 63 D, 50 mg TID, 121	Oral surgery	R: immediately after surgery (1 dose) D: immediately after surgery TID (3 doses)	R > D; R > PLC
80	R, 50 mg, 82 V, 40 mg, 80	PLC, 41	Oral surgery	Within first 4 h after surgery (1 dose)	V > R > PLC
81	R, 50 mg, 90 CEL 200 mg, 91	PLC, 45 I, 400 mg, 46	Oral surgery	Postoperatively as soon as mod-severe pain (1 dose)	R = I > CEL > PLC but R has longer duration than I
82	R, 50 mg, 50	PLC, 50	Oral surgery	Postoperatively as soon as moderate to severe pain (1 dose)	R = I > PLC but R has longer duration than I
83 (6 trials)	1. R, 50 mg, 32; R 250, 8; R 500, 20	1. PLC, 32; I, 400 mg, 20	Oral surgery	Postoperatively as soon as	R 25, 50, 100, and 200 mg = I/N > PLC
	2. R, 7.5 mg, 39; R 25, 37; R 50, 38, R 100, 39	2. PLC, 39; NAP, 550 mg, 39		moderate to severe pain (1 dose)	R 50 > R25
	3. R, 12.5 mg, 72; R 25, 72; R 50, 72	3. PLC, 48; NAP, 550 mg, 49			
	4. R, 50 mg, 50	4. PLC, 50; I, 400 mg, 51			
	5. R, 50 mg, 50; R 100, 52; R 200, 50	5. PLC, 50; NAP, 550 mg, 52			
	6. R, 50 mg, 56; R 100, 55	6. PLC, 56; I, 400 mg, 56			
84	R, 50 mg, 110 (single dose) R, 25 mg, 56 (multidose) R, 50 mg, 54 (multidose)	PLC, 53 (single dose) NAP, 550 mg, 55 (single dose) PLC, 53 (multidose)	Major orthopedic surgery	Single dose: postoperative day 1, within 4 h of stopping routine postoperative analgesics Multidose: daily from postoperative day 2 (4 doses)	Single dose: R = N > PLC Multidose: R 50 > PLC
85	R, 50 mg, 20 CEL, 200 mg, 20	PLC, 20	Spinal fusion	1 h before surgery (1 dose)	R > CEL > PLC
86	R, 50 mg, 20 preincision R, 50 mg, 20 postincision	PLC, 20	Arthroscopic meniscectomy	Preincision: 1 h before surgery (1 dose) Postincision: 15 min after surgery (1 dose)	R preincision > R postincision > PLC
87	R, 25 mg, 50	PLC, 50	TKA	Daily starting 3 d before surgery (5 doses)	R > PLC
88	R, 50 mg, 30	PLC, 30	ENT surgery	1 h before surgery	R > PLC
89	R, 50 mg, 15	PLC, 15	Prostatectomy	1 hour before surgery (1 dose)	R = PLC
90	R, 0.625 mg/kg + A, 20 mg/kg, 40	PLC + A, 20 mg/kg, 18 I, 5 mg/kg + A, 20 mg/kg, 40	Tonsillectomy	1 h before surgery (1 dose)	I + A > PLC + A, R + A = PLC + A
Celecoxib (oral)					
81	CEL, 200 mg, 91 R, 50 mg, 90	PLC, 45 I, 400 mg, 46	Oral surgery	Postoperatively as soon as moderate to severe pain (1 dose)	R = I > CEL > PLC but R has longer duration than I
85	CEL, 200 mg, 20 R, 50 mg, 20	PLC, 20	Spinal fusion	1 h before surgery (1 dose)	R > CEL > PLC
91	CEL, 200 mg, 141 (single dose)	PLC, 141 (single dose) H, 10 mg + A, 1 g, 136 (single dose)	Ambulatory orthopedic surgery	Single-dose: within 24 h after surgery Multidose: TID from 8 h after 1st dose for up to 5 days	Single dose: CEL = H + A > PLC Multidose: CEL > H + A
	CEL, 200 mg, 185 (multidose)	H, 10 mg + A, 1 g, 181 (multidose)			
92	CEL 200 mg, 37	PLC, 36 I, 600 mg, 30	Oral surgery	8 h before surgery and 1 h before surgery (2 doses)	CEL = I > PLC
93	CEL, 200 mg, 74	PLC, 26 I, 400 mg, 74	Oral surgery	Postoperatively as soon as moderate to severe pain	I > CEL > PLC
94	CEL, 200 mg, 28 CEL + A, 200 mg + 2 g, 28	PLC, 28 A, 2 g, 28	ENT surgery	30–60 min before surgery (1 dose)	CEL + A > CEL, CEL + A > PLC, CEL = PLC

Table 2. Continued

Drug/Reference	Study Drug, Dose, No. of Patients	Comparators, Dose, No. of Patients	Surgery	Duration/Timing of Dose	Analgesic Efficacy Results
Parecoxib (intramuscular/ intravenous)					
95	PAR, 20 mg IM, 51 PAR, 20 mg IV, 50 PAR, 40 mg IM, 50 PAR, 40 mg IV, 51	PLC, IM/IV (double dummy), 51	Oral surgery	Postoperatively as soon as moderate to severe pain (1 dose)	PAR 40 IV and PAR 40 IM = K > PLC but PAR has longer duration
96	PAR, 20 mg IV, 56 PAR, 40 mg IV, 56 PAR, 80 mg IV, 56	PLC, IV, 56	Oral surgery	30–45 min before surgery (1 dose)	PAR > PLC (analgesic ceiling at 40 mg)
97	PAR, 20 mg IV, 43 PAR, 40 mg IV, 42	PLC, IV, 39 K, 30 mg IV, 42 Morphine, 4 mg IV, 42	TKA	Postoperative day 1, within 6 h of stopping PCA opioid (1 dose)	PAR 40 = K 30; PAR 40 > PLC PAR 40 > morphine 4
98	PAR, 20 mg IV, 19 PAR, 40 mg IV, 18	PLC, IV, 18	Gynecologic surgery	Postoperatively at time of 1st analgesic request, 12 h and 24 h after surgery (3 doses)	PAR 20 = PAR 40 > PLC
99	PAR, 20 mg IV, 39 PAR, 40 mg IV, 38	PLC, IV, 42 K, 30 mg IV, 41 Morphine, 4 mg IV, 42	Gynecologic surgery	Postoperatively as soon as moderate to severe pain after discontinuing PCA morphine	PAR 20 = PAR 40 = K 30 > morphine > PLC
Valdecoxib (oral)					
80	V, 40 mg, 80 R, 50 mg, 82	PLC, 41	Oral surgery	Within first 4 h after surgery (1 dose)	V > R > PLC
100	V, 20 mg, 73 V, 40 mg, 73	PLC, 71	THA	BID starting 1–3 h before surgery (4 doses)	V 20 mg/kg and V 40 mg/kg > PLC
101	V, 10 mg, 56 V, 20 mg, 113 V, 40 mg, 114 V, 80 mg, 112	PLC, 112	Oral surgery or bunionectomy	60–75 min before surgery	V 80 = V 40 > V 20 > V 10 > PLC
Nimesulide (oral)					
102	NIM, 100 mg, 35 NIM, 200 mg, 34	PLC, 33 Niflumic acid, 250 mg, 32	Oral surgery	Postoperatively as soon as moderate to severe pain (1 dose)	Niflumic acid = NIM 100 = NIM 200 > PLC
Meloxicam (oral)					
103	M, 15 mg rectally, 18	PLC, rectally, 18	Abdominal hysterectomy	Preoperatively after induction of anesthesia (1 dose)	M > PLC

A = acetaminophen; BID = twice daily; CEL = celecoxib; COD = codeine; D = diclofenac; ENT = ears, nose, and throat; H = hydrocodone; I = ibuprofen; IM = intramuscular; IV = intravenous; K = ketorolac; M = meloxicam; NAP = naproxen; NIM = nimesulide; PAR = parecoxib; PCA = patient-controlled analgesia; PLC = placebo; R = rofecoxib; THA = total hip arthroplasty; TID = three times daily; TKA = total knee arthroplasty; V = valdecoxib; =, <, > denote statistically no different, lesser, or greater.

in the six controlled trials reported by Morrison *et al.*[83], and, whereas 50 mg was significantly more efficacious than 7.5, 12.5, and 25 mg, no differences were noted between 50 mg and 100 or 200 mg, suggesting an analgesic ceiling at approximately 50 mg. During the multidose segment (postoperative days 2–5) of the orthopedic rofecoxib trial by Reicin *et al.*,[84] daily doses of 50 mg rofecoxib but not 25 mg resulted in significantly less consumption of supplemental analgesic medication (hydrocodone–acetaminophen). In the parecoxib trial by Desjardins *et al.*,[96] 40 mg intravenously was more efficacious than 20 mg but indistinguishable from 80 mg. Rasmussen *et al.*[97] also observed that 40 mg parecoxib was more effective than 20 mg after knee surgery, but higher doses were not studied. Postoperative differences between 20 and 40 mg intravenous parecoxib were not as pronounced in the oral surgery study by Daniels *et al.*[95] Camu *et al.*[100] and Tang *et al.*[98] showed no difference in pain scores or analgesic consumption between 20 and 40 mg oral valdecoxib or between 20 and 40 mg intravenous parecoxib in two other postoperative trials. A recent study of valdecoxib by Desjardins *et al.*[101] demonstrated dose-dependent analgesia between 10 and 40 mg but no difference between 40 and 80 mg, suggesting an analgesic ceiling also for valdecoxib. Finally, the oral surgery study by Ragot *et al.*[102] showed no difference between 100 and 200 mg nimesulide. In summary, these data suggest that COX-2Is, at least in the case of rofecoxib, parecoxib, and valdecoxib, have a postoperative analgesic dosage ceiling similar to that of traditional NSAIDs[41] (table 5).

Safety of COX-2Is in the Postoperative Setting

Evaluation and reporting of adverse effects varied considerably across studies from no measures at all to spontaneous patient reporting to specific measures of nausea, vomiting, or blood loss (table 3). All but six trials reported no difference between the studied COX-2I and

Table 3. Efficacy and Safety Measures Used in Postoperative COX-2 Inhibitor Trials

Drug/Reference	Efficacy Measure	Adverse Effect Assessment
Rofecoxib		
77	Analgesic use	Spontaneous patient reporting
78	Pain relief	Physical examination and spontaneous patient reporting
79	Pain relief	Spontaneous patient reporting
80	Pain intensity	Physical examination
81	Pain relief	Laboratory studies, physical examination, and spontaneous patient reporting
82	Pain intensity and pain relief	Laboratory studies, physical examination, and spontaneous patient reporting
83	Pain relief	Not specified
84	Pain intensity and relief (single dose) Analgesic use (multidose)	Spontaneous patient reporting
85	Pain intensity and analgesic use	Intraoperative blood loss
86	Pain intensity	Not specified
87	Pain intensity	Intraoperative and postoperative blood loss; hemoglobin; international normalized ratio; stool guaiac
88	Pain intensity	Spontaneous patient reporting
89	Pain intensity	Nausea and vomiting
90	Analgesic use	Intraoperative blood loss, postoperative vomiting and postoperative hemorrhage
Celecoxib		
81	Pain relief	Laboratory studies, physical examination, and spontaneous patient reporting
85	Pain intensity and analgesic use	Intraoperative blood loss
91	Pain intensity	Spontaneous patient reporting
92	Pain intensity	Not specified
93	Pain intensity	Spontaneous patient reporting
94	Pain intensity	Postoperative nausea/vomiting
Parecoxib		
95	Pain intensity and pain relief	Laboratory studies and physical examination
96	Pain intensity	Laboratory studies and physical examination
97	Pain intensity	Spontaneous patient reporting
98	Analgesic use	Laboratory studies and physical examination
99	Pain intensity and pain relief	Laboratory studies and physical examination
Valdecoxib		
80	Pain intensity	Physical examination
100	Analgesic use	Laboratory studies and physical examination
101	Pain intensity	Laboratory studies and physical examination
Nimesulide		
102	Pain intensity and pain relief	Not specified
Meloxicam		
103	Pain intensity	Nausea and sedation

placebo or active comparator in the overall incidence of adverse effects. However, it should be noted that all COX-2I trials included here were designed and statistically powered with analgesia, not adverse effects, as the primary outcome. One trial did not report adverse effects,[86] and in two trials, a significantly greater incidence of postdental extraction alveolitis ("dry socket") was observed with 50 mg oral rofecoxib as compared to placebo.[80,83] Four trials reported significantly fewer adverse effects with the studied COX-2I in comparison with placebo or the active comparator.[78,81,91,94] Only three perioperative studies incorporated specific measures of blood loss in the trial design (table 3), and none of these three reported any difference in blood loss between the studied COX-2I and placebo.[85,87,90] In addition to adverse effects reported in the postoperative trials cited in this review, single isolated cases of celecoxib-induced oliguria[105] and rofecoxib-induced aseptic meningitis[106] after brief postoperative use have been recently reported.

Side Effect Profiles from Postoperative COX-2I Trials

Common (5–28%) treatment-emergent signs and symptoms associated with COX-2Is (rofecoxib, parecoxib, and valdecoxib) from postoperative clinical trials that tabulated adverse effects[79,80,84,95–97,100] include headache, nausea, vomiting, dizziness, and postdental extraction alveolitis. However, only one of these, postdental extraction alveolitis, occurred more frequently with rofecoxib than with placebo,[80] which was also observed in one of the trials reported by Morrison *et al.*[83]

Summary

Postoperative pain management has gone through revolutionary innovations over the past century with the

Table 4. Placebo-controlled Trials Comparing COX-2Is to Nonselective NSAIDs

Drug/Reference	NSAID Comparator	Primary Outcome Measure of Trial	Analgesic Efficacy Results	Adverse Effect Results*
Rofecoxib (oral)				
79	Diclofenac	Pain relief	R > D	R = D
81	Ibuprofen	Pain relief	R = I > CEL	R = I = CEL
82	Ibuprofen	Pain intensity and relief	R = I	R = I
83 (6 trials)	1. Ibuprofen 2. Naproxen 3. Naproxen 4. Ibuprofen 5. Naproxen 6. Ibuprofen	Pain relief	R = I; R = N	R = I; R = N
84	Naproxen	Pain intensity and relief	R = N	R = N
90	Ibuprofen	Analgesic use	I + A = R + A	I + A = R + A
Celecoxib (oral)				
81	Ibuprofen	Pain relief	R = I > CEL	R = I = CEL
92	Ibuprofen	Pain intensity	CEL = I	Not reported
93	Ibuprofen	Pain intensity and relief	I > CEL	I = CEL
Parecoxib (intravenous)				
86	Ketorolac	Pain intensity and relief	PAR = K	PAR = K
88	Ketorolac	Pain intensity	PAR = K	PAR = K
99	Ketorolac	Pain intensity	PAR = K	PAR = K

* Reported trials are designed and statistically powered to detect differences in the primary outcome of pain intensity or relief, not adverse effects.

CEL = celecoxib; COX = cyclooxygenase; D = diclofenac; I = ibuprofen; K = ketorolac; N = naproxen; NSAID = nonsteroidal antiinflammatory drug; PAR = parecoxib; R = rofecoxib; =, <, > denote statistically no different, lesser, or greater.

widespread clinical introduction of systemic and neuraxial opioids, regional local anesthetic techniques, patient-controlled analgesia, and coanalgesic therapies such as NSAIDs.[107] Current needs for improvement in postoperative pain management include (1) more effective relief of pain and suffering for *all* postoperative patients[108,109]; (2) preventing and/or treating other postoperative symptoms (which may or may not be related to analgesic therapies) such as nausea, pruritus, sedation, and cognitive dysfunction[110]; and (3) promoting recovery from surgery by preventing and/or treating postoperative physiologic dysfunction such as atelectasis and ileus.[111,112] Thus, therapeutic improvements in postoperative pain management should advance at least one of these goals without impeding the others. In the interest of relieving postoperative pain for all patients, further attention needs to be given to special populations such as patients undergoing tonsillectomy, ocular procedures, spinal fusion, and other surgeries for which nonselective NSAIDs have a relative contraindication.

Current evidence published to date does not suggest that COX-2Is provide a major advantage over traditional NSAIDs. However, it is possible that their development will lead to specific drugs with a superior therapeutic profile. For example, after oral surgery, valdecoxib was recently shown to be significantly more effective than rofecoxib,[80] which in turn was shown to be more effective than codeine–acetaminophen[78] or diclofenac.[79] It remains to be determined whether these differences in analgesic efficacy can be replicated using multidose trials with equipotent dose comparisons and after other, more painful procedures. However, such observations lead to

Table 5. Postoperative Analgesic Dose–Response Studies

Drug/Reference	Doses Studied	Study Results
Rofecoxib (oral)		
83	7.5, 12.5, 25, 50, 100, and 200 mg	Analgesic ceiling at 50 mg; 50 mg more efficacious than 25 mg
84	25 and 50 mg	50 mg more efficacious than 25 mg
Parecoxib (intravenous)		
95	20 and 40 mg	NS
96	20, 40, and 80 mg	Analgesic ceiling at 40 mg; 40 mg more efficacious than 20 mg
97	20 and 40 mg	40 mg more efficacious than 20 mg
98	20 and 40 mg	NS
99	20 and 40 mg	NS
Valdecoxib (oral)		
100	20 and 40 mg	NS
101	10, 20, 40, and 80 mg	Dose-dependent up to 40 mg; analgesic ceiling at 40 mg
Nimesulide (oral)		
102	100 and 200 mg	NS

NS = no significant difference.

Table 6. Unresolved Questions Regarding the Utility of COX-2Is for Postoperative Pain

- Do COX-2Is demonstrate *preemptive* analgesic efficacy?
- Do COX-2Is cause *clinically* significantly less perioperative *blood loss* than non-selective NSAIDs?
- Do COX-2Is impair postoperative *bone healing* in humans?
- Do COX-2Is cause gastrointestinal *toxicity* in patients at risk (*e.g.*, previous gastric ulceration)?
- Does perioperative use of COX-2Is result in *cardiovascular toxicity* (*e.g.*, hypertension, CVA, MI)?
- Do COX-2Is provide more favorable cost-benefit or cost-effectiveness than non-selective NSAIDs?

COX = cyclooxygenase; CVA = cerebrovascular accident; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug.

the anticipation that future advances in drug development may result in COX-2Is with clinically important advantages over traditional NSAIDs.

Several COX-2I trials have demonstrated an opioid-sparing effect after surgery,[85,100] and comparisons with opioids have reported fewer postoperative side effects.[78,91] Thus, COX-2Is are at least as effective as nonselective NSAIDs in reducing opioid requirements and/or opioid-related adverse effects after surgery. Provided that recent evidence of fewer gastrointestinal complications with COX-2Is from arthritis studies[67,68] holds true in the postoperative setting, it is hoped that patients with gastrointestinal risk factors (*e.g.*, previous gastritis, ulcers), in whom NSAIDs are contraindicated, may safely benefit from the addition of a COX-2I to their postoperative analgesic regimen. Both experimental and clinical evidence suggest that NSAIDs impair bone healing.[113,114] Thus, spinal fusion surgery patients present another group who may be denied the benefits of NSAIDs because of fear of postoperative deleterious effects on bone graft healing. Early evidence from a rabbit model[115] and a small spinal fusion clinical trial[85] suggesting that COX-2Is do not interfere with bone healing has led to the optimistic proposal that COX-2Is may be a useful alternative for these patients.[116] More recent data does in fact support a role for COX-2 in bone healing,[117] and further clinical investigation is needed to address this problem.[118]

Issoui *et al.*[94] were unable to demonstrate any difference in postoperative recovery times across postoperative patients receiving acetaminophen, celecoxib, their combination, or placebo. No study has been reported to date that compares COX-2Is to nonselective NSAIDs with respect to postoperative recovery or postoperative physiologic impairment. Such investigations as have been previously conducted with nonselective NSAIDs[119] are needed to identify whether COX-2Is have any advantage.

Cardiovascular risks of COX-2Is discussed above remain controversial, and more recent evidence suggests that COX-2Is may not confer greater cardiovascular danger than nonselective NSAIDs.[120,121,122] However, comparative postoperative studies that carefully track cardiovascular outcomes are needed to resolve this controversy.

Discovery of the COX-2 enzyme and subsequent development of selective COX-2Is has contributed to a resurgence of therapeutic research in postoperative pain. However, whether these developments have resulted in any tangible improvements in patient care requires further study. Comparative COX-2I trials published to date generally suggest similar analgesic efficacy to nonselective NSAIDs in postoperative pain. Also, these mostly single-dose studies suggest similar safety and tolerability as compared to currently used NSAIDs. Additional data from larger, multicenter, multidose comparative trials could determine whether individual COX-2Is are more efficacious, cost-effective, and/or safe *versus* nonselective NSAIDs with respect to gastric, renal, and coagulation problems and whether COX-2Is confer greater cardiovascular risk in the postoperative setting. Multiple unresolved questions (table 6) remain to be answered. Until then, cost–benefit considerations[123] will likely guide therapeutic choices in the absence of strong evidence supporting any major advantage of COX-2Is.

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