Regional Anesthesia and Pain

NSAID-analgesia, pain control and morbidity in cardiothoracic surgery

[L'analgésie avec des AINS, le contrôle de la douleur et la morbidité en chirurgie cardiothoracique]

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Objective: While narcotics remain the backbone of perioperative analgesia, the adjunctive role of other analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), is being recognized increasingly. This meta-analysis sought to determine whether adjunctive NSAIDs improve postoperative analgesia and reduce cumulative narcotic requirements.

Methods: A comprehensive search was undertaken to identify all randomized trials, in cardiothoracic patients, of NSAIDs plus narcotics *vs* narcotics without NSAIDs. Medline, Cochrane Library, EMBASE, and abstract databases were searched up to September 2005. The primary outcome was visual analogue scale (VAS) pain score. Secondary outcomes included 24-hr cumulative morphine-equivalents, rescue medications required, mortality, myocardial infarction, atrial fibrillation, stroke, renal failure, hospital readmissions, and in-hospital costs.

Results: Twenty randomized trials involving 1,065 patients were included. A significant reduction in 24-hr VAS pain score was found in patients receiving NSAIDs [weighted mean difference (WMD) -0.91 points, 95% confidence interval (CI) -1.48 to -0.34 points]. In addition, patients required significantly less morphine-equivalents in the first 24 hr (WMD -7.67 mg, 95% CI -8.97 to -6.38 mg). No significant difference was found with respect to mortality [odds ratio (OR) 0.19, 95% CI 0.01 to 4.22], myocardial infarction (OR 0.71, 95% CI 0.09 to 5.71), renal dysfunction (OR 0.95, 95% CI 0.37 to 2.46), or gastrointestinal bleeding (OR 0.96, 95% CI 0.13 to 7.09).

Conclusion: In patients less than 70 yr of age undergoing cardiothoracic surgery, the adjunctive use of NSAIDs with narcotic analgesia reduces 24-hr VAS pain score and narcotic requirements.

***Objectif** : Les narcotiques demeurent le pivot de l'analgésie périopératoire, mais le rôle complémentaire d'autres analgésiques, dont les anti-inflammatoires non stéroïdiens (AINS), est de plus en plus reconnu. La présente méta-analyse veut déterminer si les AINS d'appoint améliorent l'analgésie postopératoire et réduisent les besoins cumulatifs de narcotiques.*

***Méthode** : Nous avons recensé toutes les études randomisées sur des narcotiques, complétés ou non par des AINS, réalisées auprès de patients de cardiochirurgie thoracique. Les bases Medline, Cochrane Library, EMBASE et les résumés parus jusqu'à septembre 2005 ont été explorés. Le principal paramètre recherché était le score de douleur à l'échelle visuelle analogique (EVA). Les paramètres secondaires étaient la consommation cumulative, sur 24 h, d'analgésiques en équivalents-morphine, les besoins de médicaments d'appoint, la mortalité, la présence d'infarctus du myocarde, la fibrillation auriculaire, l'accident vasculaire, l'insuffisance rénale, la réadmission hospitalière et le coût de l'hospitalisation.*

***Résultats** : Vingt études randomisées regroupant 1 065 patients ont été retenues. Une réduction significative des scores de douleur, sur 24 h, a été trouvée chez ceux qui recevaient des AINS [différence moyenne pondérée (DMP) -0,91 points, intervalle de confiance de 95 % (IC) -1,48 à -0,34 points]. De plus, les patients ont demandé sensiblement moins d'équivalents-morphine au cours des 24 premières heures (DMP -7,67 mg, IC de 95 % -8,97 à -6,38 mg). Il n'y avait aucune différence significative quant à la mortalité [risque relatif (RR) de 0,19, IC de 95 % 0,01 à 4,22], à l'infarctus du myocarde (RR 0,71, IC de 95 % 0,09 à 5,71), à l'insuffisance rénale (RR 0,5, IC de 95 % 0,37 à 2,46) ou au saignement gastro-intestinal (RR 0,96, IC de 95 % 0,13 à 7,09).*

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***Conclusion** : Chez les patients de moins de 70 ans qui subissent une opération cardiothoracique, l'usage d'AINS d'appoint avec l'analgésie aux narcotiques réduit la douleur et les besoins de narcotiques sur 24 h.*

POSTOPERATIVE analgesia remains a primary concern in patients undergoing cardiothoracic surgery. Thoracotomy, sternotomy and the placement of pleural chest tubes result in considerable pain in the postoperative period. There has been an upsurge of interest in safer alternatives to narcotic treatment of postoperative pain as a monotherapeutic strategy. Many different regimens have been examined, including thoracic epidurals, intrathecal morphine, and non-steroidal anti-inflammatory drugs (NSAIDs).[1–5]

The use of NSAIDs has become increasingly popular in the management of postoperative pain as an adjunct to narcotic use for the purpose of achieving additive analgesia to narcotics, while purportedly reducing the side effects inherent to opioid analgesics such as drowsiness, sedation, constipation, nausea and vomiting, and ileus. Despite the existence of a number of randomized trials of NSAIDs for adjunctive analgesia post-thoracotomy, individually many of these trials lack sufficient statistical power to adequately evaluate potentially clinically important effects. No comprehensive meta-analysis has been published in this area. We therefore sought to determine, through systematic review with meta-analysis, whether NSAIDs adjunctive to either narcotic (opioid) analgesia or regional analgesia reduce postoperative pain, narcotic requirements, morbidity and resource utilization in patients undergoing cardiothoracic surgery.

Methods

Identification of trials

This meta-analysis was performed in accordance with "quality of reports of meta-analyses" (QUOROM) recommendations and according to a protocol that pre-specified outcomes, search strategies, inclusion criteria, and statistical analyses.[6] A search was undertaken in accordance with Cochrane Collaboration recommendations to identify all published or unpublished randomized trials of NSAIDs plus narcotic therapy compared with narcotics alone, or compared with regional anesthetic techniques using narcotic or local anesthetic, in any language. MEDLINE, Cochrane CENTRAL, EMBASE, Current Contents, DARE, NEED, and INAHTA databases were searched from the date of their inception to September 2005. Search terms included variants of *non-steroidal anti-inflammatory agents, cyclooxygenase (COX) inhibitors, cardiac or thoracic surgery, and individual NSAIDs (aspirin, brexidol, choline magnesium trisalicylate, diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, ketotifen, meclofenamate, nabumetone, naproxen, oxaprozin, piroxicam, phenylbutazone, salsalate, sulindac, tiaprofenic acid, tenoxicam, tolmetin)*. Tangential electronic exploration of related articles and hand searches of bibliographies, scientific meeting abstracts, and related journals were also performed.

Inclusion criteria

Studies were included if they met each of the following: 1) randomized allocation to a NSAID-containing analgesic regimen *vs* non-NSAID-containing narcotic or regional analgesic regimen given pre-, intra- or postoperatively to pre-empt pain; 2) adult patients undergoing cardiac or thoracic surgery; 3) reporting at least one pertinent clinical or economic outcome. Patients receiving COX-2 selective NSAIDs were excluded from this analysis. Blinded and unblinded studies were included. Pediatric surgical studies, and studies focused primarily on the management of pericardial effusions or postoperative atrial fibrillation rather than analgesia were excluded. Studies involving regional anesthesia techniques were excluded when the regional block was not offered to both the NSAID and control groups.

Data extraction

Two authors independently identified trials for inclusion and extracted information on demographics, interventions, and outcomes. Authors of included trials were contacted when necessary to clarify data and to identify multiple publications. Two reviewers independently assigned each trial using a Jadad quality score that evaluates randomization, blinding, and completeness of follow-up (maximum score, 5).[7] Disagreements were resolved by consensus.

Endpoints

The primary outcome was defined as the VAS pain score at 24 hr post-surgery. Secondary outcomes included cumulative morphine-equivalents required during the first 24 hr post-surgery and the need for supplementary narcotic rescue analgesia during hospitalization. Other outcomes included postoperative incidence of all-cause mortality, all-cause bleeding, gastrointestinal (GI) bleeding, GI disturbances, blood transfusion requirements, stroke, acute myocardial

infarction, atrial fibrillation, renal failure, 24-hr serum creatinine levels, surgical re-explorations for bleeding, volume of postoperative blood loss, postoperative nausea and vomiting (PONV), sedation, respiratory depression, reintubation of the trachea, heart failure, pleural effusion, readmissions, ileus, wound infections, pneumonia, neurocognitive dysfunction, severe adverse events, and drug withdrawal due to adverse events. Resource utilization outcomes included duration of ventilation, intensive care unit (ICU) length of stay (LOS), hospital LOS, and hospital costs. Visual analogue pain score was recorded as the average score over the first 24 hr post-surgery, or when the former was not available, as the last VAS reported at a time closest to 24 hr. Need for transfusion was defined as the number of patients requiring red blood cell transfusion. Renal failure was defined as a new rise in serum creatinine of > 50%, or decline in creatinine clearance of > 50%, or requirement of dialysis. Duration of ventilation was measured from end of surgery to time of tracheal extubation. Intensive care and hospital LOS were measured from end of surgery to ICU or hospital discharge, respectively. Severe adverse events were defined by the study investigators, and were generally defined as events resulting in fatality or hospitalization, or any event believed to be life threatening or otherwise medically significant. Postoperative nausea and vomiting was defined as emesis or nausea, or emesis alone. Morphine-equivalents were defined by the study authors using generally excepted equivalents: piritramide 1 mg was considered equivalent to morphine sulphate 1 mg, papaveretum 15 mg was considered equivalent to morphine sulphate 10 mg, and meperidine 10 mg was considered equivalent to morphine sulphate 1 mg.[8–11] All other outcomes, including incidence of bleeding, atrial fibrillation, acute myocardial infarction, stroke, sedation, respiratory depression, ileus, wound infections, pneumonia, and neurocognitive dysfunction were defined according to study authors' definitions.

Statistical analysis

Outcomes were analyzed as dichotomous variables, with the exception of VAS pain score, cumulative morphine-equivalents, duration of ventilation, and LOS which were analyzed as continuous variables when the mean and standard deviation were reported. For dichotomous variables, odds ratios and 95% confidence intervals (OR, 95% CI) were calculated. For continuous variables, the weighted mean difference (WMD, 95% CI) was calculated. When significant differences were found for proportions, the absolute risk reduction and number needed-to-treat were calculated.[12] Heterogeneity was explored using the Q-statistic, with $P < 0.10$ suggesting significant heterogeneity between trials. For each outcome, the Mantel-Haenszel (fixed effect) or DerSimonian and Laird (random effects) model was used when the Q-statistic suggested lack or presence of heterogeneity, respectively. Pooled effect estimates and heterogeneity between studies were analyzed by use of Comprehensive MetaAnalysis® (Englewood, NJ, USA, 2002) and RevMan (v4.2.2, Cochrane Collaboration, 2004). Statistical significance for overall effect was defined as $P < 0.05$.

Sub-analyses defined *a priori* included outcomes in patients who were elderly (age > 70 yr), undergoing cardiac *vs* thoracic surgery, or had pulmonary disease, heart failure, or renal failure at baseline. Subanalysis was also planned for trials including regional anesthesia techniques. When possible, data analysis was by intention-to-treat. Sensitivity analysis was planned to explore the potential effect of trial quality, publication status (published *vs* unpublished), and patients excluded in non-intent-to-treat trials using a worst-case scenario assumption.

Publication bias was explored through visual inspection of funnel plots in which the inverse of the estimated variance of the natural logarithm of the adjusted relative risk was plotted against the natural logarithm of the adjusted relative risk for each outcome.[13]

Results

Of over 500 citations screened, 30 apparently relevant randomized trials were identified and retrieved for evaluation. Of these, ten were excluded for the following reasons: non-random design,[14–16] NSAIDs given to all randomized groups,[17,18] non-cardiothoracic surgery[19] and use of COX-2 selective NSAIDs.[20–23] Therefore, 20 randomized trials (19 papers and one abstract) involving a total of 1,065 patients provided data for this meta-analysis.[24–43] Table I outlines the characteristics of included trials. Baseline characteristics of patients are presented in Table II. The median Jadad score was 3 (range: 2 to 5).[7] Significant heterogeneity was found for VAS pain scores, morphine-equivalents required, rescue analgesics required, and serum creatinine levels; however, no significant heterogeneity was found for other endpoints. Funnel plots showed no clear evidence of publication bias for any endpoint. Forrest plots of each outcome are presented as supplementary material online at: www.cja-jca.org.

Clinical and resource outcomes

A total of 11 different NSAIDs were examined in the 20 trials. The most commonly employed NSAIDs

TABLE I Characteristics of included trials

Author	*N*	*JADAD*	*Surgery*	*Patients*	*Intervention*	*Comparator*	*Breakthrough treatment*	*Year*	*Country*
Barilaro 01 [24]	60	1,1,1	CABG	Excluded patients with any of the following: over 75 yr, RF, LF, COPD, requiring beta-blockers or inotropes.	Tramadol 12 mg·hr^{-1} continuous infusion until 24 hr post-extubation Ketorolac 0.8 mg·hr^{-1} continuous infusion until 24 hr post-extubation Tramadol 100 mg *iv* bolus q6h	Morphine 2 mg *iv* bolus q6h	Not specified	< 2001	Italy
Bigler 92 [25]	28	1,1,1	Thoracic	Elective thoracotomy with lung resection and placement of 2 or more chest drains; excluding coagulopathy, PUD hx.	Piroxicam 40 mg *pr* at 12 hr and 1 hr preop; then 20 mg postop x 24 hr + combined epidural local anesthetic/opioid	Placebo *pr* + combined epidural local anesthetic/ opioid		< 1992	Denmark
Carretta 96 [26]	20	1,0,1	Thoracic	Elective thoracotomy; excluding associated operations, neurologic deficits, presence of preop causes of pain.	Ketorolac 30 mg *im* tid, started 30 min prior recovery, continuing x 48 hr	Control	50 mg *im* meperidine nurse administered	1993-1994	
Fayaz 03 [27]	40		CABG	ASA 1-4 CABG patients	Diclofenac 100 mg *pr* q18h x 1	Placebo	PCA morphine	< 2003	UK
Gust 99 [28]	80	1,2,1	CABG	Enrolled after tracheal extubation. Elective CABG; clinical severity score > 6, requiring significant inotrope support after extubation, reexploration, or had neurologic deficits preventing assessment; not on antidepressants, class I antiarrhythmics.	Indomethacin 50 mg tid *pr*	Control	PCA piritramide	< 1999	Germany
Hynninen 00 [29]	114	2,2,1	CABG	Elective first time CABG; excluding prolonged CPB, IABP, postoperative bleeding > 100 mL·hr^{-1}, early postoperative SCr increase > 20%, failure to extubate within 9 hr, postoperative stroke; EF < 20%, IDDM, RF, active PUD, GI bleed hx, Age >75 yr, preoperative anticoagulants	Diclofenac 75 mg bid *pr* *vs* Ketoprofen 100 mg bid *pr* *vs* Indomethacin 100 mg bid *pr*	Placebo	Morphine *iv* 2 mg bolus titrated to VAS 3.	< 2000	Canada

TABLE I *continued*

Author	*N*	*JADAD*	*Surgery*	*Patients*	*Intervention*	*Comparator*	*Breakthrough treatment*	*Year*	*Country*
Jones 85 [30]	20	1,1,1	Thoracic	ASA I–III patients undergoing thoracotomy for pulmonary resection	Acetyl salicylic acid 1 g *iv* in 24 hr and papaveretum 10 mg x 1 at end of surgery	Morphine 40 mg in 24 hr, and Papaveretum 10 mg x 1 at surgery D/C	Papaveretum 10–15 mg *im*	< 1985	UK
Kavanagh [94] [pre-emptive[31]]	30	2,2,1	Thoracic	Elective lateral thoracotomy, ASA I–II; excluding age > 80yr, preoperative analgesic use, symptomatic CAD, symptomatic PUD, uncontrolled HTN, RF, LF, CHF, CVD, opioid addiction, hx of postoperative confusional state	Preop Indomethacin 100 mg *pr* + MSO_4 0.1 $mg \cdot kg^{-1}$ *im*, + perphenazine 0.03 $mg \cdot kg^{-1}$ *im* 60 min before surgery	Placebo *pr* + Midazolam 0.05 $mg \cdot kg^{-1}$ *im*	PCA morphine	< 1994	Canada
Keenan 93 [32]	30	1,1,1	Thoracic	Full thoracotomy procedures including pulmonary resection and esophageal surgery	Indomethacin 100 mg *pr*	Control	Nurse administered *im* Papaveretum	NA (< 1983)	UK
Kulik 04[33]	98	2,1,2	CABG	Elective CABG, multi vessel, excluding EF< 20%, creatinine >130 $umol \cdot L^{-1}$ preoperative use of H_2 antagonists, proton pump inhibitors, NSAIDs (excluding ASA), narcotics	Naproxen suppository 500 mg q12h x 5 doses started 1 hr after admission to recovery area	Placebo	Nurse admin. Morphine *iv* and oral tablets on POD 1	< 2004	Canada
Merry 92 [34]	19	2,1,1	Thoracic	Lateral thoracotomy; excluding hx PUD, GI bleeding, bleeding disorder, RF, LF, cardiovascular disease, hematopoietic disease, pregnancy, NSAID/ opioid/diuretic/ ACEI use < 24 hr prior to surgery	Tenoxicam 20 mg *iv* x 1 + famotidine	Placebo *iv* + famotidine	PCA papaveretum	< 1992	New Zealand
Pavy 90 [35]	60	2,1,1	Thoracic	Patients undergoing thoracotomy	Indomethacin 200 mg *pr* stat, then 100 mg *pr* bid x 3d	Placebo controlled papaveretum infusion.	Nurse	< 1990	Australia

TABLE I *continued*

Author	*N*	*JADAD*	*Surgery*	*Patients*	*Intervention*	*Comparator*	*Breakthrough treatment*	*Year*	*Country*
Perttunen 92[36]	30	1,1,1	Thoracic	ASA I-III; excluding age >75 yr, cardiac failure, RF, LF, GI bleeding hx, PUD hx, bleeding diathesis, asthma, postop FEV_1 < 1.0 $L.sec^{-1}$, and patients with confusion.	Diclofenac 25 mg *iv* bolus, 2 $mg{\cdot}kg^{-1}$ /24 hr *iv* x 48 hr [Note: morphine 0.13 $mg{\cdot}kg^{-1}$ *im* 1 hr preoperatively] Intercostal nerve block performed postoperatively	Placebo infusion [Note: morphine 0.13 $mg{\cdot}kg^{-1}$ *im* 1 hr preoperatively] Intercostal nerve blk performed post op	PCA morphine	NA (< 1992)	Finland
Perttunen 99[37]	30	2,2,1	Thoracic	Elective video-assisted thoracoscopic surgery; excluding cardiac failure, RF, LF, hx GI bleeding, PUD hx, bleeding diathesis, asthma, preop FEV_1 < 60%, sleep apnea hx, confused patients.	Diclofenac 17 mg *iv* bolus over 30 min, 2 $mg{\cdot}kg^{-1}$/ 24 hr *iv* x 48 hr *vs* Ketorolac 10 mg *iv* bolus over 30 min, then 3.3 $mg{\cdot}kg^{-1}$ / 24 hr x 48 hr *iv* Started 1 hr before surgery [Note: morphine 0.13 $mg{\cdot}kg^{-1}$ *im* 1 hr preoperatively]	Placebo infusion [Note: morphine 0.13 $mg{\cdot}kg^{-1}$ *im* 1 hr preoperatively]	PCA morphine	NA (< 1999)	Finland
Power 94 [38]	75	2,2,1	Thoracic	Excluding PUD History of asthma, bleeding diathesis, RF, LF	Ketorolac 30 mg *im* q6h *vs* Ketorolac 10 mg *im* q6h [Note; papaveretum *im* premedication received]	Placebo *im* [Note; papaveretum *im* premedication received]	PCA morphine	< 1994	UK
Rapanos [39]	57	2,2,1	CABG	RF, chest tube drainage >100 $mL{\cdot}hr^{-1}$	Indomethacin 100 mg supp X 2 starting after surgery	Sham suppository	Morphine 2–4 mg *iv* postoperatively	< 1998	Canada
Rhodes 92 [40]	39	1,2,1	Thoracic	Excluding PUD hx, ADRs to NSAIDs hx	Diclofenac 75 mg *im* q12h, started preoperatively papaveretum + Local anesthesia at end of operation	Placebo papaveretum + local anesthesia at end of operation	Papaveretum *iv* infusion x 24 hr then *im*	< 1990	UK

TABLE I *continued*

Author	*N*	*JADAD*	*Surgery*	*Patients*	*Intervention*	*Comparator*	*Breakthrough treatment*	*Year*	*Country*
Richardson 94 [pre-emptive] [41]	56	2,0,1	Thoracic	Preop NSAID /opiate, PUD, renal dx, hepatic dysfunction	Diclofenac sodium 100 mg	Narcotic in half placebo group (morphine 10 mg)	Paravertebral in half placebo and half treatment groups (10 mL 0.5% bupivicaine prior to incision, Extrapleural catheter in all (bupivacaine 0.1 $mL \cdot kg^{-1} \cdot hr^{-1}$).	< 1994	UK
Singh 97 [42]	62	1,1,1	Thoracic	Elective thoracotomy, ASA I–III; excluding RF, opioid abuse hx, coagulopathy, GI bleeding hx, PUD hx, inability to use PCEA due to neurologic or MSK deficits	Ketorolac 60 mg *iv* bolus, then 30 mg *iv* q6h	Placebo	Patient controlled Epidural hydromorphone both groups	<1997	US
Stouten 92 [43]	117	1,2,1	Cardio-thoracic	Major surgery (sternotomy 115, thoracotomy 2)	Ketorolac 10–30 mg *iv* x 1 + placebo	MSO_4 10 mg + placebo	Rescue meds	< 1992	Netherlands
Summary, Of NSAIDs studies (20 studies)	1,065 patients	Median: 3 (2-5)	Cardio-thoracic surgery		Various non-selective NSAIDs	Conventional analgesia		1990-2003	Multi-national

***** Unpublished study, abstract only. CABG = coronary artery bypass graft; RF = renal failure; LF = liver failure;Scr = serum creatinine; COPD = chronic obstructive pulmonary disease; PUD = peptic ulcer disease; PCA = patient-controlled analgesia; IABP = intra-aortic balloon pump; IDDM = insulin-dependent diabetes mellitus; EF = ejection fraction; GI = gastrointestinal; VAS = visual analogue score; D/C = discontinued; CAD = coronary artery disease; HTN = hypertension; CHF = congestive heart failure; CVD = cerebrovascular disease; hx = history; NSAID = non-steroidal anti-inflammatory drug; POD = postoperative day; FEV_1 = forced expiratory volume in one second; ADRs = adverse drug reactions; PCEA = patient-controlled epidural analgesia**;** MSK = musculoskeletal.

TABLE II Patient characteristics

	Control	*Treatment*
Age (yr)	52.7	54.2
Duration of surgery (hr)	2.7	2.9
Female	23%	23%

TABLE III Clinical outcomes at 24 hr or during hospitalization

Outcome	*Trials n*	*NSAIDs %*	*Control %*	*OR [95%CI]*	*Heterogeneity P-value*	*I^2*	*P for overall effect*
Rescue Analgesics	3	20.8	38.8	0.46 [0.20 to 1.07]	0.01	79	0.07
Death, all cause	2	0	5	0.19 [0.01 to 4.22]	-	-	0.29
Stroke	-	-	-	-	-	-	-
AMI	3	1.1	1.5	0.71 [0.09 to 5.71]	0.51	0	0.75
AF	3	10.1	14.3	0.62 [0.24 to 1.56]	0.29	12	0.3
Heart failure	-	-	-	-	-	-	-
Bleeding, all-causes	3	1.1	1.0	0.72 [0.09-5.66]	0.70	0	0.75
Units transfused pRBCs	1	-	-	-	-	-	-
Reexploration for bleeding	1	-	-	-	-	-	-
Postoperative nausea & vomiting	9	20.2	22.1	1.24 [0.79-1.95]	0.87	0	0.34
GI disturbance	3	2.3	4.8	0.52 [0.13-2.1]	0.54	0	0.36
GI bleeding	4	1.3	1.5	0.96 [0.13-7.09]	N /A	N/A	0.97
Renal dysfunction	7	4.9	5.5	0.95 [0.37-2.46]	0.6	0	0.92
Pneumonia	2	1.7	0	3.15 [0.12-82.16]	N/A	N/A	0.49
Reintubation	2	0	1.6	0.33 [0.01-8.70]	-	-	0.51
Respiratory depression	2	0	0	-	-	-	-
Excess sedation	4	27.7	21.9	1.96 [0.53-7.19]	0.68	0	0.31
Wound infection	1	-	-	-	-	-	-
Readmission	1	-	-	-	-	-	
Severe complications	3	0	0	0	N/A	N/A	N/A
Withdrawal due to adverse effects	2	-	-	-	-	-	-

Outcome	*N*	*WMD [95% CI]*	*Heterogeneity P-value*	*I^2*	*P for overall effect*
VAS, 24 hr	7	-0.91 points [-1.48 to -0.34 points]	0.008	66	0.002
Morphine equivalents, Cumulative, 24 hr	13	-7.67 [-8.97 to -6.38 mg]	< 0.0001	70	< 0·00001
SCr, umol·L^{-1}	4	1.13 umol·L^{-1} [-10.79 to 13.04]	0.0001	89	0.85
LOS, days	2	-0.07 [-0.55 to 0.40]	0.85	0	0.7

NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; CI = confidence interval; pRBC's = packed red blood cells;AMI = acute myocardial infarction; AF = atrial fibrillation; GI = gastrointestinal; WMD = weighted mean difference; VAS = visual analogue scale; SCr = serum creatinine; LOS = length of stay.

were diclofenac (seven trials), ketorolac (six trials) and indomethacin (six trials). The following NSAIDs were used in one trial each: tenoxicam, ibuprofen, *iv* acetylsalicylic acid , ketoprofen, and piroxicam. Some trials used more than one NSAID. Drug dosages are listed in Table I. Table III outlines primary and secondary outcomes in NSAIDs *vs* control group.

At 24 hr, VAS pain scores were significantly reduced in the NSAID group (WMD -0.91, 95% CI -1.48 to -0.34), and cumulative morphine-equivalents were significantly reduced (WMD -7.67mg, 95% CI -8.97 to -6.38 mg). Visual analogue score at 48 hr was reported in one trial only and was not significantly reduced (WMD -0.90 mg, 95% CI -2.32 to 0.52 mg). The use of rescue analgesics was not statistically different between groups (OR 0.46, 95% CI 0.20 to 1.07). Despite the reduction in cumulative morphine-equivalents consumed, there was no detectable decrease in narcotic-related side effects, with no significant difference in either the rates of excessive sedation (OR 1.96, 95% CI 0.53 to 7.19), or PONV (OR 1.24, 95% CI 0.79 to 1.95).

All-cause mortality at 30 days did not differ (OR 0.19, 95% CI 0.01 to 4.22). Similarly, there was no difference in risk of myocardial infarction (OR 0.71, 95% CI 0.09 to 5.71), atrial fibrillation (OR 0.62, 95% CI 0.24 to 1.56), or all-cause bleeding (OR 0.72, 95% CI 0.09 to 5.66). There was no statistically significant increase in side effects commonly associated with the use of NSAIDs. Specifically, the rates of GI disturbance (OR 0.52, 95% CI 0.13 to 2.10), GI bleeding (OR 0.96, 95% CI 0.13 to 7.09), renal failure (OR 0.95, 95% CI 0.37 to 2.46), serum creatinine levels (WMD 1.13 umol·L^{-1}, 95% CI -10.79 to 13.04 umol·L^{-1}) and pneumonia (OR 3.15, 95% CI 0.12 to 82.16) were not statistically different. Other outcomes including stroke, heart failure, respiratory depression, need for reintubation, neurocognitive dysfunction, severe adverse events, adverse events, wound infections, pleural effusion, blood transfusions, re-exploration for bleeding, readmissions, volume of blood loss, and ileus were insufficiently reported to perform meta-analysis.

Subgroup and sensitivity analysis

There were no significant differences in 24-hr morphine consumption between groups when sub-group analysis was performed by the presence or absence of regional anesthesia block. Patients who received regional block experienced a mean reduction of 5.43 mg (range 9.85 to 1.01 mg; $P = 0.01$) morphine equivalents in 24 hr while those without regional block experienced a mean reduction of 7.77 mg (range 9.12 to 6.41 mg; $P < 0.0001$). This difference may be explained by the lack of cardiac patients in the regional block group, and therefore lower baseline scores. Subgroup analysis by presence or absence of regional block was not possible for the endpoint of VAS pain score, since only one trial reporting this outcome used regional anesthesia block.[40]

A significant difference between groups in 24-hr morphine consumption was found when subgroup analysis was performed for cardiac *vs* thoracic surgery patients. Thoracic surgical patients experienced significantly greater reductions in morphine consumption at 24 hr compared with cardiac surgical patients, whereby thoracic surgical patients experienced a mean reduction of 9.55 mg (range 11.32 to 7.78 mg; $P < 0.00001$) compared with a mean reduction in the cardiac surgical group of 5.31 mg (range 7.20 to 3.42 mg; $P < 0.00001$). Sub-analysis of thoracic *vs* cardiac surgery trials was not possible for the endpoint of VAS pain score due to insufficient data.

Excluding unpublished trials did not materially affect the results.[27] Due to insufficient data, subgroup analysis was not possible for age, pulmonary disease, renal dysfunction, heart failure, and by dose of NSAID. Adding excluded patients in pre-specified sensitivity analysis showed that the results were robust across reasonable assumptions. Sensitivity analysis by Jadad score showed no association between trial quality and outcome.

Resource utilization and economic outcomes

Hospital LOS was not statistically different between groups (WMD -0.07 days, 95% CI -0.55 to 0.4 days). Other indicators of resource utilization including ventilation time, blood transfusions,[33] and re-exploration for bleeding[29, 32] were insufficiently reported to allow for pooled analysis. No trials reported costs.

Discussion

This meta-analysis demonstrated that the addition of NSAIDs to narcotic analgesics or regional anesthetic regimens for control of postoperative analgesia in patients undergoing cardiothoracic surgery reduces VAS pain scores at 24 hr by approximately one point, while reducing narcotic consumption by over 7 mg morphine equivalents in the first 24 hr following surgery.

We chose to combine both thoracic and cardiac surgical operations. While the surgeries themselves are dissimilar, they both employ chest incisions and typically result in indwelling chest tubes following surgery. In addition, there is an increase in the number of cardiac procedures being performed through

thoracotomy incisions including mitral valve surgery and minimally invasive direct coronary artery bypass techniques. Sub-analysis of these two groups revealed a statistically significant reduction in morphine consumption over 24 hr of over 5 mg for cardiac procedures and 9 mg for thoracic procedures. The use of regional anesthetic techniques is commonly employed in patients undergoing thoracic procedures. Numerous studies have supported the use of regional anesthesia to reduce pain scores and improve respiratory function after thoracic surgery.[44] As such, trials employing regional anesthesia techniques were not excluded from this analysis. When sub-analysis was performed, the difference in morphine consumption was not found to be significantly different for those with or without regional anesthesia blocks.

Sub-analysis was undertaken to determine if greater benefit was realized for cardiac patients receiving NSAIDs as compared to thoracic patients. Sub-analysis revealed a greater reduction in morphine requirements in thoracic surgical patients as compared with the cardiac surgical patients suggesting that the former subgroup may benefit more. This may be related to the greater intensity of pain following thoracic procedures, leading to increased baseline narcotic consumption, and therefore a greater potential for benefit.[45]

This meta-analysis does not suggest that NSAIDs will significantly impact the risk of respiratory depression, tracheal reintubation, excessive sedation, atrial fibrillation, stroke, myocardial infarction, pneumonia, postoperative nausea/vomiting and hospital readmissions. However, most of these outcomes were infrequently reported in the randomized trials.

Potential disadvantages of NSAIDs

The analgesic and anti-inflammatory mechanism of NSAIDs has been attributed to their capacity for inhibiting the enzyme COX. Cyclooxygenase catalyzes the initial step in the conversion of arachidonic acid to prostaglandins. It exists as two distinct isoenzymes, termed COX-1 and COX-2. While COX-1 isoenzymes are believed to play an important role in normal physiologic body functions (platelet adhesion, gastric protection and renal function), COX-2 is primarily expressed as part of the inflammatory reaction, resulting in increased prostaglandin synthesis, which causes further pain and inflammation. The majority of NSAID-related side effects can be attributed to inhibition of prostaglandin production. Traditional NSAIDs (indomethacin, ketorolac, ibuprofen and diclofenac) act by non-selectively inhibiting both COX-1 and COX-2 isoenzymes, and are known to increase the risk of renal dysfunction, hypertension, bleeding, and GI bleeding.

Despite their well-documented risks in other settings,[46–49] many of the purported risks of NSAID analgesia were not significantly increased in this pooled analysis of randomized trials, including all cause bleeding, transfusions, re-exploration for suspected bleeding, GI bleeding, GI disturbance, heart failure, and renal failure. Few trials reported on these outcomes thus, for some outcomes such as GI bleeding (OR 0.96, 95% CI 0.13 to 7.09) the CI remain wide, and the existence of significant differences cannot be ruled out at this time. No significant differences were found for either renal failure or serum creatinine levels in patients receiving NSAIDs. This finding is similar to a meta-analysis of miscellaneous surgeries, where the incidence of clinically-significant renal failure was not increased following surgery.[50]

Some concern has been raised over the ability of NSAIDs to interfere with the effects of aspirin on inhibition of platelet function. Non-steroidal anti-inflammatory drugs bind to COX-1 and compete with aspirin's acetylation of Ser-530. Preliminary in vitro trials demonstrated reductions in platelet inhibition when NSAIDs were combined with aspirin.[51] However, several recent prospective and retrospective trials have found either no association or reductions in cardiovascular complications in patients using both aspirin and NSAIDs.[52–54] The clinical importance, therefore, of the interaction between aspirin and NSAIDs remains to be determined.

In preliminary clinical investigations NSAIDs have been shown to inhibit osteoclast/blast activity resulting in reduced bone formation.[55, 56] Whether NSAIDs have a clinical effect on bone healing postoperatively is especially relevant in coronary artery bypass grafting patients who undergo sternotomy. In a retrospective study involving patients undergoing spinal fusion, a significant increase in bone non-union was reported in the group using ketorolac.[57] In a single trial, Ott *et al.* demonstrated an increase in sternal wound infections in patients receiving the COX-2 inhibitor parecoxib/valdecox compared with placebo (3.2% *vs* 0%, respectively),[22] which may be the result of delayed bone healing. However, given the lack of prospective trials examining the effects of NSAIDs on bone healing, the clinical significance remains unclear.

Several studies involving COX-2 inhibitors have demonstrated an increase in adverse events in the perioperative cardiac setting,[22, 23] which lead to the exclusion of COX-2 inhibitors from this meta-analysis. Concerns of significantly increased risk of severe adverse events with COX-2 inhibitors with long term treatment in the ambulatory setting have also been raised elsewhere.[58,59] Recently, the COX-2 selective

inhibitor rofecoxib was withdrawn from the market amid concern over an increase in adverse cardiovascular thrombotic events.[60] A comprehensive and recent cumulative meta-analysis of the risk of cardiovascular events with rofecoxib *vs* non-selective NSAIDs or placebo suggests that this concern is valid (and was apparent as early as the year 2000) since the risk of fatal or non-fatal MI is significantly increased with rofecoxib when compared with placebo, naproxen, or other NSAIDs (OR 2.24, 95% CI 1.24 to 4.02, $P < 0.01$).[61] Cardiovascular events were unrelated to the duration of exposure to rofecoxib in this meta-analysis, such that patients receiving four weeks to six months of rofecoxib experienced a similar risk increase when compared with those treated for greater than six months. This information, coupled with the higher risk of severe adverse events reported with valdecoxib in the cardiovascular surgical setting, suggests that COX-2 specific inhibitors should not be recommended for cardiac surgical patients.

Comparison with other randomized clinical trials in the surgical literature

The findings of reductions in narcotic requirements and improvement in VAS pain scores are congruent with other studies examining the role of NSAIDs for postoperative analgesia in other surgical groups such as orthopedic surgery.[62–64] It is therefore not surprising that these drugs are becoming increasingly a routine part of a multimodal pain management regimen. The lack of elevation in creatinine in the treatment group is congruent with other perioperative literature. A systematic review with meta-analysis of non-cardiac surgery patients with previously normal renal function scheduled to receive perioperative NSAIDs was unable to demonstrate a rise in serum creatinine postoperatively (19 included trials, 1,204 patients).[50] However, significant reductions in both creatinine clearance (WMD 16 $mL \cdot min^{-1}$, 95% CI 5 to 28 $mL \cdot min^{-1}$) and potassium excretion (WMD 38 $mmol \cdot day^{-1}$; 95% CI 19 to 56 $mmol \cdot day^{-1}$) were observed. Notably, this earlier meta-analysis included only patients with normal preoperative renal function. While serum creatinine levels are typically employed to determine renal function they are affected additionally by gender, age, and muscle mass.[65] This may result in a reduced ability to detect renal dysfunction using serum creatinine measures alone.

Strengths, limitations, and generalizability

Patients included in these randomized studies were generally of low risk since enrollment was limited to those under 70 yr of age, with no history of GI hemorrhage, and with normal renal function. Dosage regimens varied across trials with some administering NSAIDs preoperatively while others administered the medication six hours postoperatively to avoid excessive bleeding (Table I). In addition, most NSAIDs were administered for a short duration including: one preoperative dose,[31] a single postoperative dose,[34] for 12 hr postoperatively,[29 39] for 24 hr postoperatively,[24,25,27,30] for 48 hr postoperatively,[26,33,36–38,41–43] and for 72 hr postoperatively.[28,32,35,40] One trial used *iv* aspirin, which is not readily available in North America.[30] A number of included trials were conducted in the early 1990s, and may not represent contemporaneous anesthetic and surgical practices. Finally, the limited sample size of these trials was insufficient to establish the true risk of important endpoints, even when combined by meta-analysis, suggesting future trials are warranted.

The rigor of this meta-analysis, as evidenced by comprehensive searches for randomized trials in any language and the adherence to QUOROM recommendations, serves to increase confidence that this represents a complete summary of best available evidence. When statistically significant heterogeneity was identified, it was accounted for statistically by using the more conservative random effects model instead of the fixed effects model. This meta-analysis provides the best available outline of existing evidence for the effect of NSAIDs postoperatively. This systematic review also highlights gaps that remain. Most notable is the lack of research defining clinical outcomes of particular relevance to NSAIDs (i.e., renal failure, bleeding) in high risk groups. In addition, few studies reported on resource utilization (i.e., ability to fast-track patients and reduce LOS), economic, and quality of life outcomes associated with differing postoperative analgesic regimens.

Conclusions and implications

In conclusion, patients undergoing cardiothoracic surgery who received NSAIDs adjunctive to narcotics experienced improved analgesia (reduced VAS pain score, and reduced narcotic consumption). Risks such as bleeding, renal failure, wound and bone healing have not been shown to be significantly higher with perioperative NSAID use; however, further research is required to rule out the existence of potentially important differences. Whether NSAIDs reduce resource utilization (reduced LOS, ventilation time, transfusion requirements, costs) remains to be adequately explored in further trials. Whether NSAIDs add to multi-modal therapy with epidural analgesia remains to be studied. Overall, the short-term use

of NSAIDs should be encouraged as a perioperative adjunct to narcotic analgesia in patients undergoing cardiothoracic surgery.

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