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REVIEW ARTICLE

Preoperative preemptive drug administration for acute postoperative pain: A systematic review and meta-analysis

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Abstract

Preoperative administration of pharmacological substances, such as non-steroidal anti-inflammatory drugs or opioids, has been gaining acclaim as a preemptive measure to minimize postoperative pain. This systematic review and meta-analysis aimed at evaluating the effectiveness of this approach in adults undergoing surgical procedures. MEDLINE, EMBASE and the Cochrane Central Register were searched from inception through January 2015. Data from randomized placebo-controlled trials were screened, extracted and assessed for risk of bias according to The Cochrane Collaboration's Tool by two independent authors. The primary outcome measure was reduction in postoperative analgesic consumption during 24 h post surgery; effects were described as mean differences between the drug and placebo arms with corresponding 95% confidence intervals (CIs) and were pooled using random-effects models. Potential publication bias was tested using funnel plots and Egger's regression test for funnel plot asymmetry. Screened were 511 records, of which 39 were included in the final synthesis with data from 3172 patients. A significant reduction in postoperative analgesic consumption was observed using preoperative administration of non-steroidal anti-inflammatory drugs (NSAIDs; 95% CI, −0.61 to −0.14; 31 comparisons), chiefly by the COX-2 inhibitors class (95% CI, −0.95 to −0.33; 13 comparisons). Significant reduction was also observed for gabapentin (95% CI, −1.60 to −0.38; 6 comparisons). No significant effects were observed using opioids, propionic acids or oxicam derivatives.

What does this review add?: Current analyses endorse the effectiveness of COX-2 inhibitors and gabapentin in reducing acute postoperative pain when administered preemptively presurgery.
Such corroboration is not found for opioids and other NSAID classes.

1. Introduction

The common medical postoperative approach to acute pain management is to provide symptomatic relief to pain that has already occurred. Conversely, there is increasing popularity for administering analgesic medication before surgery, with the rationale that such a preemptive approach reduces postoperative pain (Woolf and Chong, 1993). This clear clinical benefit extends to minimizing psychological distress, sleep disturbances and the need for further analgesics with the associated adverse effects (Akca et al., 2004; Celik et al., 2005; Riest et al., 2008; Srivastava et al., 2012). The net result facilitates faster recovery and an earlier and safer discharge (Horattas et al., 2004).

Surgical damage of tissue leads to peripheral and central sensitization (Woolf and Chong, 1993;

Finnerup et al., 2012; Finnerup et al., 2013). This results in a state of neuronal hyperexcitability or a 'wind-up' phenomenon, which partly explains painful postoperative states and hyperalgesia (Viel et al., 1994). Although still inconclusive, preventive analgesia is hypothesized to avert the central sensitization caused by incisional and inflammatory stimuli during the perioperative and early postoperative periods (Kissin, 2000). Consequently, there may be a diminished risk of patients developing long-term complications and chronic pain states that typically occur within weeks or months after surgery (Woolf and Chong, 1993; Macrae, 2001). Chronic pain states have their own associated physical, psychological and social debilities (Macrae, 2001). Thus, effective preemptive analgesia allows a return to quality of life and a reduction in financial costs that are clearly a matter of great concern to both patients and healthcare providers.

There is growing evidence showing the benefits of various pharmaceutical agents applied preoperatively to reduce postoperative pain, including opioid analgesics (e.g. Juhlin-Dannfelt et al., 1995; Liukkonen et al., 2002; Reiter et al., 2003; Wilder-Smith et al., 2003; Pozos-Guillen et al., 2007), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. Takada et al., 2009; Kesimci et al., 2011; Mowafi et al., 2011), neuromodulatory agents (e.g. Al-Mujadi et al., 2006; Agarwal et al., 2008; Grover et al., 2009; Kinney et al., 2012) and clonidine (e.g. Mayson et al., 2000; Marchal et al., 2001; Yu et al., 2003). Yet, the effects of different preoperative analgesics on the level of postoperative pain have not been thoroughly investigated and compared using vigorous and established protocols. We carried out a systematic review and meta-analysis of all relevant and available randomized placebo-controlled trials in adults to date, to evaluate the effectiveness of preoperative administration of analgesic agents on reducing postoperative analgesic consumption 24 h post surgery. This was with the objective of providing substantiated recommendations as to which pharmaceutical agents we should be focusing on in future research efforts when using a preemptive approach to postoperative pain reduction.

2. Literature search methods

2.1. Search strategy

An electronic search was conducted in January 2015 for English-language references in the following databases: EMBASE, Medline, and Cochrane Central Register of Controlled Trials. All databases were searched since their inception. The reference lists of all included articles were hand searched to identify additional studies that were not identified by the electronic search.

Search terms were free text and included 'postoperative pain prevention' OR 'preoperative prevention postoperative pain' OR 'preoperative prophylaxis postoperative pain' OR 'preemptive analgesia' OR 'prophylactic analgesia' OR 'preoperative pain therapy' OR 'preemptive analgesia postoperative pain' OR 'prophylactic analgesia postoperative pain'.

Our review followed an *a priori* determined protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42015019717) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019717.

2.2. Inclusion and exclusion criteria and study selection

Eligibility criteria included randomized controlled trial (RCTs) reports, which compared preoperative administration of pharmaceutical substances with placebo in adults undergoing elective surgical procedures. Importantly, the definition of 'preoperative' was prior to anaesthesia induction. The primary outcome measure was reduction in postoperative analgesic consumption, and the secondary outcome (not addressed in the current report) was pain relief at rest; both assessed at the first 24 h after surgery. The pharmaceutical substances of interest were (1) NSAIDs: COX-2 inhibitors, oxicam derivatives, propionic acids, acetic acids and acetaminophen; (2) opioids: buprenorphine, fentanyl, morphine, sufentanil and tramadol; (3) neuromodulatory drugs: gabapentin and pregabalin and (4) clonidine. Included were studies in which postoperative analgesics were administered in standard quantities upon patients' need for pain relief, either at fixed dosages offered by clinical personnel at predetermined frequent time intervals or using staff-monitored self-controlled devices; a meta-analysis by Walder et al. (2001) did not find significant differences in postoperative cumulative opioid consumption, pain scores, pain relief, duration of hospital stay and opioid-related adverse effects between conventionally treated groups and patient-controlled analgesia patients.

Studies were excluded if the preoperatively administered pharmaceutical substances were either (1)

steroids, as their effects are manifold and well beyond nociceptive, thus making the interpretation of results intricate, or (2) local anaesthetics, since their mechanism of action is incomparable to those of systemic drugs. Studies with paediatric populations were also excluded.

Studies which compared more than a single treatment group to the same control group were reviewed and meta-analysed, should the aforementioned criteria were met per treatment-control comparison.

Two investigators independently read all the retrieved abstracts and selected pertinent studies. Discrepancies between the investigators' selections were resolved by discussion and agreement with a senior investigator (D.Y.). Full texts of potentially eligible studies were retrieved (Fig. 1).

2.3. Data extraction and assessment of risk of bias and quality

Both investigators (R.-R.N. and H.N.-A.) extracted data to a bespoke database form, recording the primary outcome measure data, which are summarized in Tables 1 and 2. In case information was incomplete, we contacted authors by e-mail.

The risk of bias was assessed independently by both investigators (R.-R.N. and H.N.-A.) in accordance with The Cochrane Collaboration's Tool for Assessing Risk of Bias using six assessment domains (Higgins and Altman, 2008) (Table 3). Types of bias examined were (1) selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence and/or inadequate concealment of allocations prior to assignment; (2) performance bias due to knowledge of the allocated interventions by participants and personnel during the study; (3) detection bias due to knowledge of the allocated interventions by outcome assessors; (4) attrition bias due to amount, nature or handling of incomplete outcome data and (5) reporting bias due to selective outcome reporting. The Cochrane Collaboration's Tool for Assessing Risk of Bias lists the criteria for judging low, unclear or high risk of bias per assessment domain (Higgins et al., 2011). All pivotal concerns regarding bias were covered by the aforementioned assessment domains; therefore, no additional bias categories were included in the risk of

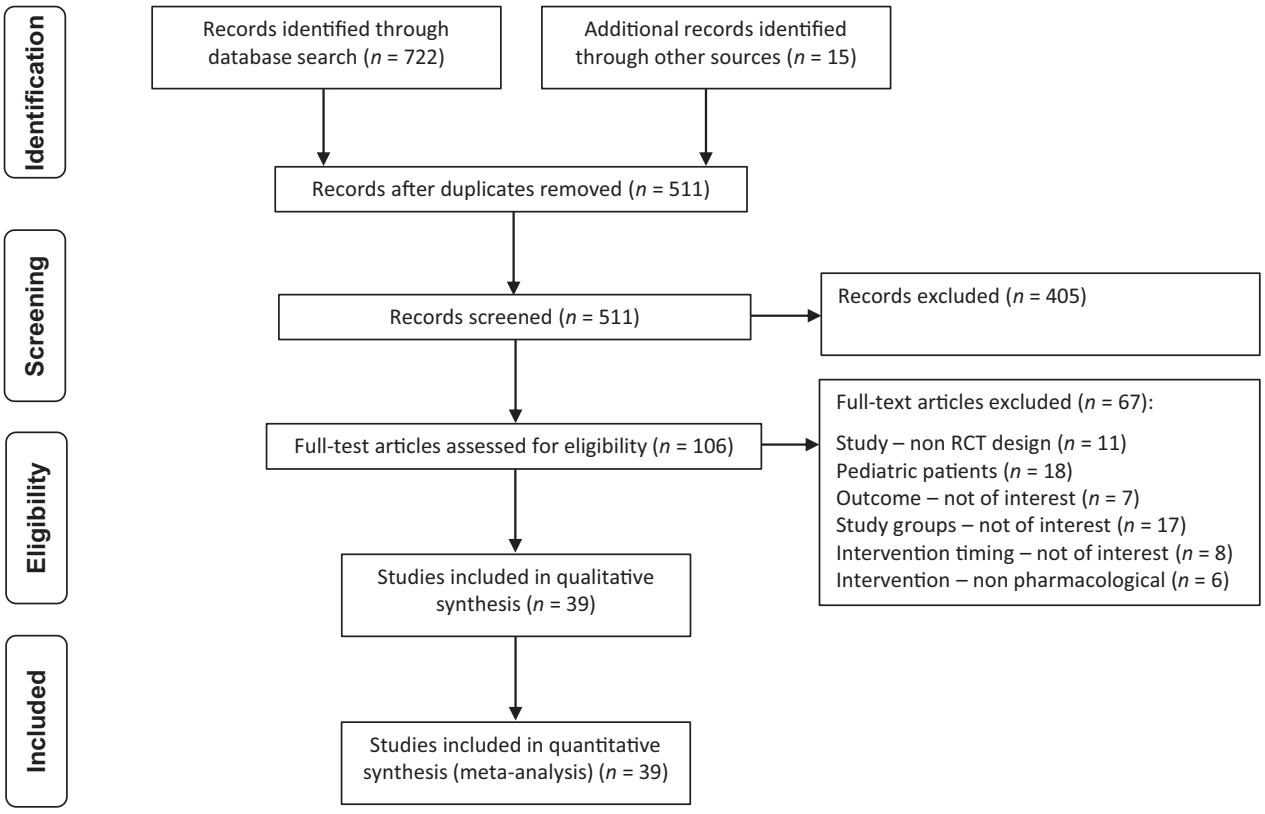

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram.

Table 1 Characteristics of the RCTs included in this systematic review and meta-analysis.

Reference	Country	Surgical procedure	Sample Size[1,2]		% Female Participants		Administered Substance		Dose Level	Follow-Up Period		Immediate postoperative drug
			Placebo group	Drug group	Placebo group	Drug group	Family	Type		≤24 h	>24 h	
Higgins et al. (1994)	United States	OBGYN: laparoscopic tubal ligation	15	15	100	100	NSAID	Ketorolac	High	+		Morphine
			15	15	100	100	NSAID	Ibuprofen	High	+		Morphine
Dunn et al. (1995)	Scotland	OBGYN: laparoscopic sterilization	35 (32)	39 (35)	100	100	NSAID	Naproxen	High	+		Morphine
Juhlin-Dannfelt et al. (1995)	Sweden	Joint: knee arthroscopy	42	40	19	7.5	Opioid	Buprenorphine	NA	+		Morphine
Dahl et al. (1996)	Norway	OBGYN: hysterectomy	21	23	100	100	NSAID	Ibuprofen	High	+	+	Morphine
			21	22	100	100	NSAID	Paracetamol	High	+	+	Morphine
Trombelli et al. (1996)	Italy	Oral: periodontal disease	21	22	62	77	NSAID	Ketorolac	Medium	+	+	NSAID
Mayson et al. (2000)	Canada	Urology: radical prostatectomy	19	24	Males	Males	Clonidine	Clonidine	Medium	+	+	Morphine
Weinbroum et al. (2001)	Israel	General/abdominal: laparoscopic cholecystectomy/inguinal hernioplasty	13	13	31	38	DXM	NA	NA	+		Morphine
Huang et al. (2001)	United States	Urology: prostatectomy	15	15	Males	Males	NSAID	Rofecoxib	High	+		Morphine
Marchal et al. (2001)	Spain	Ear: middle ear microsurgery	19	21	57	63	Clonidine	NA	Medium	+		Morphine
Liukkonen et al. (2002)	Finland	Joint: knee arthroscopy	81	75	52	53	Opioid	Tramadol	NA	+		Morphine
Reiter et al. (2003)	Austria	Joint: knee/hip replacement	49	49	58	62	Opioid	Morphine	NA	+		Morphine
Wilder-Smith et al. (2003)[3]	The Netherlands	Spine: intervertebral disc herniation	13	15	31	20	Opioid	Fentanyl	NA	+	+	Morphine
			13	13	31	23	NSAID	Ketorolac	Medium	+	+	Morphine
Yu et al. (2003)[4]	Taiwan	General/abdominal: laparoscopic cholecystectomy	15	15	33	27	Clonidine	NA	Medium	+		Morphine
Akca et al. (2004)	Turkey	General/abdominal: laparoscopic cholecystectomy/groin hernia repair	40	40	65	68	NSAID	Tenoxicam	Medium	+		Met. Sodium
Horattas et al. (2004)[4]	United States	General/abdominal: cholecystectomy	56	58	76	71	NSAID	Rofecoxib	High	+		Morphine
Alanoglu et al. (2005)	Turkey	General/abdominal: laparoscopic nissen fundoplication	15	15	47	27	NSAID	Celecoxib	Medium	+		Morphine
			15	15	47	40	NSAID	Rofecoxib	High	+		Morphine
			15	15	47	47	NSAID	Diclofenac sodium	Medium	+		Morphine
Al-Mujadi et al. (2006)	Kuwait	General/abdominal: thyroid surgery	35	37	77	70	Gabapentin	NA	High	+		Morphine

Table 1 (*Continued*)

Reference	Country	Surgical procedure	Sample Size[1,2]		% Female Participants		Administered Substance		Dose Level	Follow-Up Period		Immediate postoperative drug
			Placebo group	Drug group	Placebo group	Drug group	Family	Type		≤24 h	>24 h	
Celik et al. (2005)	Turkey	Thoracic: thoracotomy	30	30	53	43	NSAID	Rofecoxib	High	+	+	Morphine
Chiu and Cheung (2005)	Hong Kong	Oral: third molar removal	32	33	56	64	NSAID	Rofecoxib	High	+	+	Acetaminophen
			32	33	56	64	NSAID	Ibuprofen	Low	+	+	Acetaminophen
Poomtavorn and Phupong (2005)	Thailand	OBGYN: uterine curettage	40	40	100	100	NSAID	Rofecoxib	High	+		Acetaminophen
Gramke et al. (2006)[5]	The Netherlands	General/abdominal: laparoscopic bilateral inguinal hernioplasty	27	25	15	16	NSAID	Piroxicam	High	+		Morphine
Pozos-Guillen et al. (2007)	Mexico	Oral: third molar removal	20	20	55	50	Opioid	Tramadol	NA	+		NSAID
Takada et al. (2007)	Japan	Joint: total knee arthroplasty/open anterior cruciate ligament reconstruction	16	16	13	19	NSAID	Flurbiprofen	Medium	+		Morphine
Agarwal et al. (2008)	India	General/abdominal: laparoscopic cholecystectomy	29	27	40	23	Pregabalin	NA	Medium	+		Morphine
Riest et al. (2008)[5]	Germany	Spine: discectomy	80	80	50	50	NSAID	Parecoxib	Medium	+		Morphine
Grover et al. (2009)	India	Breast: total mastectomy and axillary dissection	21	25	100	100	Gabapentin	NA	Medium	+		Morphine
Neuss et al. (2010)[3]	Germany	Lymph: radical axillary node dissection	16	16	38	31	NSAID	Parecoxib	Medium	+		Acetaminophen
Sen et al. (2009a)[4]	Turkey	General/abdominal: laparoscopic cholecystectomy	35	35	57	60	NSAID	Etofenamate	High	+		Morphine
Sen et al. (2009b)[3]	Turkey	General/abdominal: unilateral inguinal herniorrhaphy	29	30	Males	Males	Gabapentin	NA	High	+	+	Morphine
Takada et al. (2009)	Japan	Tendon: arthroscopic rotator cuff repair	22	22	18	9	NSAID	Flurbiprofen	Medium	+		Morphine
Kesimci et al. (2011)	Turkey	Spine: laminectomy (lumbar disc hernioplasty)	25	25	48	40	NSAID	Dexketoprofen	Medium	+		Morphine
			25	25	48	44	NSAID	Paracetamol	Medium	+		Morphine
Kinney et al. (2012)	United States	Thoracic: thoracotomy	63	57	52	44	Gabapentin	NA	Medium	+	+	Morphine
Mowafi et al. (2012)	Saudi Arabia	General/abdominal: tonsillectomy	20	20	55	40	NSAID	Lornoxicam	Medium	+		NSAID
Ratchanon et al. (2011)	Thailand	OBGYN: laparoscopic gynaecologic surgery	135	133	100	100	NSAID	Parecoxib	Medium	+		Morphine

Table 1 (*Continued*)

Reference	Country	Surgical procedure	Sample Size[1,2]		% Female Participants		Administered Substance		Dose Level	Follow-Up Period		Immediate postoperative drug
			Placebo group	Drug group	Placebo group	Drug group	Family	Type		≤24 h	>24 h	
Al-Sukhun et al. (2012)[6]	Finland	Oral: third molar removal	53	48	47	48	NSAID	Celecoxib	Medium	+		Acetaminophen
			53	45	47	51	NSAID	Ibuprofen	Low	+		Acetaminophen
Balaban et al. (2012)	Turkey	General/abdominal: laparoscopic cholecystectomy	30	30	80	77	Pregabalin	NA	Medium	+		Morphine
			30	30	80	73	Pregabalin	NA	Medium	+		Morphine
Lierz et al. (2012)	Germany	Joint: knee arthroscopy	33	33	61	61	NSAID	Etoricoxib	High	+		Morphine
Short et al. (2012)	Canada	General/abdominal: caesarean delivery	44	44	100	100	Gabapentin	NA	Medium	+	+	Morphine
			44	44	100	100	Gabapentin	NA	Medium	+	+	Morphine
Srivastava et al. (2012)	India	Spine: single lumbar discectomy	22	21	40	25	NSAID	Etoricoxib	High	+		Morphine

OBGYN, obstetrics and gynaecology; DXM, dextromethorphan; Met. Sodium, metamizole sodium.

[1]In case n differed for dose and pain report analyses, the dose n is reported with the pain report n in parentheses.

[2]Dose and pain report n were similar in the time periods of ≤24 h and >24 h unless otherwise stated.

[3]Dose measures were collected only during the first 24 h postoperatively; pain report measures were collected during ≤24 h and >24 h postoperatively.

[4]Outcome measure was only dose data; no pain report data were collected.

[5]The treatment group received the active drug preoperatively; the control group received the active drug postoperatively.

[6]Only dose measures were analyzed; pain report measures related to pain reduction were excluded from pain report analyses.

Table 2 Primary analysis of dose: summary of tests for heterogeneity, grand mean effect (95% CI) and publication bias.

Meta-analysis drug		No. of		Random effect model				Cochrane's *Q* test for heterogeneity			Grand mean	Egger's regression test for funnel plot asymmetry		
Preoperative	Postoperative	comparisons	Figure	τ^2 (SE)	τ	I^2 [%]	H^2	*Q*	df	*P*-value	effect size (95% CI)	*t*	df	*P*-value
At 24 h														
NSAIDs[1]	All[2]	31	2	0.2528 (0.0952)	0.5028	78.90	4.74	142.155	30	<0.0001	−0.38 (−0.61 to −0.14)*	1.0743	29	0.2915
NSAIDs[3]	All[2]	29	S1	0.2555 (0.0994)	0.5055	79.31	4.83	135.301	28	<0.0001	−0.41 (−0.65 to −0.16)*	0.9900	27	0.3310
NSAIDs[4]	Morphine	20	3	0.1607 (0.0859)	0.4009	70.17	3.35	63.7029	19	<0.0001	−0.46 (−0.71 to −0.20)*	0.0260	18	0.9796
NSAIDs[5]	Acetaminophen	6	–	0.1830 (0.1566)	0.428	75.51	4.080	20.420	5	0.001	−0.58 (−1.07 to −0.09)*	0.4063	4	0.705
COX-2 inhibitors[6]	All[7]	13	4	0.1419 (0.0911)	0.3766	72.32	3.61	43.3505	12	<0.0001	−0.66 (−0.95 to −0.33)*	−0.7155	11	0.4892
COX-2 inhibitors[8]	Morphine	9	S2	0.1421 (0.1132)	0.3770	72.88	3.69	29.4986	8	0.0003	−0.68 (−1.07 to −0.29)*	−0.8402	7	0.4285
COX-2 inhibitors[9]	Acetaminophen	4	–	0.2277 (0.2456)	0.4772	77.98	4.54	13.6229	3	0.0035	−0.61 (−1.39 to 0.18)	0.1881	2	0.8682
Propionic acids[10]	All[11]	8	S3	0.2357 (0.1733)	0.4855	75.09	4.02	28.1064	7	0.0002	−0.24 (−0.70 to 0.23)	0.7431	6	0.4855
Propionic acids[12]	Morphine	6	–	0.2133 (0.1968)	0.4618	69.74	3.30	16.5212	5	0.0055	−0.13 (−0.71 to 0.46)	−0.0428	4	0.9679
Oxicams[13]	All[14]	3	–	1.2658 (1.3803)	1.125	93.94	16.51	33.013	2	<0.0001	0.06 (−3.02 to 3.13)	272.2988	1	0.002
Ketorolac	All[15]	3	–	0.1433 (0.2652)	0.3785	54.08	2.18	4.3551	2	0.1133	0.27 (−0.99 to 1.53)	−2.4395	1	0.2477
Opioids[16]	All[17]	5	–	0.0842 (0.1029)	0.2901	60.52	2.53	10.1319	4	0.0383	−0.32 (−0.81 to 0.18)	−0.0900	3	0.9340
Gabapentin	Morphine	6	–	0.3569 (0.2729)	0.5974	85.74	7.01	35.0706	5	<0.0001	−0.99 (−1.60 to −0.38)*	−1.6844	4	0.1674
Pregabalin	Morphine	3	–	0.3283 (0.4021)	0.5730	81.82	5.50	11.0034	2	0.0041	−0.53 (−2.14 to 1.07)	−2.8131	1	0.2174
Pregabalin, Gabapentin	Morphine	9	5	0.3316 (0.2037)	0.5758	84.06	6.27	50.1939	8	<0.0001	−0.84 (−1.31 to −0.37)*	−1.424	7	0.1975
Clonidine	Morphine	3	–	0.0005 (0.1195)	0.022	0.410	1.000	2.008	2	0.366	−0.85 (−1.71 to 0.00)*	−0.3598	1	0.780
All[18]	All[19]	49	6	0.2317 (0.0684)	0.4813	77.86	4.52	216.797	48	<0.0001	−0.47 (−0.65 to −0.30)*	0.1561	47	0.8767

Table 2 (*Continued*)

Meta-analysis drug		No. of comparisons	Figure	Random effect model				Cochrane's *Q* test for heterogeneity			Grand mean effect size (95% CI)	Egger's regression test for funnel plot asymmetry		
Preoperative	Postoperative			τ^2 (SE)	τ	I^2 [%]	H^2	*Q*	df	*P*-value		*t*	df	*P*-value
At 48 h														
NSAIDs[20]	All[21]	6	–	0.5095 (0.3822)	0.7138	86.31	7.31	36.5300	5	<0.0001	0.19 (−0.79 to 1.17)	2.9459	4	0.0421
NSAIDs[22]	Morphine	3	–	0 (0.0837)	0.0	0.0	1.0	1.2678	2	0.5305	−0.27 (−0.84 to 0.30)	6.1655	1	0.1024
Gabapentin	Morphine	3	–	1.7434 (1.8610)	1.320	96.92	96.92	64.836	2	<0.0001	−1.41 (−4.80 to 1.99)	−48.2802	1	0.013
All[23]	All[24]	10	S4	1.0111 (0.5404)	1.0055	93.48	15.34	138.090	9	<0.0001	−0.31 (−1.19 to 0.57)	1.1033	8	0.3020

τ^2, Estimate of total amount of heterogeneity; τ, square root of τ^2; I^2, percent of total variability due to heterogeneity; H^2, total variability/within-study variance; SE, standard error; *t*, *t*-statistic; df, degrees of freedom; NSAID, non-steroidal anti-inflammatory drug.

*$P < 0.05$.

[1]COX-2 inhibitors [rofecoxib ($n = 6$), celecoxib (2), parecoxib (3), etoricoxib (2)], propionic acids [ibuprofen (4), naproxen (1), flurbiprofen (2), dexketoprofen (1)], oxicams [piroxicam (1), tenoxicam (1), lornoxicam (1)], ketorolac (3), diclofenac sodium (1), etofenamate (1), acetaminophen (2).

[2]Morphine (20), acetaminophen (6), metamizole sodium (1), diclofenac sodium (1), naproxen (1).

[3]Same as 1, without acetaminophen (2).

[4]COX-2 inhibitors [rofecoxib (4), celecoxib (1), parecoxib (2), etoricoxib (2)], propionic acids [ibuprofen (2), naproxen (1), flurbiprofen (2), dexketoprofen (1)], piroxicam (1), ketorolac (2), diclofenac sodium (1), etofenamate (1).

[5]Ibuprofen (2), celecoxib (1), parecoxib (1), rofecoxib (2).

[6]Celecoxib (2), rofecoxib (6), parecoxib (3), etoricoxib (2).

[7]Acetaminophen (4), morphine (9).

[8]Celecoxib (1), rofecoxib (4), parecoxib (2), etoricoxib (2).

[9]Celecoxib (1), rofecoxib (2), parecoxib (1).

[10]Dexketoprofen (1), flurbiprofen (2), ibuprofen (4), naproxen (1).

[11]Acetaminophen (2), morphine (6).

[12]Dexketoprofen (1), flurbiprofen (2), ibuprofen (2), naproxen (1).

[13]Lornoxicam (1), piroxicam (1), tenoxicam (1).

[14]Metamizole sodium (1), morphine (1), NSAIDs (Diclofenac Sodium) (1).

[15]Morphine (2), NSAIDs (Naproxen) (1).

[16]Buprenorphine, fentanyl, morphine, tramadol.

[17]Morphine (4), ketorolac (1).

[18]NSAIDs (31), opioids (5), gabapentin (6), pregabalin (3), clonidine (3), dextromethorphan (1).

[19]Acetaminophen (6), morphine (39), metamizole sodium (1), NSAIDs (diclofenac sodium, ketorolac, naproxen).

[20]Ketorolac (1), ibuprofen (2), paracetamol (1), rofecoxib (2).

[21]Morphine (4), acetaminophen (2), naproxen (1).

[22]Ibuprofen (1), Paracetamol (1), rofecoxib (1).

[23]NSAIDs [ketorolac (1), ibuprofen (2)], acetaminophen (1), clonidine (1), rofecoxib (2), gabapentin (3).

[24]Morphine (7), NSAID (naproxen), acetaminophen (2).

Table 3 The Cochrane collaboration's tool for assessing risk of bias.

		a.	b.	c.	d.	e.	f.
Higgins	1994	+	?	+	+	+	+
Dunn	1995	+	?	+	+	+	+
Juhlin-Dannfelt	1995	+	+	+	+	+	+
Trombelli	1996	+	?	+	+	+	+
Dahl	1996	?	?	+	+	+	+
Mayson	2000	+	+	+	+	+	+
Weinbroum	2000	?	?	+	+	+	+
Huang	2001	+	+	+	+	+	+
Marchal	2001	?	?	+	+	+	+
Liukkonen	2002	+	?	+	+	+	+
Wilder-Smith	2003	+	+	+	+	?	+
Reiter	2003	+	+	+	+	+	+
Yu	2003	?	?	+	+	+	+
Akca	2004	+	+	+	+	+	+
Horattas	2004	+	+	+	+	+	+
Celik	2005	?	?	+	+	+	+
Chiu	2005	+	+	+	+	+	+
Poomtavorn	2005	+	+	+	+	+	+
Alanoglu	2005	+	+	+	+	+	+
Al-Mujadi	2005	+	+	+	+	+	+
Gramke	2006	+	+	+	+	+	+
Takada	2007	?	?	+	+	+	+
Pozos-Guillen	2007	?	?	+	+	+	+
Riest	2008	+	+	+	+	+	+
Agarwal	2008	+	+	+	+	+	+
Neuss	2009	+	?	+	+	+	+
Takada	2009	+	?	+	+	+	+
Grover	2009	+	+	+	+	+	+
Sen	2009[a]	+	?	+	+	+	+
Sen	2009[b]	+	?	+	+	+	+
Kesimci	2011	+	?	+	+	+	+
Mowafi	2011	+	?	+	+	+	+
Ratchanon	2011	?	?	+	+	+	+
Kinney	2011	+	+	+	+	+	+
Lierz	2012	+	+	+	+	+	+
Al-Sukhun	2012	?	?	+	+	+	+
Srivastava	2012	?	?	+	+	+	+
Short	2012	+	+	+	+	+	+
Balaban	2012	?	?	+	+	+	+

Legend:

+ Low bias risk ? Unclear bias risk - High bias risk

	Type of Bias	Relevant domains in the Collaboration's 'Risk of bias' tool
a.	Selection Bias	Random sequence generation
b.	Selection Bias	Allocation concealment
c.	Performance Bias	Blinding of participants and personnel
d.	Detection Bias	Blinding of outcome assessment
e.	Attrition Bias	Incomplete outcome data
f.	Reporting Bias	Selective reporting

bias assessment. Risk of bias assessment for the primary outcome measure across domains, both within and across RCTs, was summarized according to the Cochrane handbook for systematic reviews of interventions (Higgins and Altman, 2008). Any disagreement was resolved by discussion and consensus with a senior investigator (D.Y.).

Funnel plots were drawn to assess the quality of the RCTs. The current review and meta-analysis adhered to the Cochrane review guiding principle to refrain from using scales for assessing quality or risk of bias since this approach has not been supported by empirical evidence (Emerson et al., 1990; Schulz et al., 1995; Higgins and Altman, 2008; Higgins et al., 2011). Calculating a summary score unavoidably entails assigning 'weights' to different items in the scale, and it is problematic to justify the weights assigned (Higgins et al., 2011). Moreover, scales have been shown to be unreliable assessments of validity (Jüni et al., 1999), and they are less likely to be transparent to users of the review.

The extracted data include first author, year, country, surgical procedure, sample size of both the placebo and the active drug groups, percent of female participants in each group, preoperatively administered substance (both family and type, where relevant, e.g. NSAID and ketorolac, respectively), NSAIDs dose level (where relevant, a categorical variable of low, medium, or high), follow-up period (based on the timing categories detailed hereunder), administered postoperative drug used to assess postoperative pain, means and standard deviations of administered postoperative drug dosage in both the placebo and treatment groups, means and standard deviations of pain reports in both the placebo and treatment groups.

2.4. Data synthesis and analysis

R statistical software (R Development Core Team, 2008), the R meta-analysis package metaphor (Viechtbauer, 2010) and R-Studio were employed to meta-analyse outcome data. Effects were described as mean differences between the drug and placebo groups and were pooled using random-effects models in keeping with the Cochrane methods guidance (Higgins and Altman, 2008).

Cochrane's Q tests for heterogeneity were applied for each comparison. Effect sizes are reported using grand means and corresponding 95% confidence intervals (CI). Potential publication bias and the quality of the RCTs were tested using funnel plots and Egger's regression test for funnel plot asymmetry,

using random-effects models, which were sample size-based; the employed R statistical software scripts were adjusted so as to allow funnel plot asymmetry tests with a minimum number of three studies using the k.min argument (Richter and Yang, 2013). Where medians and interquartile ranges were reported, standard approaches to include these data were applied. Statistical significance was set at $P < 0.05$.

Both analgesic consumption and pain outcomes were categorized by timing of outcome assessment (0–24 and 24–48 h) for analysis. Opioids used as postoperative analgesics were recorded as morphine equivalents, and other opioids used were converted using standard conversion charts (Doyon, 2011; Yaksh and Wallace, 2011).

3. Results

3.1. Overall characteristics

We screened 511 unique records and finally included 39 RCTs studying 3172 adult patients who received preemptive analgesia preoperatively in order to reduce postoperative pain (1583 received pharmaceutical substances and 1589 received placebo) (Fig. 1, PRISMA flow chart). Thirty RCTs compared a single active drug to placebo, eight RCTs compared two active drug groups to placebo and a single RCT compared three active drug groups to placebo (Table 1). Thus, a total of 49 separate comparisons were made between active drug and placebo groups. The core features of the meta-analysed RCTs are summarized in Table 1.

Studies were conducted in Asia (19 studies: Hong Kong, India, Israel, Japan, Kuwait, Saudi Arabia, Taiwan, Thailand, Turkey), Europe (13 studies: Austria, Finland, Germany, Italy, the Netherlands, Norway, Scotland, Spain, Sweden), North America (6 studies: Canada, USA) and South America (1 study: Mexico) (Table 1). Ten studies were conducted exclusively in females and three were conducted only in male participants (Table 1).

Various surgical procedures were employed across the studies (Table 1), including general or abdominal (13 studies), joint (5), obstetrics and gynaecology (5), oral (4), spine (4), thoracic (2), urology (2), breast (1), ear (1), lymph nodes (1) and tendon (1).

Non-steroidal anti-inflammatory drugs were administered preoperatively in 23 studies (59%) that included 30 comparisons (63%); opioids in five studies (13%), five comparisons (10%); gabapentin in five studies (13%), six comparisons (13%); pregabalin in two studies (5%), three comparisons (6%); clonidine in three studies (8%), three comparisons (6%); and dextromethorphan in one study (3%), one comparison (2%) (Table 1). All 39 RCTs addressed the primary outcome measure at the timing outcome assessment of 24 h postoperatively, of which 10 studies (26%) that include 14 comparisons (29%) also addressed the timing outcome assessment of 48 h postoperatively (Table 1).

3.2. Risk of bias assessment

Based on The Cochrane Collaboration's Tool for Assessing Risk of Bias (Higgins and Altman, 2008; Higgins et al., 2011), 17 RCTs (44%) were judged as having low risk for bias of all key domains (Table 3). No RCT was judged as high risk for any key risk assessment. As to selection bias, 11 RCTs were judged as having unclear risk for bias of random sequence generation (28%), all of which were also judged as having unclear risk for bias of allocation concealment (Table 3). Twenty-one studies (54%) were judged as having unclear risk for bias of random sequence generation, and one study was judged as unclear risk for bias of attrition (incomplete outcome data) (Table 3).

Based on the Cochrane guidelines for systematic reviews of interventions (Higgins and Altman, 2008), the aforementioned 17 RCTs were summarized as having low risk of within a trial bias (low risk of bias on all key domains), and the remaining 22 RCTs were summarized as having unclear risk of bias within a trial (low or unclear risk of bias for all key domains).

Four RCTs (10%) were funded by industry and seven (18%) received no funding or were supported by non-industry organizations. Information on financial support was not reported in 28 RCTs (72%), and the authors of one of these studies declared no conflict of interest.

3.3. Primary perioperative efficacy outcomes

3.3.1 Non-steroidal anti-inflammatory drugs

A total of 24 RCTs that included 31 comparisons were incorporated in the meta-analyses, studying 1973 adult patients who received preemptive NSAID analgesia preoperatively in order to reduce postoperative pain (983 received NSAIDs, 990 received placebo; Table 1; Table 2, notes 1, 2; Fig. 2). Eighteen RCTs compared a single NSAID group to a single placebo group, five RCTs compared two NSAID groups to placebo and a single RCT compared three NSAID groups to placebo (Table 1).

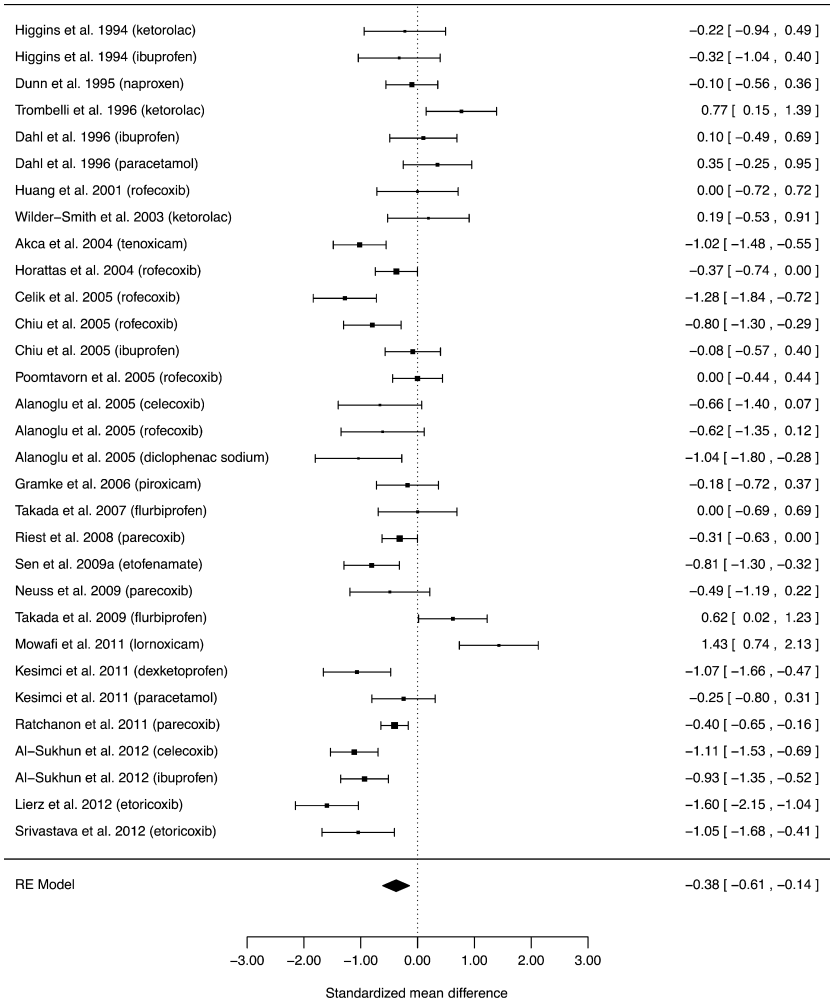

Figure 2 Forest plot of studies using preoperative NSAIDs[1] including acetaminophen and various postoperative substances[2] (in accordance with Table 2). [1]COX-2 inhibitors, propionic acids, oxicams, ketorolac, diclofenac sodium, etofenamate, acetaminophen. [2]Morphine, acetaminophen, metamizole sodium, diclofenac sodium, naproxen.

When excluding acetaminophen, being an atypical NSAID, a significant reduction was observed in postoperative analgesics consumption (morphine, acetaminophen, metamizole sodium, diclofenac sodium and naproxen) at 24 h post surgery (see details in Table 2, notes 2, 3). Analysed were 24 RCTs, yielding 29 comparisons with unclear risk of bias across studies; data from 1887 patients were meta-analysed (940 received NSAIDs, 950 received placebo), yielding grand mean effect and 95% CI of −0.41 (−0.65 to −0.16) (Table 2; Supporting information Fig. S1). No publication bias was evident (Table 2).

Meta-analysing RCTS in which the effect of preoperatively administered NSAIDs was assessed postoperatively by reduction in morphine consumption only, resulted in a significant effect at 24 h post surgery (see details in Table 2, note 4). Analysed were 17 RCTs, yielding 20 comparisons and unclear risk of bias across studies; data from 1283 patients were meta-analysed (643 received NSAIDs, 640 received placebo), yielding grand mean effect and 95% CI of −0.46 (−0.71 to −0.20) (Table 2; Fig. 3). No publication bias was evident (Table 2).

A significant reduction was also observed in postoperative acetaminophen consumption at 24 h post surgery (see details in Table 2, note 5). Analysed were four RCTs, yielding six comparisons and unclear risk of bias across studies; data from 441 patients were meta-analysed (215 received NSAIDs, 226 received placebo), yielding grand mean effect and 95% CI of −0.58 (−1.07 to −0.09) (Table 2). No publication bias was evident (Table 2).

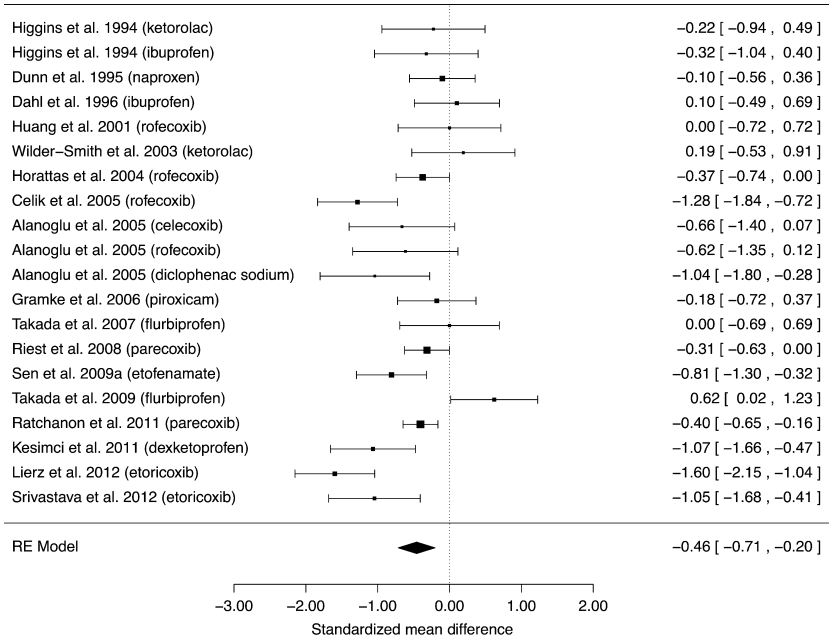

Figure 3 Forest plot of studies using preoperative NSAIDs[1] and postoperative morphine (in accordance with Table 2). [1]COX-2 inhibitors, propionic acids, piroxicam, ketorolac, diclofenac sodium, etofenamate.

COX-2 inhibitors

A total of 12 RCTs yielded 13 comparisons, in which the COX-2 inhibitors class of NSAIDs were administered preoperatively, were incorporated in the meta-analyses, studying 1079 adult patients (537 received COX-2 inhibitors, 542 received placebo; Table 1; Table 2, notes 6,7; Fig. 4). The meta-analysed COX-2 inhibitors were rofecoxib (six studies), etoricoxib (2), celecoxib (2) and parecoxib (3). Eight of the meta-analysed comparisons administered high-dose COX-2 inhibitors, namely all rofecoxib and etoricoxib studies (six and two studies, respectively). The remaining five meta-analysed comparisons administered medium-dose COX-2 inhibitors, namely all celecoxib and parecoxib studies (2 and 3, respectively).

Preoperative administration of COX-2 inhibitors resulted in a significant reduction in postoperative morphine consumption at 24 h post surgery (nine studies, low risk of bias across studies) with grand mean effect and 95% CI of −0.68 (−1.07 to −0.29)

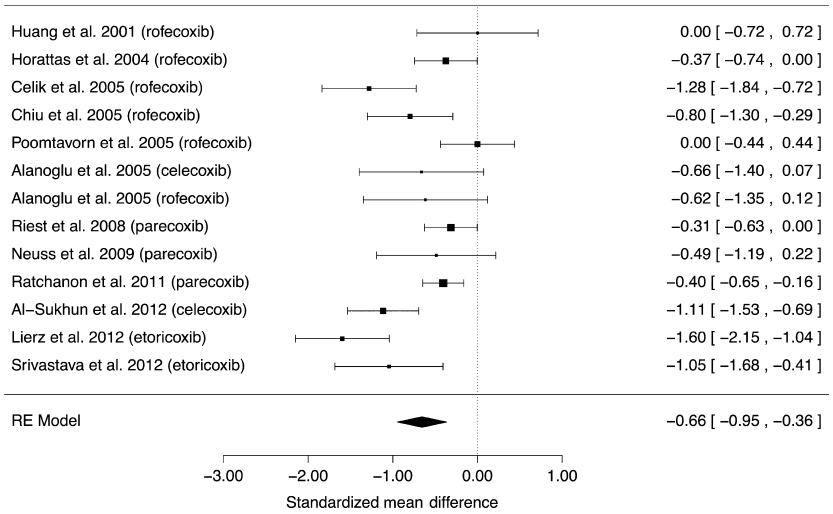

Figure 4 Forest plot of studies using preoperative COX-2 inhibitors[1] and various postoperative substances[2] (in accordance with Table 2). [1]Celecoxib, rofecoxib, parecoxib, etoricoxib. [2]Acetaminophen, morphine.

(Table 2, note 8; Supporting information Fig. S2). No significant reduction was observed in studies using acetaminophen as the postoperative analgesic (four studies, unclear risk of bias across studies), yielding grand mean effect and 95% CI of −0.61 (−1.39 to 0.18) (Table 2, note 9). No publication bias was evident for either morphine or acetaminophen (Table 2).

Propionic acids

A total of eight RCTs yielded eight comparisons, in which the propionic acids class of NSAIDs were administered preoperatively, were incorporated in the meta-analyses, studying 437 adult patients (218 received propionic acids, 219 received placebo; Table 1; Table 2, notes 10, 11; Supporting information Fig. S3). The meta-analysed propionic acids were ibuprofen (four studies), flurbiprofen (2), naproxen (1) and dexketoprofen (1). Two of the four ibuprofen comparisons administered a high dose and two administered a low dose. Both flurbiprofen and the single dexketoprofen comparisons administered a medium dose. The naproxen comparison administered a high dose.

Preoperative administration of propionic acids resulted in an insignificant reduction in postoperative morphine consumption at 24 h post surgery (six studies, unclear risk of bias across studies) with grand mean effect and 95% CI of −0.13 (−0.71 to 0.46) (Table 2, note 12). No significant reduction was observed in the meta-analysis of all propionic acid studies, incorporating both morphine (six studies) and acetaminophen (2) as the postoperative analgesic (eight studies, unclear risk of bias across studies), yielding grand mean effect and 95% CI of −0.24 (−0.70 to 0.23) (Table 2). No publication bias was evident for either morphine or acetaminophen (Table 2).

Oxicams

A total of three RCTs yielded three comparisons, in which the oxicams class of NSAIDs were administered preoperatively, were incorporated in the meta-analyses, studying 172 adult patients (85 received oxicams, 87 received placebo; Table 1; Table 2, notes 13,14) (Akca et al., 2004; Gramke et al., 2006; Mowafi et al., 2011). The meta-analysed oxicams were lornoxicam (1 study, medium dose; Mowafi et al., 2011), piroxicam (1 study, high dose; Gramke et al., 2006) and tenoxicam (1 study, medium dose; Akca et al., 2004).

Preoperative administration of oxicams resulted in an insignificant reduction in postoperative analgesic consumption (Metamizole sodium, morphine, diclofenac sodium) at 24 h post surgery (three studies, low risk of bias across studies) with grand mean effect and 95% CI of 0.06 (−3.02 to 3.13) (Table 2). A publication bias was evident for this meta-analysis (Table 2).

Additional NSAIDs

Three RCTs used ketorolac [one study, high dose (Higgins et al., 1994); two studies, medium dose (Trombelli et al., 1996; Wilder-Smith et al., 2003)], two used acetaminophen [one study, high dose (Dahl et al., 1997); one study, medium dose (Kesimci et al., 2011)], one used diclofenac sodium (one study, medium dose; Alanoglu et al., 2005) and one used etofenamate (one study, high dose; Sen et al., 2009a; Table 1). All seven RCTs compared a single NSAID group to a single placebo group (Table 1).

Only ketorolac studies could be meta-analysed (as they comprised more than two studies), studying 110 adult patients (50 received ketorolac, 60 received placebo; Table 1; Table 2, note 15). Preoperative

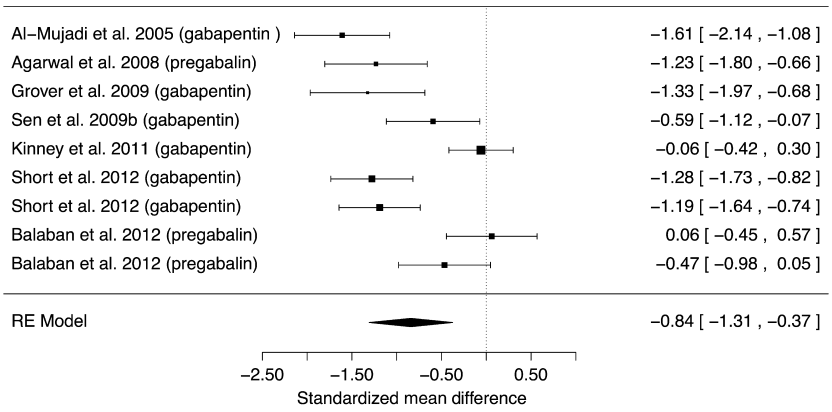

Figure 5 Forest plot of studies using preoperative pregabalin or gabapentin and postoperative morphine (in accordance with Table 2).

administration of ketorolac resulted in an insignificant reduction in postoperative morphine or naproxen consumption at 24 h post surgery (three studies, unclear risk of bias across studies) with grand mean effect and 95% CI of 0.27 (−0.99 to 1.53). No publication bias was evident (Table 2).

3.3.2 Opioids

A total of five RCTs yielding five comparisons were incorporated in the meta-analyses, studying 404 adult patients who received preemptive opioids preoperatively in order to reduce postoperative pain (199 received opioids, 205 received placebo; Table 1; Table 2, notes 16,17) (Juhlin-Dannfelt et al., 1995; Liukkonen et al., 2002; Reiter et al., 2003; Wilder-Smith et al., 2003; Pozos-Guillen et al., 2007). All five RCTs compared a single opioid group to a single placebo group (Table 1).

Preoperative administration of opioids resulted in an insignificant reduction in postoperative analgesic consumption (morphine, ketorolac) at 24 h post surgery (five studies, unclear risk of bias across studies) with grand mean effect and 95% CI of −0.32 (−0.81 to 0.18; Table 2). Incorporating only the studies using morphine as postoperative analgesic (Juhlin-Dannfelt et al., 1995; Liukkonen et al., 2002; Reiter et al., 2003; Wilder-Smith et al., 2003) yielded comparable results, namely −0.32 (−0.78 to 0.33). No publication bias was evident for either morphine and ketorolac (Table 2) or morphine alone ($t(4) = 0.625$; $P = 0.596$).

3.3.3 Gabapentin

A total of five RCTs that include six comparisons were incorporated in the meta-analyses, studying 473 adult patients who received gabapentin preoperatively in order to reduce postoperative pain (237 received opioids, 236 received placebo; two studies, high dose: Al-Mujadi et al., 2006, Sen et al., 2009b; three studies, medium dose: Grover et al., 2009, Kinney et al., 2012, Short et al., 2012; Tables 1, 2). Five RCTs compared a single opioid group to a single placebo group and a single RCT compared two gabapentin groups to a third placebo group (Table 1).

Preoperative administration of gabapentin resulted in a significant reduction in postoperative morphine consumption at 24 h post surgery (five studies, six comparisons, low risk of bias across studies) with grand mean effect and 95% CI of −0.99 (−01.60 to −0.38) (Table 2). No publication bias was evident (Table 2).

3.3.4 Pregabalin

A total of two RCTs yielding three comparisons were incorporated in the meta-analyses, studying 176 adult patients who received preemptive pregabalin analgesia preoperatively in order to reduce postoperative pain (87 received opioids, 89 received placebo; two studies, medium dose: Agarwal et al., 2008, Balaban et al., 2012; Tables 1, 2). One RCT compared a single pregabalin group to a single placebo group, and a single RCT compared two pregabalin groups to a third placebo group (Table 1).

Preoperative administration of pregabalin resulted in an insignificant reduction in postoperative morphine consumption at 24 h post surgery (two studies, three comparisons, unclear risk of bias across studies) with grand mean effect and 95% CI of −0.53 (−2.14 to 1.07) (Table 2). No publication bias was evident (Table 2).

Combining the effect of preoperatively administered gabapentin and pregabalin resulted in a significant reduction in postoperative morphine consumption at 24 h post surgery (seven studies, nine comparisons, unclear risk of bias across studies) with grand mean effect and 95% CI of −0.84 (−1.31 to −0.37) (Table 2; Fig. 5). No publication bias was evident (Table 2).

3.3.5 Clonidine

A total of three RCTs yielding three comparisons were incorporated in the meta-analyses, studying 113 adult patients who received preemptive clonidine analgesia preoperatively in order to reduce postoperative pain (60 received clonidine, 53 received placebo; three studies, medium dose: Mayson et al., 2000, Marchal et al., 2001, Yu et al., 2003; Tables 1, 2). All three RCTs compared a single clonidine group to a single placebo group (Table 1).

Preoperative administration of clonidine resulted in a borderline significant reduction in postoperative morphine consumption at 24 h post surgery (three studies, three comparisons, unclear risk of bias across studies) with grand mean effect and 95% CI of −0.85 (−1.71 to 0.00) (Table 2). No publication bias was evident (Table 2).

3.3.6 Dextromethorphan

A single RCT used dextromethorphan as the preemptive drug (Weinbroum et al., 2001), enrolling 26 adult patients (13 in each of the treatment and placebo groups, unclear risk of bias). The study reported

a significantly greater reduction in postoperative morphine consumption in the active drug versus placebo group (2.1 ± 1.2 vs. 4.7 ± 2.3 mg, respectively; $P < 0.01$).

The forest plot in Fig. 6 addresses the meta-analysis of all 49 separate comparisons that were made between active drug and placebo groups within 24 h postoperatively (see details in Table 1; Table 2, notes 18, 19).

3.4. Outcome assessment at 48 h post surgery

A total of seven RCTs that include 10 comparisons, in which analgesics consumption was recorded during 48 h postoperatively, were meta-analysed, studying 659 adult patients [332 received pharmaceutical substances, 327 received placebo; Table 1; Table 2; Supporting information Fig. S4 (Dahl et al., 1996; Trombelli et al., 1996; Mayson et al., 2000; Celik et al., 2005; Chiu and Cheung, 2005; Kinney et al. 2011; Short et al., 2012)].

Meta-analysing all RCTs resulted in an insignificant effect at 48 h post surgery. Meta-analysed were RCTs using ibuprofen (2 trials), ketorolac (1), acetaminophen (1), rofecoxib (2), gabapentin (3) and clonidine (1), with low risk of bias across studies. The meta-analysed postoperatively administered analgesics were morphine (seven studies), acetaminophen (2) and naproxen (1). The grand mean effect and 95% CI were −0.31 (−1.19 to 0.57) (see details in Table 2, notes 23, 24). No publication bias was evident (Table 2).

Meta-analysing four RCTs yielding six comparisons, in which the effect of preoperatively administered NSAIDs was assessed postoperatively by reduction in analgesics consumption, resulted in an insignificant effect at 48 h post surgery. Meta-analysed were RCTs using ibuprofen (2 trials), ketorolac (1), acetaminophen (1) and rofecoxib (2) with unclear risk of bias across studies. The meta-analysed postoperatively administered analgesics were morphine (3 studies), acetaminophen (2) and naproxen (1). Data from 320 patients were meta-analysed (163 received NSAIDs, 157 received placebo), yielding grand mean effect and 95% CI of 0.19 (−0.79 to 1.17) (see details in Table 2, notes 20, 21). A publication bias was evident (Table 2).

Meta-analysing two RCTs that include three comparisons, in which the effect of preoperatively administered NSAIDs was assessed postoperatively by morphine reduction, resulted in an insignificant effect at 48 h post surgery. Meta-analysed were RCTs using ibuprofen (1 trial), acetaminophen (1) and rofecoxib (1) with unclear risk of bias across studies. Data from 147 patients were meta-analysed (75 received NSAIDs, 72 received placebo), yielding grand mean effect and 95% CI of −0.27 (−0.84 to 0.30) (see details in Table 2, note 22). No publication bias was evident (Table 2).

Meta-analysing two RCTs yielding three comparisons, in which the effect of preoperatively administered gabapentin was assessed postoperatively by morphine reduction, resulted in an insignificant effect at 48 h post surgery, with unclear risk of bias across studies. Data from 296 patients were meta-analysed (145 received NSAIDs, 151 received placebo), yielding grand mean effect and 95% CI of −1.41 (−4.80 to 1.99; see details in Table 2. A publication bias was evident (Table 2).

4. Discussion and conclusions

More than 3100 patients included in this review and meta-analysis were examined in an analogous experimental design, aimed at assessing the effectiveness of preoperative preventive drug administration for acute postoperative pain. The findings suggest that the COX-2 inhibitors of the NSAID class and gabapentin are effective in reducing postoperative pain when taken preoperatively, whereas opioids and other NSAID classes have no significant effects using this preemptive approach.

The preoperative pharmaceutical approach may minimize postoperative pain by various complex mechanisms. In the case of COX-2 inhibitors, these agents act to inhibit cyclooxygenase and reduce prostaglandin synthesis both in the spinal cord and at the periphery (McCormack, 1994) and provide analgesia by decreasing peripheral pain receptor sensitivity to mechanical stimulation and reducing tissue inflammation (Higgins et al., 1994). Injury to tissue during surgical procedures results in the release of chemical mediators of inflammation. Some of these mediators evoke pain (histamine, acetylcholine and bradykinin), and others (such as prostaglandins) cause hyperalgesia, which is characterized by decreased pain threshold and increased sensitivity to supra threshold stimuli (Trombelli et al., 1996). The preoperative administration of NSAIDs may augment postoperative analgesia, as seen in the present study (95% CI, −0.61 to −0.14; 31 comparisons), chiefly by the COX-2 inhibitors class (95% CI, −0.95 to −0.33; 13 comparisons), by preventing the establishment of central sensitization in nociceptive pathways (Higgins et al., 1994; Celik et al., 2005).

Gabapentin was also found in the current meta-analysis to be effective in reducing postoperative

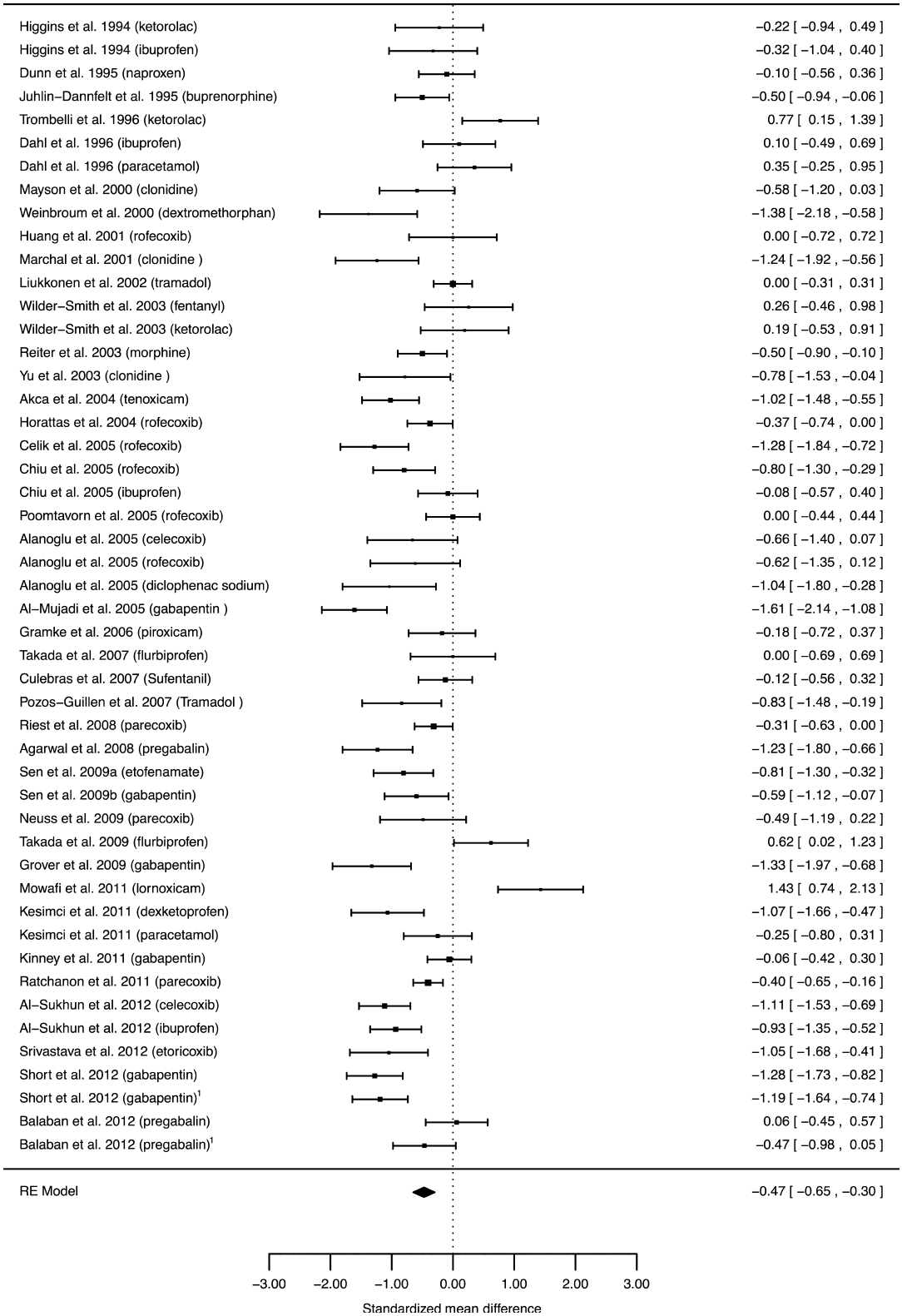

Figure 6 Forest plot of studies using various preoperative[1] and postoperative[2] substances (in accordance with Table 2). [1]NSAIDs, opioids, gabapentin, pregabalin, clonidine, dextromethorphan. [2]Acetaminophen, morphine, metamizole sodium, NSAIDs (diclofenac sodium, ketorolac, naproxen).

analgesic consumption when given as a single dose preoperatively (95% CI, −1.60 to −0.38; 6 comparisons). Pretreatment with a single dose of gabapentin blocks the development of hyperalgesia [which is N-methyl-D-aspartate (NMDA) mediated] and tactile allodynia [which is α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and metabotropic receptor mediated] for up to 2 days in a rat model of postoperative pain (Field et al., 1997). This preemptive analgesia may again be effective due to preventing nociceptive inputs from inducing prolonged hyperexcitability of the central nervous system (Reiter et al., 2003). Based on the findings of the relevant studies investigated in this meta-analysis, oral administration of gabapentin approximately 2 h before surgery allows for maximal plasma concentration at the time of surgical stimuli. This is particularly interesting as gabapentin's use for existing pain takes several weeks to induce pain relief (Finnerup et al., 2012; Finnerup et al., 2013). Gabapentin is also considered an anxiolytic (Chouinard et al., 1998; Pollack et al., 1998); due to the possible association between preoperative anxiety and postoperative pain (Chouinard et al., 1998), reducing the former with gabapentin may facilitate improved postoperative analgesia and, consequently, help to reduce morphine requirements. In addition, studies have shown that both gabapentin and NSAID COX-2 inhibitors have synergistic effects with opioids and so decrease the requirements for intraoperative and postoperative opioids (Eckhardt et al., 2000; Mayson et al., 2000; Chow et al., 2001). Data from patients undergoing lumbar discectomy who received gabapentin or placebo preoperatively and postoperatively suggest that gabapentin may be associated with less pain intensity and improved functional outcomes 3 months postoperatively (Burke and Shorten, 2010); however, recent evidence from opioid-naive patients undergoing total knee arthroplasty indicates that the role of gabapentin in acute postoperative pain management may be limited (Lunn et al., 2015).

Opioids were not found to be effective as preemptive agents to reduce postoperative pain. This could be due to the drug preparations having unsuitable pharmacokinetic properties where peak activity is too slow to achieve sufficient postoperative analgesia (Reiter et al., 2003). The fact that opioid analgesics have many unwanted side-effects such as nausea, vomiting, urinary retention, sedation, respiratory depression, drug dependence, dizziness and dry mouth (Higgins et al., 1994; Liukkonen et al., 2002; Akca et al., 2004; Horattas et al., 2004) tends to reduce their appeal further by complicating recovery and lengthening hospitalization (Higgins et al., 1994). Nevertheless, combinations of analgesics with different pharmacokinetic properties, either two opioids or an opioid with another class of analgesic agent, may increase analgesic effectiveness while reducing the worst of the side-effects (Culebras et al., 2007).

The findings from this systematic review and meta-analysis have given an overall consolidated picture in which to compare preemptive analgesic agents. For example, mixed results have been reported with NSAIDs in individual studies, but the current review and meta-analysis has clarified that more focus needs to be made on the COX-2 inhibitors. Likewise, the capacity of gabapentin as a preventive pain medication may be further explored in future studies.

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Author contributions

All authors have participated in the preparation of the manuscript in a significant way: R.-R.N. contributed to the conception and design of the study, statistical analysis and interpretation of data and the drafting and review of the manuscript; R.-R.N. and H.N.-A. carried out the study; R.M. contributed to the interpretation of the data and wrote the introduction and discussion sections; E.S. contributed to the statistical analysis and the review of the manuscript; and D.Y. contributed to the conception and design of the study, interpretation of the data and review of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Forest plot of studies using preoperative NSAIDs[1] excluding acetaminophen and various postoperative substances[2] (in accordance with Table 2). [1]COX-2 inhibitors, propionic acids, oxicams, ketorolac, diclofenac sodium, etofenamate; acetaminophen was not included in this analysis. [2]Morphine, acetaminophen, metamizole sodium, diclofenac sodium, naproxen.

Figure S2. Forest plot of studies using preoperative COX-2 inhibitors[1] and morphine (in accordance with Table 2). [1]Celecoxib, rofecoxib, parecoxib, etoricoxib.

Figure S3. Forest plot of studies using preoperative propionic acids[1] and various postoperative substances[2] (in accordance with Table 2). [1]Dexketoprofen, flurbiprofen, ibuprofen, naproxen. [2]Acetaminophen, morphine.

Figure S4. Forest plot of studies using various preoperative[1] and postoperative[2] substances (48 h postoperative assessment; in accordance with Table 2). [1]NSAIDs (ketorolac, ibuprofen), acetaminophen, clonidine, rofecoxib, gabapentin. [2]Morphine, NSAID (naproxen), acetaminophen.