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Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery (Review)

Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD

Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD.
Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery.
Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD013290.
DOI: 10.1002/14651858.CD013290.pub2.

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[Intervention Review]

Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery

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Editorial group: Cochrane Breast Cancer Group.
Publication status and date: New, published in Issue 11, 2021.

Citation: Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD. Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery. *Cochrane Database of Systematic Reviews* 2021, Issue 11. Art. No.: CD013290. DOI: 10.1002/14651858.CD013290.pub2.

ABSTRACT

Background

Breast surgery encompasses oncologic, reconstructive, and cosmetic procedures. With the recent focus on the over-prescribing of opioids in the literature, it is important to assess the effectiveness and safety of non-opioid pain medication regimens including nonsteroidal anti-inflammatory drugs (NSAIDs) or NSAID pain medications. Clinicians have differing opinions on the safety of perioperative (relating to, occurring in, or being the period around the time of a surgical operation) NSAIDs for breast surgery given the unclear risk/benefit ratio. NSAIDs have been shown to decrease inflammation, pain, and fever, while potentially increasing the risks of bleeding complications.

Objectives

To assess the effects of perioperative NSAID use versus non-NSAID analgesics (other pain medications) in women undergoing any form of breast surgery.

Search methods

The Cochrane Breast Information Specialist searched the Cochrane Breast Cancer Group (CBCG) Specialized Register, CENTRAL (the Cochrane Library), MEDLINE, Embase, The WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov registries to 21 September 2020. Full articles were retrieved for potentially eligible trials.

Selection criteria

We considered all randomized controlled trials (RCTs) looking at perioperative NSAID use in women undergoing breast surgery.

Data collection and analysis

Two review authors independently screened studies, extracted data and assessed risk of bias, and certainty of the evidence using the GRADE approach. The main outcomes were incidence of breast hematoma within 90 days (requiring reoperation, interventional drainage, or no treatment) of breast surgery and pain intensity 24 hours following surgery, incidence rate or severity of postoperative nausea, vomiting or both, bleeding from any location within 90 days, need for blood transfusion, other side effects of NSAID use, opioid use within 24 hours of surgery, length of hospital stay, breast cancer recurrence, and non-prescribed NSAID use. Data were presented as risk ratios (RRs) for dichotomous outcomes and standardized mean differences (SMDs) for continuous outcomes.

Main results

We included 12 RCTs with a total of 1596 participants. Seven studies compared NSAIDs (ketorolac, diclofenac, flurbiprofen, parecoxib and celecoxib) to placebo. Four studies compared NSAIDs (ketorolac, flurbiprofen, ibuprofen, and celecoxib) to other analgesics (morphine, hydrocodone, hydromorphone, fentanyl). One study compared NSAIDs (diclofenac) to no intervention.

NSAIDs compared to placebo

Most outcomes are judged to have low-certainty evidence unless stated otherwise. There may be little to no difference in the incidence of breast hematomas within 90 days of breast surgery (RR 0.33, 95% confidence interval (CI) 0.05 to 2.02; 2 studies, 230 participants; I^2 = 0%). NSAIDs may reduce pain intensity 24 (± 12) hours following surgery compared to placebo (SMD -0.26, 95% CI -0.49 to -0.03; 3 studies, 310 participants; I^2 = 73%). There may be little to no difference in the incidence rates or severities of postoperative nausea, vomiting, or both (RR 1.15, 95% CI 0.58 to 2.27; 4 studies, 939 participants; I^2 = 81%), bleeding from any location within 90 days (RR 1.05, 95% CI 0.89 to 1.24; 2 studies, 251 participants; I^2 = 8%), or need for blood transfusion compared to placebo groups, but we are very uncertain (RR 4.62, 95% CI 0.23 to 91.34; 1 study, 48 participants; very low-certainty evidence). There may be no difference in other side effects (RR 1.12, 95% CI 0.44 to 2.86; 2 studies, 251 participants; I^2 = 0%). NSAIDs may reduce opioid use within 24 hours of surgery compared to placebo (SMD -0.45, 95% CI -0.85 to -0.05; 4 studies, 304 participants; I^2 = 63%).

NSAIDs compared to other analgesics

There is little to no difference in the incidence of breast hematomas within 90 days of breast surgery, but we are very uncertain (RR 0.33, 95% CI 0.01 to 7.99; 1 study, 100 participants; very low-certainty evidence). NSAIDs may reduce pain intensity 24 (± 12) hours following surgery (SMD -0.68, 95% CI -0.97 to -0.39; 3 studies, 200 participants; I^2 = 89%; low-certainty evidence) and probably reduce the incidence rates or severities of postoperative nausea, vomiting, or both compared to other analgesics (RR 0.18, 95% CI 0.06 to 0.57; 3 studies, 128 participants; I^2 = 0%; moderate-certainty evidence). There is little to no difference in the development of bleeding from any location within 90 days of breast surgery or in other side effects, but we are very uncertain (bleeding: RR 0.33, 95% CI 0.01 to 7.99; 1 study, 100 participants; other side effects: RR 0.11, 95% CI 0.01 to 1.80; 1 study, 48 participants; very low-certainty evidence). NSAIDs may reduce opioid use within 24 hours of surgery compared to other analgesics (SMD -6.87, 95% CI -10.93 to -2.81; 3 studies, 178 participants; I^2 = 96%; low-certainty evidence).

NSAIDs compared to no intervention

There is little to no difference in pain intensity 24 (± 12) hours following surgery compared to no intervention, but we are very uncertain (SMD -0.54, 95% CI -1.09 to 0.00; 1 study, 60 participants; very low-certainty evidence).

Authors' conclusions

Low-certainty evidence suggests that NSAIDs may reduce postoperative pain, nausea and vomiting, and postoperative opioid use. However, there was very little evidence to indicate whether NSAIDs affect the rate of breast hematoma or bleeding from any location within 90 days of breast surgery, the need for blood transfusion and incidence of other side effects compared to placebo or other analgesics. High-quality large-scale RCTs are required before definitive conclusions can be made.

PLAIN LANGUAGE SUMMARY

Pain medications (NSAIDs: nonsteroidal anti-inflammatory drugs) around the time of surgery in women undergoing breast surgery

What is the aim of this review?

The aim of this review was to find out whether NSAID pain medication reduces pain around the time of any breast surgery compared to no medication (placebo) or other pain medication (e.g. opioids). Possible side effects from NSAIDS were reviewed and compared to side effects for patients either having no medication or other types of pain relief. NSAID pain medications include ketorolac, flurbiprofen, ibuprofen, and celecoxib.

Why does it matter?

NSAIDs have been shown to decrease inflammation, pain, and fever, while potentially increasing the risks of bleeding complications. There are concerns about the safety of NSAID pain medication during breast surgery, but they still may be better than other drugs (opioids) which have different side effects of concern.

What was studied in the review?

Studies included women who received either a NSAID pain medication or placebo, other pain medication, or no medication. We wanted to assess breast bleeding, pain following surgery, postoperative nausea and vomiting, bleeding from any location, need for blood transfusion, any other side effects reported from NSAID use, opioid use within 24 hours of surgery, length of hospital stay, breast cancer recurrence, and non-prescribed NSAID use.

What did we find?

We found 12 studies with a total of 1596 participants. The evidence is current to September 2020. Seven studies compared NSAIDs (ketorolac, diclofenac, flurbiprofen, parecoxib and celecoxib) to placebo. Four studies compared NSAIDs (ketorolac, flurbiprofen, ibuprofen, and celecoxib) to other pain medications. One study compared NSAIDs (diclofenac) to no medication.

NSAIDs compared to placebo :the use of NSAIDs seems to make little difference to the incidence of breast hematoma (a collection of blood inside the armpit or breast surgical site) and bleeding from any location or increase in blood transfusions within 90 days of breast surgery. There was no increase in postoperative nausea and vomiting. NSAIDs may reduce pain within 24 hours after surgery and reduce the use of opioids within 24 hours after surgery.

NSAIDs compared to other pain medications : the use of NSAIDs may make little difference to the incidence of breast hematoma or bleeding from any location or need for blood transfusion within 90 days of breast surgery. NSAIDs may reduce pain within 24 hours and reduce the chance of nausea and vomiting after surgery. There is little to no difference in the incidence of other side effects. NSAIDS may reduce opioid use within 24 hours of surgery compared to other pain medications.

NSAIDs compared to no medication : the use of NSAIDs appears to make little to no difference in pain within 24 hours after surgery compared to no medication.

Many studies did not collect or report data on the need for blood transfusions, length of hospital stay, breast cancer recurrence, and non-prescribed NSAID pain medication use.

What do the findings mean?

In summary, the studies were small, different to each other and did not report all the possible side effects well. Therefore we could not make firm conclusions about the benefits or harms of NSAIDs. This review provides preliminary evidence, but more studies are needed to make sure there is no harm from the use of NSAIDS after breast surgery. Good-quality large-scale studies are required before any definitive conclusions can be made.

How up-to-date is this review?

The review authors searched for studies that had been published up to 21 September 2020.

SUMMARY OF FINDINGS

Summary of findings 1. NSAID compared to placebo in women undergoing breast surgery

NSAID compared to placebo in women undergoing breast surgery

Patient or population: women undergoing breast surgery
Setting: inpatient and outpatient
Intervention: NSAID
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments: types of NSAIDs
	Risk with placebo	Risk with NSAID				
Incidence of breast hematoma	35 per 1000	12 per 1000 (2 to 71)	RR 0.33 (0.05 to 2.02)	230 (2 RCTs)	⊕⊕⊖⊖ Low[a,b,c,g]	parecoxib, celecoxib
Preoperative	15 per 1000	15 per 1000 (1 to 230)	RR 1.00 (0.06 to 15.66)	136 (1 RCT)	⊕⊕⊖⊖ Low[a,g,h]	parecoxib
Pain intensity 24 (± 12) hours following surgery	The mean pain intensity 24 (± 12) hours following surgery - perioperative was 0	SMD 0.26 lower (0.49 lower to 0.03 lower)	-	310 (3 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,e,j]	ketorolac, diclofenac
Preoperative	The mean pain intensity 24 (± 12) hours following surgery - preoperative was 0	SMD 0.19 lower (0.46 lower to 0.09 higher)	-	202 (1 RCT)	⊕⊕⊖⊖ Low[b,h]	ketorolac
Postoperative	The mean pain intensity 24 (± 12) hours following surgery - postoperative was 0	SMD 0.04 higher (0.50 lower to 0.57 higher)	-	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d,e,h,i]	ketorolac
Incidence rate or severity of postoperative nausea, vomiting, or both	111 per 1000	128 per 1000 (64 to 252)	RR 1.15 (0.58 to 2.27)	939 (4 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,e,i,k]	ketorolac, diclofenac, celecoxib, parecoxib
Preoperative	60 per 1000	177 per 1000 (25 to 1000)	RR 2.95 (0.42 to 20.64)	831 (2 RCTs)	⊕⊖⊖⊖	celecoxib, parecoxib

					Very low[a,b,c,e,f,i,j]	
Postoperative	700 per 1000	399 per 1000 (252 to 644)	RR 0.57 (0.36 to 0.92)	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d,e,i]	ketorolac
Bleeding from any location within 90 days	169 per 1000	178 per 1,000 (151 to 210)	RR 1.05 (0.89 to 1.24)	251 (2 RCT)	⊕⊕⊖⊖ LOW[a,b,g]	ketorolac, diclofenac
Preoperative	0 per 1000	0 per 1000 (0 to 0)	RR 3.34 (0.14 to 81.03)	203 (1 RCT)	⊕⊖⊖⊖ Very low[b,g,h]	ketorolac
Need for blood transfusion	0 per 1000	0 per 1000 (0 to 0)	RR 4.62 (0.23 to 91.34)	48 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,g,i]	diclofenac
Preoperative	0 per 1000	0 per 1000 (0 to 0)	RR 4.62 (0.23 to 91.34)	48 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,g,i]	diclofenac
Other side effects of NSAID use	62 per 1000	69 per 1000 (27 to 176)	RR 1.12 (0.44 to 2.86)	251 (2 RCTs)	⊕⊕⊖⊖ Low[a,b,g]	ketorolac, diclofenac
Preoperative	65 per 1000	83 per 1000 (31 to 221)	RR 1.27 (0.48 to 3.38)	203 (1 RCT)	⊕⊕⊖⊖ Low[b,h]	ketorolac
Opioid use within 24 (± 12) hours of surgery	The mean opioid use within 24 (± 12) hours of surgery - preoperative was 0	SMD 0.45 lower (0.85 lower to 0.05 lower)	-	304 (4 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,e,j]	ketorolac, diclofenac, parecoxib, flurbiprofen
Preoperative	The mean opioid use within 24 (± 12) hours of surgery - preoperative was 0	SMD 0.85 lower (1.20 lower to 0.50 lower)	-	136 (1 RCT)	⊕⊕⊖⊖ Low[a,h]	parecoxib
Postoperative	The mean opioid use within 24 (± 12) hours of surgery - postoperative was 0	SMD 0.29 lower (0.83 lower to 0.25 higher)	-	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d,e,g,h]	ketorolac

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NSAID**: nonsteroidal anti-inflammatory drug; **RCT**: randomized controlled trial; **RR:** risk ratio; **SMD**: standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We downgraded by 1 point for ≥ 1 of the following and 2 points for > 4 of the following due to risk of bias.
[a]Unclear or high risk selective reporting.
[b]Unclear or high risk incomplete outcomes data.
[c]Unclear or high risk allocation concealment.
[d]Unclear or high risk random sequence generation.
[e]Unclear or high risk blinding of outcome assessment.
[f]Unclear or high risk blinding of participants and personnel.
We downgraded by 1 point for each of the following.
[g]Imprecision.
[h]Single study.
[i]Sample < 100 participants.
[j]Heterogeneity > 50%.
[k]Heterogeneity > 75%.

Summary of findings 2. NSAID compared to other analgesic in women undergoing breast surgery

NSAID compared to other analgesic in women undergoing breast surgery

Patient or population: women undergoing breast surgery
Setting: inpatient and outpatient
Intervention: NSAID
Comparison: other analgesic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments: types of NSAIDs; types of other analgesics
	Risk with other analgesic	Risk with NSAID				
Incidence of breast hematoma within 90 days of breast surgery	20 per 1000	7 per 1000 (0 to 160)	RR 0.33 (0.01 to 7.99)	100 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e,f]	celecoxib; hydrocodone
Pain intensity 24 (± 12) hours following surgery	The mean pain intensity 24 (± 12) hours following	SMD 0.68 lower (0.97 lower to 0.39 lower)	-	200 (3 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,i]	celecoxib, flurbiprofen, ibuprofen; fentanyl, hy-

	surgery - perioperative was 0					drocodone, hydromorphone
Postoperative	The mean pain intensity 24 (± 12) hours following surgery - postoperative was 0	SMD 0.12 lower (0.51 lower to 0.27 higher)	-	100 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	flurbiprofen, ibuprofen; fentanyl, hydromorphone
Incidence rate or severity of postoperative nausea, vomiting, or both	243 per 1000	44 per 1000 (15 to 138)	RR 0.18 (0.06 to 0.57)	128 (3 RCTs)	⊕⊕⊕⊖ Moderate[a,c]	ketorolac, ibuprofen, flurbiprofen; morphine, hydromorphone, fentanyl
Bleeding from any location within 90 days	20 per 1000	7 per 1000 (0 to 160)	RR 0.33 (0.01 to 7.99)	100 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e,f]	celecoxib; hydrocodone
Other side effects of NSAID use	233 per 1000	26 per 1000 (2 to 420)	RR 0.11 (0.01 to 1.80)	48 (1 RCT)	⊕⊖⊖⊖ Very low[e,f,g]	ibuprofen; hydromorphone
Opioid use within 24 (± 12) hours of surgery	The mean opioid use within 24 (± 12) hours of surgery - perioperative was 0	SMD 6.87 lower (10.93 lower to 2.81 lower)	-	178 (3 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,i]	celecoxib, ketorolac, flurbiprofen; hydrocodone, morphine, fentanyl
Postoperative	The mean opioid use within 24 (± 12) hours of surgery - postoperative was 0	SMD 9.56 lower (18.48 lower to 0.64 lower)	-	78 (2 RCTs)	⊕⊕⊖⊖ Low[a,c,g,i]	ketorolac, flurbiprofen; morphine, fentanyl

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NSAID**: nonsteroidal anti-inflammatory drug; **RCT**: randomized controlled trial; **RR:** risk ratio; **SMD**: standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
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[a]Unclear or high risk selective reporting.
[b]Unclear or high risk allocation concealment.
[c]Unclear or high risk blinding of outcome assessment.
[d]Unclear or high risk blinding of participants and personnel.

We downgraded by 1 point for each of the following
[e]Imprecision.
[f]Single study.
[g]Sample < 100 participants.
[h]Heterogeneity > 50%.
[i]Heterogeneity > 75%.

Summary of findings 3. NSAID compared to no intervention in women undergoing breast surgery

NSAID compared to no intervention in women undergoing breast surgery

Patient or population: women undergoing breast surgery
Setting: inpatient and outpatient
Intervention: NSAID
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments: types of NSAIDs
	Risk with no intervention	Risk with NSAID				
Pain intensity 24 (±12) hours following surgery	The mean pain intensity 24 (± 12) hours following surgery - perioperative was 0	SMD 0.54 lower (1.09 lower to 0.00)	-	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]	diclofenac
Preoperative	The mean pain intensity 24 (± 12) hours following surgery - preoperative was 0	SMD 0.35 lower (0.97 lower to 0.28 higher)	-	40 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]	diclofenac
Postoperative	The mean pain intensity 24 (± 12) hours following surgery - postoperative was 0	SMD 0.66 lower (1.30 lower to 0.02 lower)	-	40 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]	diclofenac

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NSAID**: nonsteroidal anti-inflammatory drug; **RCT**: randomized controlled trial; **SMD**: standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We downgraded by 1 point for ≥ 1 of the following and 2 points for > 4 of the following due to risk of bias.
[a]Unclear or high risk selective reporting.
[b]Unclear or high risk allocation concealment.
[c]Unclear or high risk blinding of outcome assessment.
We downgraded by 1 point for each of the following.
[d]Sample < 100 participants.
[e]Single study.

BACKGROUND

Description of the condition

A breast hematoma, or a collection of blood inside the axilla or surgical breast site, is one potential complication following breast surgery. A hematoma can require additional surgery to drain and/or readmission to the hospital, and it may predispose patients to infection (Cheng 2011). Addressing these complications may limit the amount of money reimbursed to providers (Smith 2017), factoring into their decision to perform a lower yield procedure with a lower risk of complications (De Souza 2012; Smith 2017). Furthermore, hematomas may increase patients' emotional stress and physical pain (Kaoutzanis 2017). While the incidence of hematomas associated with breast surgery requiring return to the operating room is relatively low (less than 2.1%) (Collins 2012; Gobble 2014; Yan 2015), the large number of breast surgery procedures performed every year makes its negative consequences significant at a population level. Nonsteroidal anti-inflammatory drugs (NSAIDs) are being increasingly used to treat postoperative pain, and it is unclear whether there is an association between perioperative (relating to, occurring in, or being the period around the time of a surgical operation, Merriam-Webster 1966) NSAID use and potential increased risks of hematoma development at the surgical site.

Breast surgery encompasses oncologic, reconstructive, and cosmetic procedures. An estimated 316,120 women were diagnosed with breast cancer in 2017 in the USA, with approximately 97% of stage I and II, 93% of stage III, and 31% of stage IV patients undergoing surgical treatment (ACS 2017). Commonly performed oncologic breast procedures include lumpectomy, mastectomy, sentinel lymph node biopsy, and axillary dissection. In 2017, members of the American Society for Plastic Surgery (ASPS) performed over 600,000 reconstructive and cosmetic breast cases, including implant-based reconstruction, autologous flap reconstruction, mastopexy, and augmentation, among others (ASPS 2017). Approximately 29% of these were reconstructive procedures, while the remaining 71% were cosmetic procedures (ASPS 2017).

Description of the intervention

The American Society of Anesthesiologists (ASA) released its most recent practice guidelines for acute pain management in the perioperative period in 2016 (Chou 2016). Medication selection for perioperative pain management is guided by patient factors, but an underlying principle is a multimodal approach, that is, where two or more drugs with differing modes of action are used to treat acute surgical pain.

Opioid drugs remain a mainstay of analgesia; however, 20 years ago Kehlet 1997 introduced the now-common recommendation of an 'around-the-clock' regimen of a nonsteroidal anti-inflammatory drug (NSAID, for example ketorolac, flurbiprofen, diclofenac, celecoxib) and/or acetaminophen (paracetamol), unless contraindicated. This concept has been more recently adapted into standardized breast surgical treatment plans (Batdorf 2015; Bonde 2015; Bonde 2016; Davidge 2013). NSAID use has demonstrated equivalent efficacy to opioids and similar postoperative bleeding when compared to controls in a wide range of surgical procedures (Gobble 2014). Perioperative NSAID use for patients undergoing endoscopic sinus surgery reduced postoperative rescue analgesics that included opioid use in many studies, with bleeding seen in 0.8% of patients (Svider 2018). Perioperative NSAID use in pediatric patients undergoing tonsillectomy concluded there was insufficient evidence to exclude an increased risk of bleeding (Lewis 2013).

How the intervention might work

NSAIDs inhibit cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis and an inflammatory response that causes pain. There are two types of COX enzymes: COX-1 and COX-2. Both types produce prostaglandins that promote inflammation, pain, and fever. Most NSAIDs are reversible inhibitors; however, aspirin binds permanently to COX enzymes, leading to a prolonged duration of effect.

The use of NSAIDs perioperatively may be associated with bleeding complications. This is because NSAID inhibition of COX-1 reduces thromboxane A2, which mediates platelet aggregation. Most cells, including those in the stomach, express COX-1, which provides a protective effect in gastric tissue, so NSAIDs' inhibition of COX-1 enzymes can lead to bleeding from the stomach.

Non-selective NSAIDs also inhibit COX-2, and their effects can be different to those that inhibit COX-1 enzymes. COX-2 is the most important contributor to inflammation, hypertension, and possibly cancer. It is induced by immune cell factors, shear stress, and tumour promoters. Selective COX-2 inhibitors target the inflammatory process while minimizing gastric and non-gastric bleeding. They may reduce the risks of hematoma and other significant bleeding after breast surgery, while still providing adequate pain control in comparison to non-selective COX-1/COX-2 inhibitors by reducing endothelial prostacyclin and consequently increasing platelet aggregation. In this regard, focusing on the NSAID ketorolac may be misleading, as this has the highest COX-1 selectivity of all the NSAIDs (Cheng 2016; Jarupongprapa 2013; Schmidt 2016).

A retrospective analysis of perioperative ketorolac use in patients undergoing breast reduction surgery demonstrated ketorolac was associated with a three-fold increase in developing a hematoma and the need to return to the operating room for hematoma removal (Cawthorn 2012). A randomized controlled trial (RCT) comparing a NSAID (ketorolac) to a non-NSAID (metamizol) for postoperative pain in elective plastic surgery reported postoperative bleeding in two patients receiving a NSAID that required a return to the operating room (Marin-Bertolin 1997). Other studies have demonstrated no difference in bleeding rates between different NSAIDs (i.e. flurbiprofen or ketorolac) and placebo (Gobble 2014; Sun 2013). In patients receiving perioperative diclofenac, the risk associated with postoperative bleeding was higher than placebo; however, none of the patients needed reoperation for bleeding or hematoma (Cheng 2016).

A large number of studies have investigated whether NSAIDs are efficacious in reducing postoperative pain. Meta-analyses of RCTs comparing opioid medication alone versus opioids plus NSAIDs in surgical patients found that the addition of ketorolac to intravenous morphine significantly improved pain scores and reduced analgesic use compared to intravenous morphine alone; however, these benefits were not as clear when intravenous patient-controlled opioid analgesia was compared alone to a selective COX-2 inhibitor or a non-selective NSAID (ASA 2012).

Another meta-analysis of RCTs found the addition of a NSAID to be superior to placebo in reducing postoperative pain (Gobble 2014). When selective COX-2 inhibitors (rofecoxib, etoricoxib, celecoxib, and parecoxib) were administered preoperatively, they significantly reduced postoperative pain when compared to placebo (Nir 2016). However, COX-2 inhibitors have been associated with early failure of vascular free flaps (i.e. tissue that is disconnected from its original blood supply and reconnected at another location in the body) due to thrombosis from a lack of thromboxane A2 inhibition and platelet aggregation (Al-Sukhun 2006; Bonde 2017).

Recent evidence suggests perioperative NSAIDs (flurbiprofen axetil and ketorolac) may be associated with decreased recurrences of breast cancer by inhibiting pro-inflammatory and pro-tumorigenic factors in patients undergoing surgery. These inflammatory factors may impair the immune system and promote tumour recurrence and metastasis (Desmedt 2018; Forget 2013). Other non-NSAID pain medications lack these anti-inflammatory characteristics. Even within the different classes of NSAIDs, results vary within patient demographics. A comparison of intraoperative ketorolac versus diclofenac in patients with an increased body mass index showed that ketorolac but not diclofenac was associated with reductions in the incidence of distant metastasis (Desmedt 2018).

Why it is important to do this review

With the recent focus on the over-prescribing of opioids in the literature, it is important to assess the effectiveness and safety of non-opioid pain medication regimens including NSAIDs (HHS 2016). Clinicians have differing opinions on the safety of perioperative NSAIDs for breast surgery given the unclear risk/benefit ratio. A hematoma during a plastic surgery procedure can result in complete loss of the reconstruction (Mikhaylov 2018).

Previous systematic reviews, focused on evaluating NSAID analgesics in breast surgery, were limited in scope (Cheng 2016; Gobble 2014; Stephens 2015). Stephens 2015 conducted a systematic review to assess the association between perioperative use of ketorolac and the incidence of hematomas in 981 patients undergoing face and breast plastic surgery procedures. Although they found a two-fold increase in the incidence of hematomas in patients who received ketorolac, this difference was not statistically significant (Stephens 2015). A single-institution study by Sharma 2001 also did not find any significant association between the use of ketorolac and the incidence of hematomas in breast reconstruction procedures. The relatively small sample sizes included in these studies may potentially account for the lack of association demonstrated between perioperative NSAID use and hematoma development. Additionally, these results addressed very specific patient populations, so the conclusions may not be generalizable to patients undergoing alternate breast surgery procedures. Furthermore, some countries rarely use ketorolac as the perioperative NSAID. An evaluation of other NSAIDs more commonly used around the world needs to be completed.

As perioperative NSAID use was associated with a clinical decrease of recurrence of breast cancer, it needs to be determined if this clinical effect would outweigh contraindications to receiving NSAIDs in these patients. The American Society of Plastic Surgeons (ASPS) recommends that patients stop taking NSAIDs, including aspirin, prior to breast surgery (ASPS 2018). Research has not yet clarified the risks and benefits of all NSAIDs between cosmetic and reconstructive breast surgery patients. Assessing different proportions of COX-1/COX-2 inhibition and patient outcomes may provide a more uniform standard of care. There is currently no Cochrane Review on perioperative NSAID use for breast surgery. These results will help lead to more conclusive surgical practice guidelines for plastic surgeons encountering perioperative outcomes.

The impact of NSAID use is a very complex topic. The focus of this Cochrane review is on surgical site bleeding outcomes, however there are a multitude of important perioperative outcomes, including venous thromboembolism, major adverse cardiac events, acute kidney injury, gastrointestinal ulceration, and potential cancer recurrence or remission. These outcomes increase with age (Wongrakpanich 2018). In addition, other comorbidities can increase the frequency of these outcomes (Harirforoosh 2013; Wongrakpanich 2018). COX-1 and COX-2 inhibitor selectivity is highly relevant when assessing the risk-benefit balance in this regard.

OBJECTIVES

To assess the effects of perioperative NSAID use versus non-NSAID analgesics (other pain medications) in women undergoing any type of breast surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) looking at perioperative NSAID use in women undergoing breast surgery, and prioritized and presented them separately in the review.

Types of participants

We included women over the age of 18 who underwent any type of breast surgery. This included oncologic, reconstructive or cosmetic surgery. Trials included participants receiving a specified perioperative NSAID. We excluded studies that did not report results of our desired population separately.

Types of interventions

All interventions that compared perioperative systemic NSAID use. The comparisons included:

- NSAID versus placebo (provides psychological effect of taking a medication with no physical effect);
- NSAID versus other analgesic drug (morphine, hydrocodone, hydromorphone, fentanyl);
- NSAID versus no intervention.

Terms used to refer to NSAIDs included aspirin, salicylic acid, diflunisal, propyphenazone, indomethacin, diclofenac, aceclofenac, etodolac, ketorolac, sulindac, ibuprofen, naproxen, fenoprofen, flurbiprofen, ketoprofen, mefenamic acid, meclofenamate, meloxicam, piroxicam, nabumetone, celecoxib, etoricoxib, parecoxib, and rofecoxib.

This included any non-selective COX or selective COX-2 inhibitors administered by the following routes (intravenous, intramuscular, rectal, or oral) during hospital admission.

Types of outcome measures

Primary outcomes

- Incidence of breast hematoma within 90 days of breast surgery (requiring reoperation, interventional drainage, or no treatment). Hematomas were measured with clinical diagnosis alone or imaging.
- Pain intensity 24 (± 12) hours following surgery. Pain was measured with validated pain scales including the numerical rating scale (NRS), visual analogue scale (VAS), and verbal categorical rating scale (VRS), which are ascertained from reviews on pain assessment (Hjermstad 2011; Younger 2009).

Secondary outcomes

- Incidence rate or severity of postoperative nausea, vomiting, or both
- Bleeding from any location within 90 days
- Need for blood transfusion
- Other side effects of NSAID use
- Opioid use within 24 (± 12) hours of surgery
- Length of hospital stay
- Breast cancer recurrence
- Non-prescribed NSAID use

Severity of postoperative nausea and vomiting was reported with the following scales: Likert scales, VAS, postoperative nausea and vomiting (PONV) intensity scale (Wengritzky 2010), or PONV impact scale (Myles 2012).

We determined opioid use in studies that permitted co-administration of opioids, evaluated mean opioid use (in mg) over various study time intervals and standardized into morphine equivalents using opioid conversion tables (Jacox 1994).

Other secondary outcomes were based on the measures used by the included studies.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- The Cochrane Breast Cancer Group (CBCG) Specialized Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined on the Group's website (breastcancer.cochrane.org/sites/breastcancer.cochrane.org/files/public/uploads/specialised_register_details.pdf). We considered trials with the key words "non-steroidal anti-inflammatory agents", "NSAID", "NSAIDS", "breast surgery", "breast augmentation", "mammoplasty" and/or "mastectomy" for inclusion in the review.
- CENTRAL (the Cochrane Library, Issue 8, 2020). See Appendix 1.
- MEDLINE (via OvidSP) from 1950 to 21 September 2020. See Appendix 2.
- Embase (via embase.com) from 1980 to 21 September 2020. See Appendix 3.
- The WHO International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials on 21 September 2020. See Appendix 4.
- ClinicalTrials.gov (clinicaltrials.gov) on 21 September 2020. See Appendix 5.

Searching other resources

We identified further studies by handsearching reference lists of identified relevant trials or reviews and obtained a copy of the full article for each reference reporting a potentially eligible trial. Where this was not possible, we attempted to contact authors to provide additional information.

Data collection and analysis

Selection of studies

Two review authors (KMK, AE) independently screened all study titles and abstracts from the results of our search strategy. In case of disagreement on study inclusion, these two review authors met to discuss eligibility and involved a third review author (GDR) if necessary. We followed a similar process during full-text screening. The selection process was recorded in the PRISMA flow diagram and at every step, and we recorded the reasons for exclusion in the Characteristics of excluded studies tables. There were no language restrictions; if necessary, we had non-English papers translated. References were managed with Covidence.

Data extraction and management

Two review authors (KMK, AE) independently extracted quantitative data related to the primary and secondary outcomes using standardized data extraction forms and Covidence systematic review software (Covidence). Information extracted from each included trial consisted of the following.

- Characteristics of trial participants (age, type of breast surgery, breast cancer history)
- Type of intervention (type, dose, duration, frequency, and perioperative administration timing of NSAID and/or non-NSAID, placebo, or no treatment)
- Type of outcome measure (occurrence and treatment of breast hematoma, level of pain, occurrence or severity of PONV, length of stay)
- Study information data (e.g. study design, sample size of each study group, year, location, author list), recorded for the purposes of identification and quality appraisal
- Risk of bias domains (Higgins 2011)

These study authors met and determined whether any disagreements exist in the data extracted and resolved disagreements through discussion, involving a third review author (GDR) when necessary. We identified reports pertaining to the same study, selected a single one as the primary reference for inclusion based on completeness of reporting. We did not include non-randomized studies in our review, so we did not extract data on the following: methods used to control for confounders, adjusted and unadjusted outcome measures, and the list of variables authors have included in analyses for adjusted estimates.

Assessment of risk of bias in included studies

Two review authors (KMK, AE) independently assessed risk of bias using the Cochrane RoB 1 tool (Higgins 2011), resolved any

disagreement through discussion and involved a third review author (GDR) when necessary. We evaluated the following items using the risk of bias table.

Randomized studies

- Random sequence generation (to assess possible selection bias)
- Allocation concealment (to assess possible selection bias)
- Blinding of participants and personnel (to assess possible performance bias)
- Blinding of outcome assessment (to assess possible detection bias)
- Incomplete outcome data (to assess possible attrition bias)
- Selective outcome reporting (to assess possible reporting bias)

Moreover, we assessed all studies to evaluate if they were at overall high risk of bias according to Higgins 2011. We considered the magnitude of bias with random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. We considered studies to be at low overall risk of bias if they used a truly random process for sequence generation, concealed allocation, had no missing outcomes data, did not selectively report prespecified outcomes, blinded participants and personnel and blinded outcome assessments. Otherwise, we classified the studies as high risk of overall bias. We did not assess the impacts of risk using a sensitivity analysis with funnel plots due to fewer than 10 studies in comparative groups.

Review question

Does perioperative (preoperative, intraoperative, postoperative) administration of NSAIDs control postoperative pain without increasing the risk of hematoma within the first 90 days of the operation?

Confounding factors

We considered the following factors to be relevant to all or most studies.

- Primary diagnosis
- Age (age > 75 years associated with increased risk of bleeding)
- Previous severe bleeding on NSAIDS (WHO grade 3 or 4)
- Prior major cardiac event (serious cardiovascular thrombotic events, myocardial infarction, and stroke)
- Use of anticoagulation during the study
- Performance status (Eastern Cooperative Oncology Group (ECOG))
- Presence of bleeding disorder
- Stage 4 or 5 chronic kidney disease
- Dialysis

Co-interventions

These potential co-interventions could be different between treatment groups and have an impact on outcomes.

- Use of over-the-counter NSAIDs
- Use of anticoagulation
- Use of antiplatelet medication
- Use of over-the-counter or herbal medicines

Measures of treatment effect

For dichotomous outcomes (i.e. incidence of hematoma requiring reoperation within 90 days of breast surgery; incidence of hematoma requiring drainage within 90 days of breast surgery; and incidence of hematoma, regardless of treatment, within 90 days of breast surgery), we measured the effect using risk ratio (RR) and 95% confidence intervals (CIs).

For continuous outcomes collected with different scales (i.e. pain 24 (± 12) hours following surgery, postoperative nausea and vomiting at 24 (± 12) hours from surgery), we measured the effect using standardized mean differences (SMDs) with 95% CIs.

For continuous outcomes collected on the same scale (i.e. length of stay and opioid use), we measured the effect using mean differences (MDs) with corresponding standard deviation (SD) and 95% CIs.

Unit of analysis issues

We did not find any cluster-randomized trials. Chan 1996 had five treatment arms. We only assessed treatment arms with comparable interventions. In three treatment arms bupivacaine was administered postoperatively. The first treatment arm administered diclofenac preoperatively, placebo postoperatively and bupivacaine postoperatively. The second treatment arm administered placebo preoperatively, diclofenac postoperatively and bupivacaine postoperatively. The third control arm (no intervention) only administered bupivacaine postoperatively. We compared both the first and second treatment arms to the control arm. To avoid duplicating control arm results during combined perioperative comparisons, we combined the first treatment and second treatment arms into a single group to create a single pair-wise comparison, as outlined in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions*. We made separate comparisons of the first treatment arm and control arm (preoperative) and second treatment arm and control arm (postoperative).

Dealing with missing data

We attempted to obtain missing data from study authors and perform intention-to-treat (ITT) analyses if possible. Otherwise, we performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-up and withdrawals) and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We initially assessed clinical and methodological heterogeneity of included trials qualitatively with regard to patient characteristics, type of breast surgery, NSAIDs use, timing of NSAID administration, and measurement of outcomes. We extracted, recorded, and qualitatively evaluated possible sources of heterogeneity from the data.

We assessed statistical heterogeneity by calculating I^2 (Higgins 2011), considered statistical heterogeneity as substantial if I^2 was greater than 50% and the τ^2 was greater than zero or there was a difference detected using P values in the Chi^2 test for heterogeneity (Higgins 2011).

Assessment of reporting biases

We planned to use funnel plots to assess reporting bias if we had 10 or more studies for the primary outcome. However, the meta-analysis for the primary outcomes included fewer than 10 studies (Higgins 2011).

Data synthesis

We conducted statistical analysis using Review Manager 5 software (Review Manager 2020). We used a fixed-effect model for the meta-analysis if it was acceptable to assume the trials were estimating the same treatment effect. We used a random-effects model for incidence rate or severity of postoperative nausea, vomiting, or both, other side effects of NSAID use, and opioid use within 24 (± 12) hours of surgery to produce an overall summary of the average clinical treatment effect. If we detected substantial statistical heterogeneity, we did not pool results from the meta-analysis but instead reported the data narratively.

We pooled dichotomous outcomes using Mantel-Haenszel analysis for a fixed-effect model or DerSimonian and Laird for a random-effects model, and we pooled continuous outcomes using the inverse-variance method.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for timing of drug administration (preoperative and postoperative). Information and an adequate number of studies and population samples were not available to perform a subgroup analysis for type of breast surgery, type of NSAID (non-selective, COX-2 inhibitor, aspirin), different drug doses, route of drug administration, timing of drug administration (intraoperative), and breast cancer status of included women (history of breast cancer, no history of breast cancer).

Sensitivity analysis

Information and an adequate number of studies and population samples were not available to perform a sensitivity analysis for studies with unclear or high risk of bias for all risk of bias domains.

Summary of findings and assessment of the certainty of the evidence

Two review authors (KMK, AE) assessed the certainty of evidence according to the GRADE approach for seven outcomes of interest, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We prepared a summary of findings table using GRADE software (GRADEproGDT), and presented findings for the following seven outcomes: incidence of breast hematoma (requiring reoperation or interventional drainage or no treatment); pain intensity 24 (± 12) hours following surgery; postoperative nausea, vomiting, or both; bleeding from any location; need for blood transfusion; other side effects of NSAID use; and opioid use within 24 (± 12) hours of surgery.

RESULTS

Description of studies

Results of the search

We searched the main databases and trial registries on 21 September 2020. The search resulted in 5085 references imported for screening. Upon removal of duplicate records, we screened 4595 records. Following title/abstract review, 87 references were eligible for full-text review. We excluded 74 studies after full-text review. Figure 1 illustrates details of the process of screening and selecting studies for inclusion in the review. Following full-text review, we included 12 studies (Bakr 2016; Bosek 1996; Chan 1996; Forget 2019; Freedman 2006; Legeby 2005; Oh 2016; Parsa 2005; Romundstad 2006a; Sun 2013; van Helmond 2016; Wen 2015). One study is ongoing (NCT03535116 2018).

Figure 1. Study flow diagram.

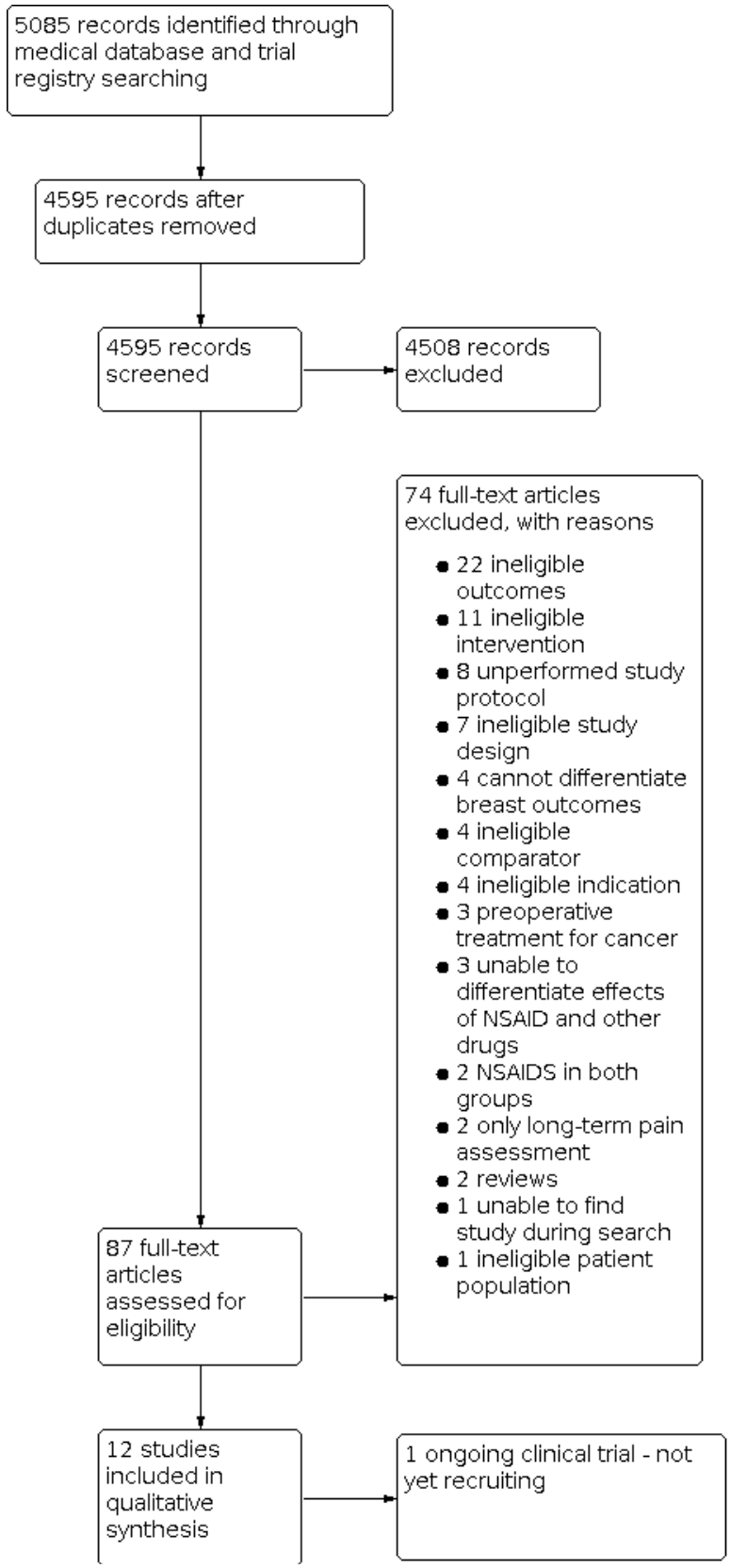
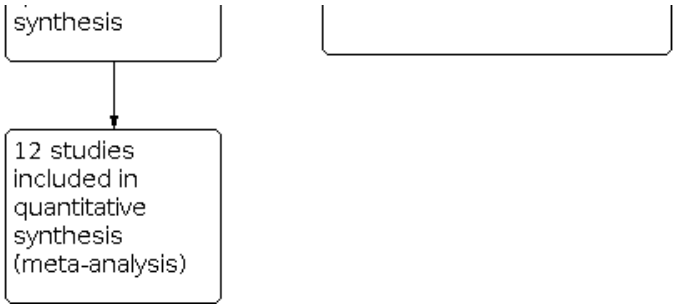


Figure 1. (Continued)



Included studies

The 12 studies included a total of 1596 participants. Data for at least one outcome was reported in all 12 studies.

Seven studies compared 654 patients receiving NSAIDs (ketorolac (Bosek 1996; Forget 2019), diclofenac (Legeby 2005), flurbiprofen (Sun 2013), parecoxib (Romundstad 2006a), celecoxib (Parsa 2005), parecoxib and celecoxib (van Helmond 2016)) to 642 patients receiving placebo for breast surgery (prepectoral breast augmentation (Romundstad 2006a), subpectoral breast augmentation (Parsa 2005), mastectomy or lumpectomy with axillary lymph node dissection (Bosek 1996; Forget 2019), mastectomy with immediate tissue-expander prosthesis (Legeby 2005), mastectomy with axillary lymph node dissection (Sun 2013), lumpectomy, total simple mastectomy or modified radical mastectomy (van Helmond 2016)). Of the seven studies comparing NSAIDs to placebo, six reported preoperative administration (Forget 2019; Legeby 2005; Parsa 2005; Romundstad 2006a; Sun 2013; van Helmond 2016), zero reported intraoperative administration, and four reported postoperative administration (Bosek 1996; Legeby 2005; Sun 2013; van Helmond 2016).

One study compared 40 patients receiving NSAIDs (diclofenac with bupivacaine (Chan 1996)) to 20 patients receiving no intervention (bupivacaine alone) at the beginning or end of breast surgery (lumpectomy). Chan 1996 reported preoperative and postoperative administration.

Four studies compared 120 patients receiving NSAIDs (ketorolac (Bakr 2016), flurbiprofen (Wen 2015), ibuprofen (Oh 2016), and celecoxib (Freedman 2006)) to 120 patients receiving other analgesics (morphine or tramadol (Bakr 2016), fentanyl (Wen 2015), hydromorphone (Oh 2016), hydrocodone (Freedman 2006) for breast surgery (modified radical mastectomy (Bakr 2016), modified radical mastectomy (Wen 2015), excisional biopsy or partial mastectomy or total mastectomy or modified radical mastectomy with or without lymph node dissection (Oh 2016), and subpectoral breast augmentation (Freedman 2006)). Of the four studies comparing NSAIDs to other analgesics, one reported preoperative administration (Freedman 2006), zero reported intraoperative administration, and four reported postoperative administration (Bakr 2016; Freedman 2006; Oh 2016; Wen 2015).

We present a summary of the condition, comparison, number randomized and number included in the review analyses for each study in Characteristics of included studies and summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3).

Ongoing studies

Of the 80 studies eligible for full-text review we identified one ongoing study (NCT03535116 2018). This study is not yet recruiting and will compare preoperative NSAIDs (ketorolac) to placebo and assess the development of breast hematomas. See: Characteristics of ongoing studies.

Excluded studies

We excluded 74 records with some of the reasons provided in the Characteristics of excluded studies and Figure 1. The main reasons for excluding studies were due to ineligible interventions or outcomes.

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of the risk of bias judgments of the included studies.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

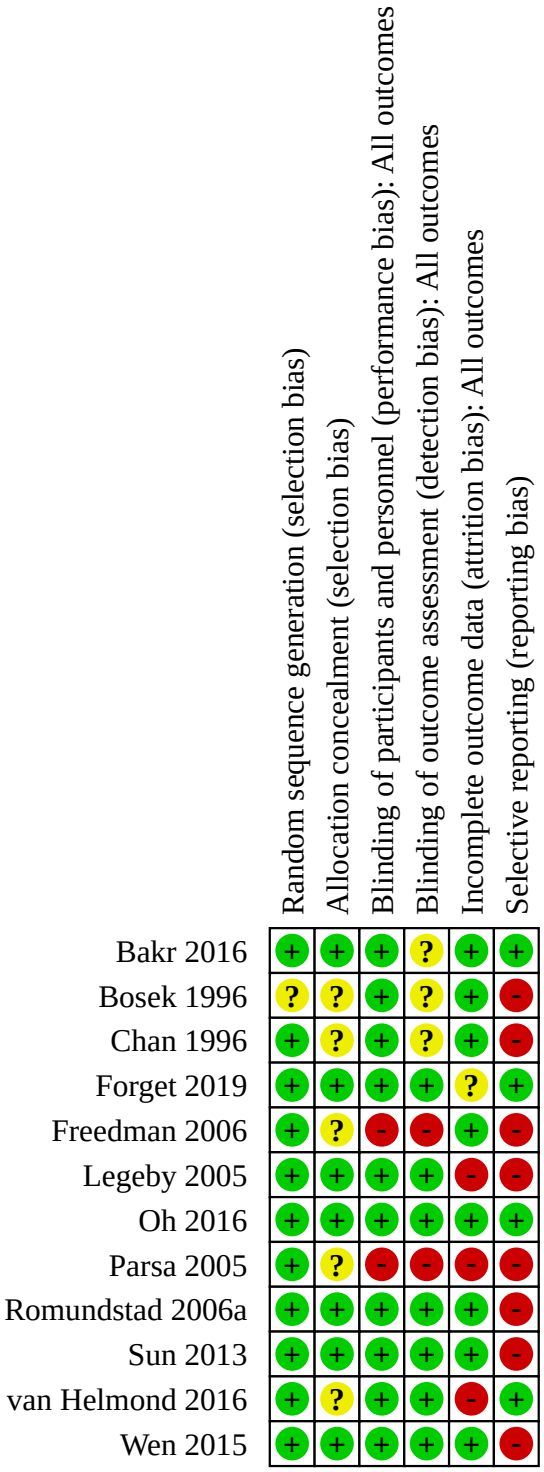
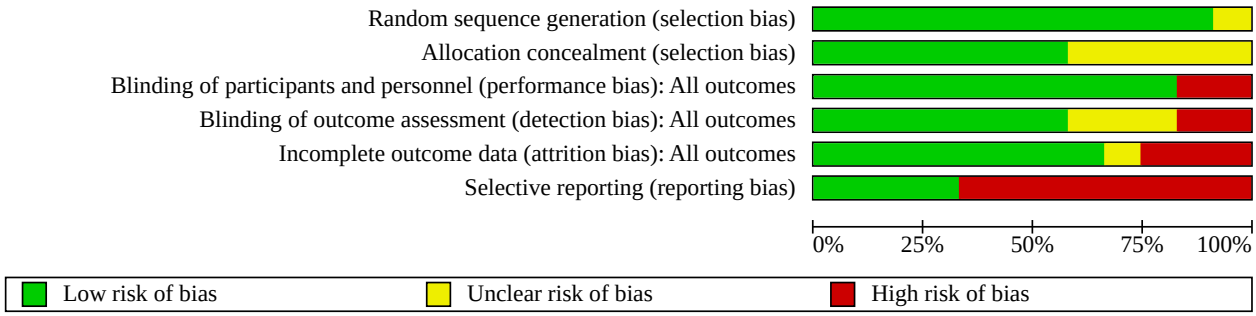


Figure 3.



Allocation

If the study adequately described the method of random sequence generation, we categorized the study to be at low risk of bias. Eleven studies were described as randomized and provided adequate information relating to the random sequence generation used (Bakr 2016; Chan 1996; Forget 2019; Freedman 2006; Legeby 2005; Oh 2016; Parsa 2005; Romundstad 2006a; Sun 2013; van Helmond 2016; Wen 2015). The randomisation process was unclear in one study due to the lack of information provided (Bosek 1996).

No information was provided or it was unclear what method of allocation concealment was used in 5 of the 12 studies (Bosek 1996; Chan 1996; Freedman 2006; Parsa 2005: van Helmond 2016). Seven studies clearly reported the allocation concealment (Bakr 2016; Forget 2019; Legeby 2005; Oh 2016; Romundstad 2006a; Sun 2013; Wen 2015).

Blinding

Ten studies clearly reported blinding of participants and personnel (Bakr 2016; Bosek 1996; Chan 1996; Forget 2019; Legeby 2005; Oh 2016; Romundstad 2006a; Sun 2013; van Helmond 2016; Wen 2015). The risk of performance bias was high in two studies (Freedman 2006; Parsa 2005). Freedman 2006 and Parsa 2005 did not blind either their participants or their personnel.

The method of blinding of outcome assessment was reported in seven studies (Forget 2019; Legeby 2005; Oh 2016; Romundstad 2006a; Sun 2013; van Helmond 2016; Wen 2015). Three studies had unclear risk of detection bias (Bakr 2016; Bosek 1996; Chan 1996). No information was provided regarding the method used to blind the assessment of outcomes in three studies (Bakr 2016; Bosek 1996; Chan 1996). Studies by Freedman 2006 and Parsa 2005 had high risk of detection bias as both studies did not blind their study personnel to outcome assessment.

Incomplete outcome data

In eight studies the completeness of outcome data was adequate and we classified them as having a low risk of bias for this domain. Legeby 2005 and van Helmond 2016 reported high rates of exclusions and we judged incomplete reporting of outcomes as high risk of bias. Parsa 2005 did not report SDs with mean opioid use within 24 (± 12) hours of surgery. We judged incomplete reporting of outcome data as a high risk of attrition bias. Forget 2019 reported missing data from one patient for pain intensity 24 (± 12) hours following surgery in a participant receiving placebo.

Selective reporting

The results for the primary and secondary outcomes were reported in four studies (Bakr 2016; Forget 2019; Oh 2016; van Helmond 2016). We judged studies with trial registrations or protocols confirming reported outcomes as low risk of reporting bias. Bosek 1996, Chan 1996, Freedman 2006, Legeby 2005, Parsa 2005, Romundstad 2006a, Sun 2013 and Wen 2015 did not have available trial registrations or protocols. We considered studies without trial or protocol registrations at high risk of reporting bias.

Other potential sources of bias

None identified.

Effects of interventions

See: **Summary of findings 1** NSAID compared to placebo in women undergoing breast surgery; **Summary of findings 2** NSAID compared to other analgesic in women undergoing breast surgery; **Summary of findings 3** NSAID compared to no intervention in women undergoing breast surgery

NSAID versus placebo

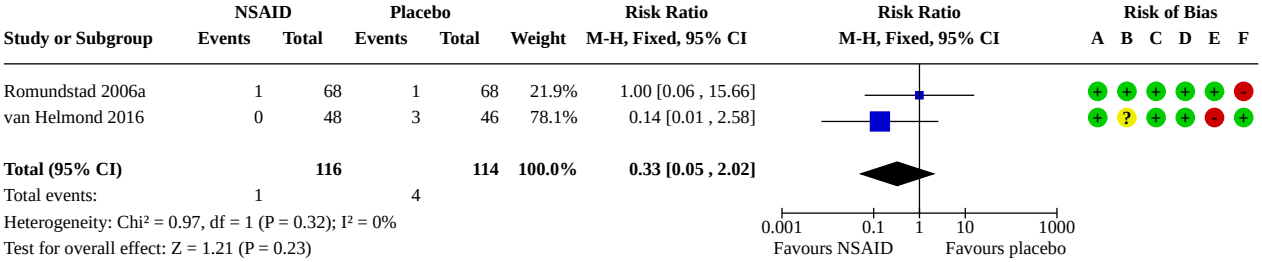
See: Summary of findings 1.

Incidence of breast hematoma within 90 days of breast surgery (requiring reoperation, interventional drainage, or no treatment)

Of the seven studies comparing perioperative NSAIDs to placebo, two reported incidence of breast hematoma within 90 days of breast surgery. Pooled analysis from two studies (Romundstad 2006a; van Helmond 2016) suggests that administering NSAIDs (parecoxib, celecoxib) may not result in a difference in the incidence of breast hematomas within 90 days of breast surgery compared to placebo groups (RR 0.33, 95% CI 0.05 to 2.02; 2 studies, 230 participants; $I^2 = 0\%$; low-certainty evidence; Figure 4; Analysis 1.1). Romundstad 2006a reported one incidence of breast hematoma in 68 patients taking one dose of parecoxib 40 mg IV (preoperative) compared to one incidence of breast hematoma in 68 patients taking saline IV placebo, administered before the start of sedation for breast augmentation surgery. van Helmond 2016 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. van Helmond 2016 reported no incidences of breast hematoma in 48 patients taking two doses of parecoxib 40 mg IV (preoperative) administered 30 minutes before the start of sedation and oral

celecoxib 200 mg daily (postoperative) day 1 to 5 compared to three incidences of breast hematoma in 46 patients taking placebo IV administered 30 minutes before the start of sedation and oral tablets daily postoperative day 1 to 5, for lumpectomy, total simple mastectomy or modified radical mastectomy.

Figure 4. Forest plot of comparison: 1 NSAID versus placebo, outcome: 1.1 Breast hematoma.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Timing of drug administration

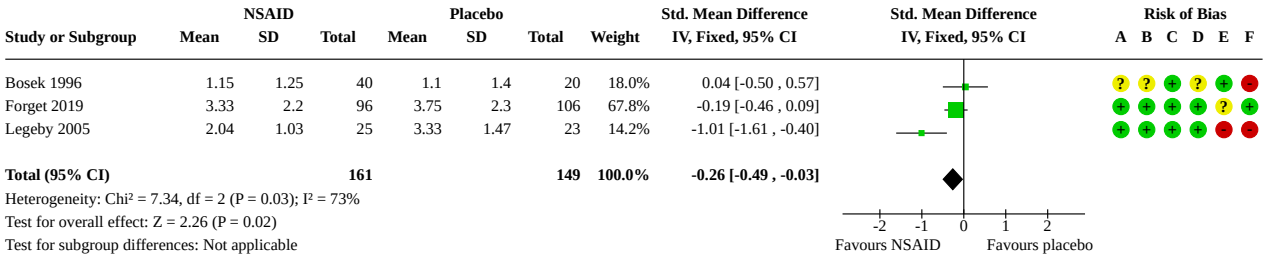
Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, one reported incidence of breast hematoma within 90 days of breast surgery. Romundstad 2006a suggests there may be no difference in the development of breast hematomas within 90 days of breast surgery between preoperative NSAIDs (parecoxib) and placebo (RR 1.00, 95% CI 0.06 to 15.66; 1 study, 136 participants; low-certainty evidence).

Pain intensity 24 (± 12) hours following surgery

Of the seven studies comparing perioperative NSAIDs to placebo, four reported pain 24 (± 12) hours following surgery (Bosek 1996; Forget 2019; Legeby 2005; Sun 2013). Pooled analysis from three studies (Bosek 1996; Forget 2019; Legeby 2005) suggest NSAIDs (ketorolac, diclofenac) may reduce pain intensity 24 (± 12) hours following surgery compared to placebo (SMD -0.26, 95% CI -0.49 to -0.03; 3 studies, 310 participants; I^2 = 73%; low-certainty evidence; Figure 5; Analysis 1.3). Sun 2013 reported pain scores of zero in the NSAID and placebo groups, and therefore we did not include this study in the analysis.

Figure 5. Forest plot of comparison: 1 NSAID versus placebo, outcome: 1.3 Pain intensity 24 (± 12) hours following surgery.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Validated pain scales included the numerical rating scale (NRS), visual analog scale (VAS), and verbal categorical rating scale (VRS), which were ascertained from reviews on pain assessment (Hjermstad 2011; Younger 2009). Bosek 1996 reported no differences in pain 18 hours after surgery in 40 patients with ketorolac 30 mg IV or ketorolac 30 mg by Jackson-Pratt drain compared to 20 patients taking saline placebo administered near the end of surgery for mastectomy or lumpectomy with axillary

lymph node dissection. Forget 2019 reported no difference in pain scores 24 hours after surgery in 96 patients with ketorolac 30 mg IV compared to 106 patients with saline IV administered during the induction of anesthesia. Legeby 2005 reported lower pain scores the first 20 hours after surgery in 25 patients with diclofenac 50 mg suppositories rectally (preoperative and postoperative) compared to 23 patients with saline suppositories rectally administered every 8 hours for 3 days administered 1 hour before the start of mastectomy with immediate tissue-expander prosthesis surgery. Sun 2013 reported no pain within 24 hours of surgery with flurbiprofen 50 mg IV (preoperative and postoperative) and intralipid placebo IV administered 15 minutes before the surgical incision and 6 hours later for mastectomy with axillary lymph node dissection. Legeby 2005 and Sun 2013 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. Pain intensity scores were reported in mean and standard deviation (SD) by Bosek 1996 and Legeby 2005. Pain intensity scores were calculated from values provided by Forget 2019.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, one reported postoperative pain within 24 hours of surgery (Forget 2019). Forget 2019 suggests preoperative NSAIDs (diclofenac) may not reduce postoperative pain intensity within 24 (± 12) hours of surgery compared to placebo (SMD -0.19, 95% CI -0.46 to 0.09; 1 study, 202 participants; low-certainty evidence).

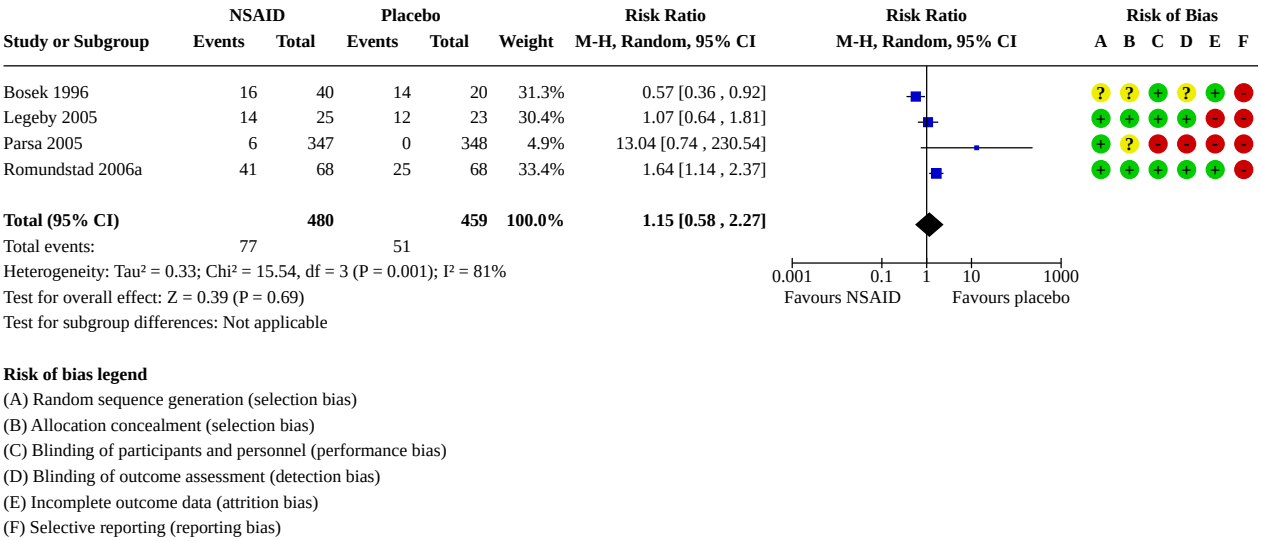
Postoperative

Of the four studies comparing postoperative NSAIDs to placebo, one reported postoperative pain within 24 hours of surgery (Bosek 1996). Bosek 1996 suggests postoperative NSAIDs (ketorolac) may not reduce postoperative pain intensity within 24 (± 12) hours of surgery compared to placebo, but we are very uncertain (SMD 0.04, 95% CI -0.50 to 0.57; 1 study, 60 participants; very low-certainty evidence).

Incidence rate or severity of postoperative nausea, vomiting, or both

Of the seven studies comparing perioperative NSAIDs to placebo, four reported incidence rate or severity of postoperative nausea, vomiting, or both (Bosek 1996; Legeby 2005; Parsa 2005; Romundstad 2006a). Pooled analysis from these four studies suggest NSAIDs (ketorolac, diclofenac, celecoxib, parecoxib) may not reduce the incidence rates or severities of postoperative nausea, vomiting, or both compared to placebo (RR 1.15, 95% CI 0.58 to 2.27; 4 studies, 939 participants; I^2 = 81%; low-certainty evidence; Figure 6; Analysis 1.5).

Figure 6. Forest plot of comparison: 1 NSAID versus placebo, outcome: 1.5 Incidence rate or severity of postoperative nausea, vomiting, or both.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Postoperative nausea, vomiting, or both were highest in the NSAID group (71/480) compared to placebo group (51/458). Bosek 1996 reported significantly less postoperative nausea, vomiting, or both measured every 6 hours, in 16/40 patients with ketorolac 30 mg IV or ketorolac 30 mg by Jackson-Pratt drain compared to 14/20 patients taking saline placebo administered near the end of surgery for mastectomy or lumpectomy with axillary lymph node dissection. Legeby 2005 reported postoperative nausea, vomiting, or both in 14/25 patients with diclofenac 50 mg suppositories rectally compared to 12/23 patients with saline suppositories rectally administered every 8 hours for 3 days administered 1 hour before the start of mastectomy with immediate tissue-expander prosthesis surgery. Legeby 2005 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. Parsa 2005 reported postoperative nausea, vomiting, or both in 6/347 patients with celecoxib 40 mg by mouth compared to 0/347 patients with placebo by mouth administered 30 minutes before subpectoral breast augmentation. Romundstad 2006a reported significantly more postoperative nausea, vomiting, or both measured during the first 24 hours in 41/68 patients taking 1 dose of parecoxib 40 mg IV compared to 25/68 patients taking saline

IV placebo, administered before the start of sedation for breast augmentation surgery.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, two reported incidence rate or severity of postoperative nausea, vomiting, or both (Parsa 2005; Romundstad 2006a). Pooled analysis from these two studies suggest preoperative NSAIDs (celecoxib, parecoxib) may not reduce the incidence rates or severities of postoperative nausea, vomiting, or both compared to placebo, but we are very uncertain (RR 2.95, 95% CI 0.42 to 20.64; 2 studies, 831 participants; I^2 = 55%; very low-certainty evidence).

Postoperative

Of the four studies comparing postoperative NSAIDs to placebo, one reported incidence rate or severity of postoperative nausea, vomiting, or both. Bosek 1996 suggests postoperative NSAIDs (ketorolac) may reduce the incidence rates or severities of postoperative nausea, vomiting, or both compared to placebo, but we are very uncertain (RR 0.57, 95% CI 0.36 to 0.92; 1 study, 60 participants; very low-certainty evidence).

Bleeding from any location within 90 days

Of the seven studies comparing perioperative NSAIDs to placebo, three reported bleeding from any location within 90 days (Forget 2019; Legeby 2005, Sun 2013). Pooled analysis from two studies (Forget 2019; Legeby 2005) suggest NSAIDs (ketorolac, diclofenac) may not increase bleeding from any location within 90 days compared to placebo (RR 1.05, 95% CI 0.89 to 1.24; 2 studies, 251 participants; I^2 = 8%; low-certainty evidence; Analysis 1.7). Sun 2013 had no estimable results with zero events in the 30 patients in the NSAID and 30 patients in the placebo groups. Forget 2019 reported no difference in the incidence of bleeding from any location within 90 days in 1/96 patients with ketorolac 30 mg IV compared to 0/107 patients with saline IV administered at induction of anesthesia. Legeby 2005 reported no difference in the incidence of bleeding from any location within 90 days in 24/25 patients with diclofenac 50 mg suppositories rectally (preoperative and postoperative) compared to 22/23 patients with saline suppositories rectally administered every 8 hours for 3 days administered 1 hour before the start of mastectomy with immediate tissue-expander prosthesis surgery. However, Legeby 2005 reported the volume of blood loss was significantly higher with diclofenac compared to placebo. Sun 2013 reported no difference in the incidence of bleeding in 0/30 patients with flurbiprofen 50 mg IV (preoperative and postoperative) compared to 0/30 patients with intralipid placebo IV administered 15 minutes before the surgical incision and 6 hours later for mastectomy with axillary lymph node dissection. Legeby 2005 and Sun 2013 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. As Sun 2013 had no estimable results, with zero events in the NSAID and placebo groups, we removed this study from the analysis.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, one reported bleeding from any location within 90 days (Forget 2019). Forget 2019 suggests preoperative NSAIDs (ketorolac) likely does not increase bleeding from any location within 90 days compared to placebo, but we are very uncertain (RR 3.34, 95% CI 0.14 to 81.03; 1 study, 203 participants; very low-certainty evidence).

Need for blood transfusion

Of the seven studies comparing perioperative NSAIDs to placebo, two reported need for a blood transfusion (Forget 2019; Legeby 2005). Legeby 2005 suggests that NSAIDs (diclofenac) may not increase bleeding from any location within 90 days compared to placebo, but we are very uncertain (RR 4.62, 95% CI 0.23 to 91.34; 1 study, 48 participants; very low-certainty evidence; Analysis 1.9). Legeby 2005 reported 2/25 patients receiving a blood transfusion with diclofenac 50 mg suppositories rectally (preoperative and postoperative) compared to 0/23 patients with saline suppositories rectally administered every 8 hours for 3 days administered 1 hour before the start of mastectomy with immediate tissue-expander prosthesis surgery. Legeby 2005 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. Forget 2019 reported no difference in the need for blood transfusion in 0/96 patients with ketorolac 30 mg IV compared to 0/107 patients with saline IV administered at induction of anesthesia. Forget 2019 had no estimable results, with zero events in the NSAID and placebo groups, and so we removed this study from the analysis.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, one reported need for a blood transfusion (Legeby 2005). Pooled analysis from Legeby 2005 suggests NSAIDs (diclofenac) may not increase bleeding from any location within 90 days compared to placebo, but we are very uncertain (RR 4.62, 95% CI 0.23 to 91.34; 1 study, 48 participants; very low-certainty evidence).

Other side effects of NSAID use

Of the seven studies comparing perioperative NSAIDs to placebo, three reported other side effects of NSAID use (Forget 2019; Legeby 2005, Sun 2013). Pooled analysis from two studies (Forget 2019; Legeby 2005) suggest NSAIDs (ketorolac, diclofenac) may not differ in other side effects compared to placebo (RR 1.12, 95% CI 0.44 to 2.86; 2 studies, 251 participants; I^2 = 0%; low-certainty evidence; Analysis 1.11). Forget 2019 reported other side effects in 8/96 patients with ketorolac 30 mg IV (preoperative) compared to 7/107 patients with saline IV administered at induction of anesthesia. Legeby 2005 reported other side effects in 0/25 patients with diclofenac 50 mg suppositories rectally (preoperative and postoperative) compared to 1/23 patients with saline suppositories rectally (hypoventilation with respiratory rate less than 6 breaths/min) administered every 8 hours for 3 days, administered 1 hour before the start of mastectomy with immediate tissue-expander prosthesis surgery. Sun 2013 reported no difference in other side effects in 0/30 patients with flurbiprofen 50 mg IV (preoperative and postoperative) compared to 0/30 patients with intralipid placebo IV administered 15 minutes before the surgical incision and 6 hours later for mastectomy with axillary lymph node dissection. Legeby 2005 and Sun 2013 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. Sun 2013 had no estimable results,

with zero events in the NSAID and placebo groups with 30 patients in each group.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, one reported other side effects of NSAID use (Forget 2019). Forget 2019 suggests preoperative NSAIDs (ketorolac) may not result in a difference in other side effects compared to placebo (RR 1.27, 95% CI 0.48 to 3.38; 1 study, 203 participants; low-certainty evidence).

Opioid use within 24 (± 12) hours of surgery

Of the seven studies comparing perioperative NSAIDs to placebo, five reported opioid use within 24 (± 12) hours of surgery (Bosek 1996; Legeby 2005; Parsa 2005; Romundstad 2006a; Sun 2013). Pooled analysis from four studies (Bosek 1996; Legeby 2005; Romundstad 2006a; Sun 2013) suggest NSAIDs (ketorolac, diclofenac, parecoxib, flurbiprofen) may reduce opioid use within 24 hours of surgery compared to placebo (SMD -0.45, 95% CI -0.85 to -0.05; 4 studies, 304 participants; I^2 = 63%; low-certainty evidence; Analysis 1.13). Parsa 2005 was not incorporated into the pooled analysis due to missing standard deviations. Parsa 2005 reported a mean hydrocodone tablet morphine equivalent use of 30.5 mg in 347 patients with celecoxib 40 mg by mouth compared to 51.5 mg in 348 patients with placebo by mouth administered 30 minutes before subpectoral breast augmentation.

Bosek 1996 reported a mean morphine IV use of 1.7 ± 3.1 mg in 40 patients with ketorolac 30 mg IV or ketorolac 30 mg by Jackson-Pratt drain (postoperative) compared to 2.7 ± 3.9 mg in 20 patients taking saline placebo 18 hours after surgery for mastectomy or lumpectomy with axillary lymph node dissection. Legeby 2005 reported a mean morphine or ketobemidone use of 26.8 ± 18.1 mg in 25 patients with diclofenac 50 mg suppositories rectally (preoperative and postoperative) compared to 35.9 ± 13.6 mg in 23 patients with saline suppositories rectally for mastectomy with immediate tissue-expander prosthesis surgery. Romundstad 2006a reported a mean acetaminophen 500 mg and codeine 30 mg tablet morphine equivalent use of 9.9 ± 5.85 mg in 68 patients taking 1 dose of parecoxib 40 mg IV (preoperative) compared to 15.3 ± 6.75 mg in 68 patients taking saline IV placebo, administered before the start of sedation for breast augmentation surgery. Sun 2013 reported a mean fentanyl IV morphine equivalent use of 0.18 ± 0.04 mg in 30 patients with flurbiprofen 50 mg IV (preoperative and postoperative) compared to 0.18 ± 0.03 mg in 30 patients with intralipid placebo IV administered 15 minutes before the surgical incision and 6 hours later for mastectomy with axillary lymph node dissection. Legeby 2005 and Sun 2013 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these.

Timing of drug administration

Preoperative

Of the six studies comparing preoperative NSAIDs to placebo, two reported opioid use within 24 (± 12) hours of surgery (Parsa 2005; Romundstad 2006a). Romundstad 2006a suggests preoperative NSAIDs (parecoxib) may not result in a difference in opioid use within 24 hours of surgery compared to placebo (SMD -0.85, 95% CI -1.20 to -0.50; 1 study, 136 participants; low-certainty evidence). As Parsa 2005 did not report SDs in the NSAID and placebo groups, we removed it from the analysis.

Postoperative

Of the four studies comparing postoperative NSAIDs to placebo, one reported opioid use within 24 (± 12) hours of surgery (Bosek 1996). Bosek 1996 suggests postoperative NSAIDs (ketorolac) may not result in a difference in opioid use within 24 hours of surgery compared to placebo, but we are very uncertain (SMD -0.29, 95% CI -0.83 to 0.25; 1 study, 60 participants; very low-certainty evidence).

Length of hospital stay

Of the seven studies comparing perioperative NSAIDs to placebo, one reported length of hospital stay (Forget 2019). Forget 2019 suggests preoperative NSAIDs (ketorolac) may not result in a difference in length of hospital stay compared to placebo (SMD 0.18, 95% CI -0.09 to 0.46; 1 study, 203 participants; low-certainty evidence). Forget 2019 reported a mean length of hospital stay of 3.9 ± 1.2 days with ketorolac 30 mg IV (preoperative) compared to 3.7 ± 1 days with saline IV administered at induction of anesthesia.

Breast cancer recurrence

None of the included studies reported breast cancer recurrence.

Non-prescribed NSAID use

None of the included studies reported non-prescribed NSAID use.

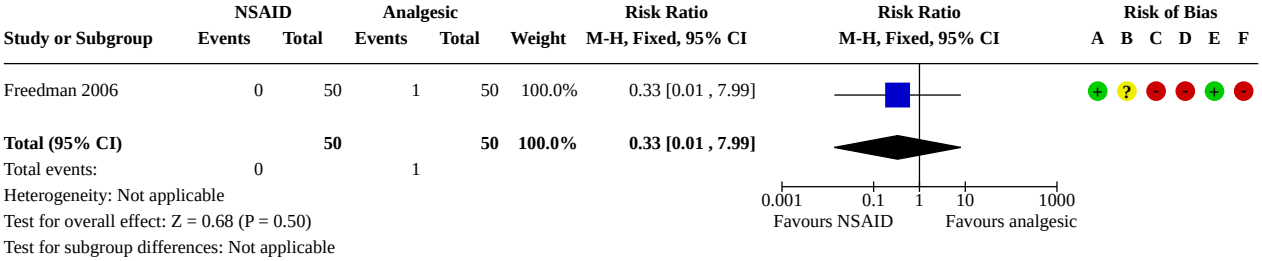
NSAID versus other analgesic

See: Summary of findings 2.

Incidence of breast hematoma within 90 days of breast surgery (requiring reoperation, interventional drainage, or no treatment)

Of the four studies comparing perioperative NSAIDs to other analgesics, one reported incidence of breast hematoma within 90 days of breast surgery (Freedman 2006). Freedman 2006 suggests administering NSAIDs (celecoxib) may not result in a difference in the development of breast hematomas within 90 days of breast surgery compared to other analgesics (hydrocodone), but we are very uncertain (RR 0.33, 95% CI 0.01 to 7.99; 1 study, 100 participants; very low-certainty evidence; Figure 7; Analysis 2.1). No incidence of breast hematoma was reported in 50 patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days compared to one incidence of breast hematoma in 50 patients taking hydrocodone 5 mg by mouth as needed, for subpectoral breast augmentation surgery. Freedman 2006 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these.

Figure 7. Forest plot of comparison: 3 NSAID vs other analgesic, outcome: 3.1 Incidence of breast hematoma within 90 days of breast surgery.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Pain intensity 24 (± 12) hours following surgery

Of the four studies comparing perioperative NSAIDs to other analgesics, four reported pain 24 (± 12) hours following surgery (Bakr 2016; Freedman 2006; Oh 2016; Wen 2015). Pooled analysis from three studies (Freedman 2006; Oh 2016; Wen 2015), suggest NSAIDs (celecoxib, flurbiprofen, ibuprofen) may reduce pain intensity 24 (± 12) hours following surgery compared to other analgesics (fentanyl, hydrocodone, hydromorphone) (SMD -0.68, 95% CI -0.97 to -0.39; 3 studies, 200 participants; I^2 = 89%; low-certainty evidence; Analysis 2.2). Bakr 2016 reported no differences in pain up to 24 hours after surgery in 20 patients with ketorolac 60 mg IV compared to 20 patients taking morphine 5 mg IV administered at the end of modified radical mastectomy. We did not include Bakr 2016 in the pooled analysis due to missing SDs.

Validated pain scales included the NRS, VAS, and VRS, which were ascertained from reviews on pain assessment (Hjermstad 2011; Younger 2009). Freedman 2006 reported a greater reduction in pain in 50 patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days compared to 50 patients taking hydrocodone 5 mg by mouth as needed, for subpectoral breast augmentation surgery. Oh 2016 reported ibuprofen 800 mg IV (postoperative) was not able to provide proper pain control compared to hydromorphone 2 mg IV in five consecutive patients for excisional biopsy or partial mastectomy or total mastectomy or modified radical mastectomy with or without lymph node dissection, therefore patient enrolment was stopped after 18 patients. Wen 2015 reported no differences in pain 24 hours after surgery in 20 patients with flurbiprofen 3 mg/kg IV (postoperative) compared to 20 patients taking fentanyl 15 µg/kg IV administered postoperatively for modified radical mastectomy. Freedman 2006 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these.

Timing of drug administration

Postoperative

Of the three studies comparing postoperative NSAIDs to other analgesics, three reported pain 24 (± 12) hours following surgery (Bakr 2016; Oh 2016; Wen 2015). Pooled analysis from two studies (Oh 2016; Wen 2015), suggests there is likely no difference in pain intensity 24 (± 12) hours following surgery between postoperative NSAIDs (flurbiprofen, ibuprofen) and other analgesics (fentanyl, hydromorphone) (SMD -0.12, 95% CI -0.51 to 0.27; 2 studies, 100 participants; I^2 = 0%; moderate-certainty evidence). We did not include Bakr 2016 in the pooled analysis due to missing SDs.

Incidence rate or severity of postoperative nausea, vomiting, or both

Of the four studies comparing perioperative NSAIDs to other analgesics, four reported incidence of postoperative nausea, vomiting or both (Bakr 2016; Freedman 2006; Oh 2016; Wen 2015). Pooled analysis from three studies (Bakr 2016; Oh 2016; Wen 2015) suggest NSAIDs (ketorolac, ibuprofen, flurbiprofen) likely reduce the incidence rates or severities of postoperative nausea, vomiting, or both compared to other analgesics (morphine, hydromorphone, fentanyl) (RR 0.18, 95% CI 0.06 to 0.57; 3 studies, 128 participants; I^2 = 0%; moderate-certainty evidence; Analysis 2.4).

Bakr 2016 reported postoperative nausea, vomiting, or both in 0/20 patients with ketorolac 60 mg IV (postoperative) compared to 4/20 patients taking morphine 5 mg IV administered at the end of modified radical mastectomy. Oh 2016 reported postoperative nausea, vomiting, or both in 0/18 patients taking ibuprofen IV (postoperative) compared to 1/30 patients taking hydromorphone IV for excisional biopsy or partial mastectomy or total mastectomy or modified radical mastectomy with or without lymph node dissection. Wen 2015 reported significantly less postoperative nausea, vomiting, or both within 48 hours in 2/20 patients with flurbiprofen 3 mg/kg IV (postoperative) compared to 12/20 patients taking fentanyl 15 µg/kg IV administered postoperatively for modified radical mastectomy. Bakr 2016, Oh 2016, and Wen 2015 examined the effect of administering NSAIDs during the postoperative phase. Freedman 2006 reported patients taking

hydrocodone 5 mg by mouth, as needed, had a significantly higher number of days (91 days) of nausea compared to 43 days of nausea in patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days. Freedman 2006 reported results in metric units that could not be converted and compared to the other studies.

Bleeding from any location within 90 days

Of the four studies comparing perioperative NSAIDs to other analgesics, four reported bleeding from any location within 90 days (Bakr 2016; Freedman 2006; Oh 2016; Wen 2015). Bakr 2016, Freedman 2006, Oh 2016 and Wen 2015 had no estimable results, with zero events in the NSAID and other analgesics groups. Freedman 2006 suggests there may be no difference in the development of bleeding from any location within 90 days of breast surgery between NSAIDs (celecoxib) and other analgesics (hydrocodone), but we are very uncertain (RR 0.33, 95% CI 0.01 to 7.99; 1 study, 100 participants; very low-certainty evidence). No incidence of bleeding from any location was reported in 50 patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days compared to one incidence of bleeding from any location in 50 patients taking hydrocodone 5 mg by mouth as needed, for subpectoral breast augmentation surgery. Freedman 2006 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these. Bakr 2016, Oh 2016, and Wen 2015 examined the effect of administering NSAIDs during the postoperative phase.

Need for blood transfusion

None of the included studies reported the need for a blood transfusion.

Other side effects of NSAID use

Of the four studies comparing perioperative NSAIDs to other analgesics, three reported other side effects of NSAID use (Bakr 2016; Freedman 2006; Oh 2016). Oh 2016 suggested there may be no difference in other side effects between postoperative NSAIDs (ibuprofen) and other analgesics (hydromorphone), but we are very uncertain (RR 0.11, 95% CI 0.01 to 1.80; 1 study, 48 participants; very low-certainty evidence; Analysis 2.6). Bakr 2016 and Freedman 2006 had no estimable results, with zero events in the NSAID and other analgesics groups, and so we did not include them in the analysis. Oh 2016 reported other side effects in 0/18 patients taking ibuprofen IV (postoperative) compared to 7/30 patients taking hydromorphone IV for excisional biopsy or partial mastectomy or total mastectomy or modified radical mastectomy with or without lymph node dissection. Bakr 2016 reported other side effects in 0/20 patients with ketorolac 60 mg IV (postoperative) compared to 0/20 patients taking morphine 5 mg IV administered at the end of modified radical mastectomy. Freedman 2006 reported other side effects in 0/50 patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days compared to 0/50 patients taking hydrocodone 5 mg by mouth as needed, for subpectoral breast augmentation surgery.

Opioid use within 24 (± 12) hours of surgery

Of the four studies comparing perioperative NSAIDs to other analgesics, three reported opioid use within 24 (± 12) hours of surgery (Bakr 2016; Freedman 2006; Wen 2015). Pooled analysis from these three studies suggest NSAIDs (ketorolac, celecoxib, flurbiprofen) may reduce opioid use within 24 hours of surgery compared to other analgesics (morphine, hydrocodone, fentanyl) (SMD -6.87, 95% CI -10.93 to -2.81; 3 studies, 178 participants; I^2 = 96%; low-certainty evidence; Analysis 2.7). Bakr 2016 reported a mean morphine IV use of 7 ± 2.51 mg in 20 patients with ketorolac 60 mg IV (postoperative) compared to 80 ± 19.47 mg in 20 patients with morphine 5 mg IV administered at the end of modified radical mastectomy. Freedman 2006 reported a mean hydrocodone tablet morphine equivalent use of 34 mg ± 22 mg in 50 patients taking celecoxib 400 mg by mouth (preoperative and postoperative) 1 to 2 hours prior to surgery and each morning after surgery for 7 days compared to 110 mg ± 34 mg in 50 patients taking hydrocodone 5 mg by mouth, as needed, for subpectoral breast augmentation surgery. Wen 2015 reported a mean fentanyl morphine equivalent use 48 hours after surgery of 26.8 mg ± 1.8 mg in 18 patients with flurbiprofen 3 mg/kg IV (postoperative) compared to 80.7 mg ± 4.8 mg in 20 patients taking fentanyl 15 µg/kg IV administered postoperatively for modified radical mastectomy. Freedman 2006 examined the effect of administering NSAIDs during both the preoperative and postoperative phase and did not report data separately for these.

Timing of drug administration

Postoperative

Of the three studies comparing postoperative NSAIDs to other analgesics, two reported opioid use within 24 (± 12) hours of surgery (Bakr 2016; Wen 2015). Pooled analysis from these two studies suggest postoperative NSAIDs (ketorolac, flurbiprofen) may reduce opioid use within 24 hours of surgery compared to other analgesics (morphine, fentanyl) (SMD -9.56, 95% CI -18.48 to -0.64; 2 studies, 78 participants; I^2 = 96%; low-certainty evidence).

Length of hospital stay

None of the included studies reported length of hospital stay.

Breast cancer recurrence

None of the included studies reported breast cancer recurrence.

Non-prescribed NSAID use

None of the included studies reported non-prescribed NSAID use.

NSAID versus no intervention

See: Summary of findings 3.

Incidence of breast hematoma within 90 days of breast surgery (requiring reoperation, interventional drainage, or no treatment)

None of the included studies reported incidence of breast hematoma.

Pain intensity 24 (± 12) hours following surgery

Only one study compared perioperative NSAIDs to no intervention (Chan 1996). Chan 1996 reported pain intensity 24 (± 12) hours following surgery. This study suggests NSAIDs (diclofenac) may not reduce pain intensity 24 (± 12) hours following surgery compared to no intervention, but we are very uncertain (SMD -0.54, 95% CI -1.09 to 0.00; 1 study, 60 participants; very low-certainty evidence;

Analysis 3.1). Chan 1996 reported pain intensity in 40 patients receiving NSAIDs (preoperative diclofenac with bupivacaine and postoperative diclofenac with bupivacaine) compared to 20 patients receiving no intervention (bupivacaine alone) for breast lumpectomy surgery. VAS were reported only at 30 minutes, 60 minutes, 120 minutes and 48 hours postoperative (Hjermstad 2011; Younger 2009). Pain intensity at 120 minutes following surgery was 0.25 ± 0.74 in patients receiving diclofenac 75 mg IM (preoperative and postoperative) compared to 0.75 ± 1.18 patients receiving no intervention.

Timing of drug administration

Preoperative

One study comparing preoperative NSAIDs to no intervention reported pain intensity 24 (± 12) hours following surgery (Chan 1996). This study suggests there may be no difference in pain intensity 24 (± 12) hours following surgery between preoperative NSAIDs (diclofenac) and no intervention, but we are very uncertain (SMD -0.35, 95% CI -0.97 to 0.28; 1 study, 40 participants; very low-certainty evidence). Chan 1996 administered diclofenac 75 mg IM to 20 patients preoperatively. Pain intensity at 120 minutes following surgery was 0.375 ± 0.92 in patients receiving diclofenac 75 mg IM compared to 0.75 ± 1.18 patients receiving no intervention.

Postoperative

One study comparing postoperative NSAIDs to no intervention reported pain intensity 24 (± 12) hours following surgery (Chan 1996). Pooled analysis from this study suggests postoperative NSAIDs (diclofenac) may reduce pain intensity 24 (± 12) hours following surgery compared to no intervention, but we are very uncertain (SMD -0.66, 95% CI -1.30 to -0.02; 1 study, 40 participants; very low-certainty evidence). Chan 1996 administered diclofenac 75 mg IM to 20 patients postoperatively. Pain intensity at 120 minutes following surgery was 0.125 ± 0.56 in patients receiving diclofenac 75 mg IM compared to 0.75 ± 1.18 in patients receiving no intervention.

Incidence rate or severity of postoperative nausea, vomiting, or both

None of the included studies reported the incidence rate or severity of postoperative nausea, vomiting, or both.

Bleeding from any location within 90 days

None of the included studies reported bleeding from any location within 90 days.

Need for blood transfusion

None of the included studies reported the need for a blood transfusion.

Other side effects of NSAID use

None of the included studies reported other side effects of NSAID use.

Opioid use within 24 (± 12) hours of surgery

None of the included studies reported opioid use within 24 (±12) hours of surgery.

Length of hospital stay

None of the included studies reported length of hospital stay.

Breast cancer recurrence

None of the included studies reported breast cancer recurrence.

Non-prescribed NSAID use

None of the included studies reported on non-prescribed NSAID use.

DISCUSSION

Summary of main results

This review provides the best available evidence from 12 studies with a total of 1596 participants on the use of perioperative NSAIDs during breast surgery. We found little to no evidence of a difference between people taking perioperative NSAIDs compared to placebo, and other analgesics (hydrocodone) in the development of breast hematomas within 90 days of breast surgery. The reported incidence of breast hematoma was one in people taking analgesics, three in patients taking placebo and one in those taking NSAIDs, demonstrating similar safety profiles for developing hematomas. The one study not yet recruiting (NCT03535116 2018), will compare NSAIDs (ketorolac) to placebo and assess the development of breast hematomas.

Among such women, perioperative NSAIDs (ketorolac, diclofenac) lowered pain intensity in the first 24 hours following surgery compared to placebo. Similarly, pain intensity was lower with perioperative NSAIDs compared to other analgesics in the first 24 hours following surgery.

When comparing NSAIDs to placebo, these was little to no evidence of a difference in postoperative nausea, vomiting or both. We found evidence to suggest that the risk of postoperative nausea, vomiting or both was lower in the NSAID group compared to other analgesics. Other analgesics included the opioid medications morphine (Bakr 2016), hydromorphone (Oh 2016), and fentanyl (Wen 2015). Opioid medications directly stimulate the chemoreceptor trigger zone in the postrema of the medulla in the central nervous system, responsible for nausea and vomiting (Brunton 2017). Our findings demonstrate NSAIDs may not have these adverse effects.

There was little to no evidence of a difference between patients taking perioperative NSAIDs (diclofenac) and placebo in bleeding from any location in 90 days and need for blood transfusion. Sun 2013 reported no bleeding from any location in the preoperative and postoperative administration of NSAID or placebo groups and so we excluded this study due to no estimable results. Forget 2019 reported no need for blood transfusion in the preoperative administration of NSAID or placebo groups and we excluded this study due to no estimable results.

Overall completeness and applicability of evidence

This review provides preliminary evidence for administering perioperative NSAIDs in women undergoing breast surgery. NSAIDs were shown to reduce pain, nausea, vomiting and opioid use postoperatively in the women undergoing breast surgery. One study evaluated implant-based reconstruction (Legeby 2005), eight studies evaluated mastectomy or lumpectomy (Bosek 1996; Chan

1996; Oh 2016; Wen 2015; Sun 2013; Bakr 2016; van Helmond 2016; Forget 2019), and three studies evaluated augmentation mammaplasty (Freedman 2006; Parsa 2005; Romundstad 2006a). None of the studies evaluated NSAIDs in women undergoing autologous breast reconstruction, breast reduction, and mastopexy surgery, limiting any conclusions with these surgeries. Women must be evaluated on an individual basis to determine appropriate patient selection for NSAID administration.

Limited evidence suggests there may be no differences in safety profiles when NSAIDs were compared to placebo, and other analgesics for the development of breast hematomas. The differences in breast cancer recurrence and non-prescribed NSAID use remain unclear for people receiving NSAIDs; no studies evaluated these outcomes. This may be due to the fact that there are many different types of breast surgeries for different indications. The people included in eight studies received mastectomy or lumpectomy and in three studies received augmentation for cosmetic purposes. Depending on the procedure performed, patients may leave the hospital that same day or may not have breast cancer and therefore recurrence is not applicable.

We evaluated six NSAIDs. These included parecoxib (Romundstad 2006a; van Helmond 2016), celecoxib (Freedman 2006; van Helmond 2016; Parsa 2005), flubiprofen (Sun 2013; Wen 2015), ibuprofen (Oh 2016), diclofenac (Chan 1996; Legeby 2005), and ketorolac (Bosek 1996; Bakr 2016; Forget 2019). Some of these medications may not be commonly used or available internationally. Evaluating alternative NSAIDs may be beneficial for these populations. Alternative routes of administration that did not include IV, IM, or oral formulations were evaluated in one study (Legeby 2005). Evaluating different routes of administration would be beneficial for people unable to tolerate oral medications after they are discharged from the hospital. Legeby 2005 assessed the efficacy of rectal diclofenac during the perioperative period. Topical medication administration using patches, creams, ointments, lotions, and emollients may provide localized pain relief without predisposing a patient to systemic exposure. This would be beneficial for patients with multiple comorbidities or complex medication regimens susceptible to drug interactions. Performing more studies will allow for comparisons between NSAIDs. There were no studies that reported intraoperative administration of NSAIDs for any of the outcomes of interest.

Intraoperative multimodal analgesic and anesthetic regimens are likely to impact outcomes associated with NSAIDs and may be responsible for differences observed between studies (Brinck 2018). Bosek 1996, Forget 2019, Legeby 2005 and Sun 2013 evaluated pain intensity 24 hours following surgery between NSAIDs and placebo. Bosek 1996 administered thiopental and isoflurane in nitrous oxide. Forget 2019 administered propofol, ketamine, clonidine, and sufentanil. Legeby 2005 administered thiopenthone or propofol, sevoflurane, fentanyl, and lidocaine injected locally into each breast. Sun 2013 administered midazolam, etomidate, fentanyl, propofol, and ramifentanil. Absence of consideration of other components of intraoperative pain management poses potential limitations.

Further questions regarding NSAID efficacy and safety that are beyond the scope of this review and impact current practice include other adverse effects, patient comorbidities, drug interactions, and pharmacogenomics. Any predisposition to risks of bleeding, cardiovascular events, liver disease, asthma, gastrointestinal disease, and kidney disease may alter medication management.

Certainty of the evidence

This review provides evidence from 12 completed RCTs and one ongoing RCT. Of the 12 completed studies, seven compared NSAIDs to placebo, four compared NSAIDs to other analgesics, and one compared NSAIDs to no intervention. As presented in Summary of findings 1; Summary of findings 2; Summary of findings 3, the quality of the body of evidence for each outcome was moderate to very low. We were unable to perform a sensitivity analysis due to few studies in the comparative groups.

Among the studies comparing NSAIDs to placebo, no outcome had moderate-certainty evidence. Outcomes with significant heterogeneity for comparisons between NSAIDs and placebo were: pain intensity 24 hours following surgery (preoperative and postoperative) with heterogeneity of 73%; incidence rate or severity of postoperative nausea, vomiting, or both (preoperative and postoperative) with heterogeneity of 81% and 55% in the preoperative subgroup; and opioid use within 24 hours of surgery (preoperative and postoperative) with heterogeneity of 63%. The high heterogeneity for pain intensity 24 hours following surgery (postoperative) is likely due to different times of pain assessments and routes of administration. Bosek 1996 assessed pain at 18 hours following surgery and administered ketorolac both systemically (IV) and locally (Jackson-Pratt drain). Legeby 2005 assessed pain intensity from 0 to 20 hours following surgery and administered diclofenac rectally. The high heterogeneity for postoperative nausea, vomiting, or both (preoperative and postoperative) is likely due to the different operative anesthesia medications. Two studies (Legeby 2005; Romundstad 2006a), both reported high rates of postoperative nausea and vomiting. However, in both studies, the opioid fentanyl was administered during general anesthesia. Fentanyl is known to cause nausea and vomiting, which was apparent in both groups. Bosek 1996 administered isoflurane, another anesthetic known to commonly cause nausea and vomiting postoperatively, which resulted in nausea and vomiting in both the NSAID and placebo group. Parsa 2005 did not administer opioids or anesthesia known to cause nausea and vomiting, but demonstrated imprecise results. The high heterogeneity for opioid use within 24 hours of surgery (preoperative and postoperative) is likely due to different breast surgeries, routes of NSAID administration, types of NSAIDs, and types of postoperative opioids. Legeby 2005 administered morphine patient-controlled analgesia following mastectomy and immediate breast reconstruction with rectal diclofenac. Romundstad 2006a administered codeine following breast augmentation with IV parecoxib. Sun 2013 administered fentanyl patient-controlled analgesia following mastectomy with IV flurbiprofen. This may explain the inconsistency of results between these studies.

Among the studies comparing NSAIDs to other analgesics, pain intensity 24 hours following surgery (postoperative) and postoperative nausea and vomiting or both (preoperative and postoperative) had moderate-certainty evidence. Outcomes with significant heterogeneity for comparisons between NSAIDs and other analgesics were pain intensity 24 hours following surgery (preoperative and postoperative) with heterogeneity of 89% and opioid use within 24 hours of surgery (preoperative and postoperative) with heterogeneity of 96% in the postoperative

group. The high heterogeneity for pain intensity 24 hours following surgery (preoperative and postoperative) is likely due to different times of pain assessments, routes of administration and times of administration. Freedman 2006 assessed pain at 24 hours following surgery and administered celecoxib orally. Oh 2016 assessed pain 30 minutes after NSAID or other analgesic administration and administered ibuprofen IV. Wen 2015 assessed pain at 24 hours following surgery and administered flurbiprofen IV. The high heterogeneity for opioid use within 24 hours of surgery (preoperative and postoperative) is likely due to different breast surgeries, routes of NSAID administration, types of NSAIDs, and types of postoperative opioids. Bakr 2016 administered morphine IV following modified radical mastectomy with IV ketorolac. Freedman 2006 administered hydrocodone orally following breast augmentation with oral celecoxib. Wen 2015 administered fentanyl IV following modified radical mastectomy with IV flurbiprofen.

The remaining outcomes had either low- or very low-certainty evidence. With low-certainty evidence, our confidence in the effect estimate is limited or the true effect may be substantially different from the estimate of the effect. Only one study reported comparing outcomes between NSAIDs and no intervention presented in Summary of findings 3. The ability to make comparisons across studies was not possible. With all comparisons between patients taking NSAIDs and no intervention, we have very little confidence in the effect estimate or the true effect is likely to be substantially different from the estimate of effect.

The ongoing study, NCT03535116 2018 will provide a double-blinded, placebo-controlled randomized trial comparing preoperative NSAIDs (ketorolac) to placebo. NCT03535116 2018 will assess breast hematomas. After publication, this study will improve evidence for this outcome.

Potential biases in the review process

We strictly followed the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* on searching, study selection, data collection, and data analysis to reduce any potential risk of bias (Higgins 2011). This review had the potential for the following limitations: (i) no assessment of publication bias through funnel plot analysis because fewer than 10 studies were included in the meta-analysis; (ii) subgroup analysis was planned, however the paucity of data did not allow us to perform many of these comparisons for each outcome; (iii) typical limitations of aggregate-data meta-analysis, where individual patient data are absent, and subgroup analysis is usually underpowered; (iv) unsuccessful attempts to obtain further outcomes information and data on the included studies from the trial authors.

Agreements and disagreements with other studies or reviews

Although thousands of women undergo oncologic, reconstructive, and cosmetic breast surgery annually, to the best of our knowledge, this is the first systematic review and meta-analysis of randomized trials on perioperative NSAIDs in women undergoing breast surgery. Three reviews have discussed perioperative NSAIDs with similar findings (Cheng 2016; Stone 2019; Walker 2019). Cheng 2016 reviewed the efficacy of perioperative analgesia for breast cancer-related surgery. The authors of this review used data from Legeby 2005 and concluded perioperative NSAIDs reduced pain intensity and required less opioids. However NSAIDs were associated with higher rates of postoperative bleeding. We also used data from Legeby 2005, however we considered five additional studies for comparisons (Bosek 1996; Forget 2019; Parsa 2005; Romundstad 2006a; Sun 2013). With additional studies, NSAIDs were not associated with higher rates of postoperative bleeding. As such, NSAIDs in multimodal analgesic regimens appear to be beneficial, with the possible risk of increased postoperative bleeding without conclusive recommendations until further research specific to breast surgery is performed. Walker 2019 performed a systematic review and meta-analysis specifically evaluating the risk of hematomas in plastic surgery with NSAIDs. When examining NSAID use in breast surgery, there was no statistically significant difference in incidence of hematoma or increased bleeding after combining studies assessing ketorolac, ibuprofen, and celecoxib.

Stone 2019 reported recommendations for enhanced recovery after surgery pathways with microsurgical breast reconstruction. The authors recommended preoperative celecoxib 400 mg in the holding area, celecoxib 200 mg twice daily for 4 days postoperatively, and ibuprofen 600 mg every 6 hours as needed for 7 days after hospital discharge. These recommendations for perioperative NSAIDs were developed by pain specialists from a single institution based on experience and available literature with subjectively reported better pain control in the postoperative period.

AUTHORS' CONCLUSIONS

Implications for practice

We found evidence to suggest that perioperative (preoperative and/or postoperative) NSAIDs may reduce pain intensity, nausea and vomiting and opioid use within 24 hours following surgery in women undergoing breast surgery. These surgeries included implant-based reconstruction, lumpectomy, mastectomy, and augmentation mammaplasty. However, there was very little evidence to suggest whether perioperative (preoperative and/or postoperative) NSAIDs may reduce or increase the rate of breast hematoma within 90 days (requiring reoperation, interventional drainage, or no treatment) of breast surgery, bleeding from any location within 90 days of breast surgery, need for blood transfusion, and other side effects of NSAID use, in comparison to placebo, other analgesics or to no intervention. Additional good-quality, large-scale, RCTs are required before definite conclusions can be made.

Implications for research

Areas of future research include evaluating the impact of perioperative NSAIDs on hospital length of stay, breast cancer recurrence and non-prescribed NSAID use. We were unable to find these outcomes in any of the 12 included studies. By administering NSAIDs and lowering opioid doses, patients may be less likely to become over sedated and ambulate earlier following surgery. This may also reduce other associated complications postoperatively. Only a few NSAIDs have been evaluated. Some of these medications may not be available to all. Evaluating alternative NSAIDs may be beneficial for these populations. Assessing outcomes based on the pharmacologic classes of NSAIDs (COX-1 inhibitors, selective COX-2 inhibitors), types of NSAIDs within pharmacologic classes (diclofenac, ketorolac, ibuprofen, flurbiprofen) and times of administration (preoperative, intraoperative, postoperative) would

provide information regarding the efficacy and safety of specific medications.

Pharmacogenomics (the science concerned with understanding how genetic differences among individuals cause varied responses to the same drug and with developing drug therapies to compensate for these differences, Merriam-Webster 1997) is an evolving specialty of medicine. The impact of pharmacogenomics on the efficacy and safety of NSAIDs in response to genetic variants may reveal which patients are appropriate candidates for NSAIDs. Understanding if certain genetic factors predispose patients to different pain responses, risks of bleeding, cardiovascular events, liver disease, asthma, gastrointestinal disease, kidney disease, and pregnancy may be beneficial prior to perioperative administration of an NSAID for women undergoing breast surgery. Evaluating different routes of administration would be beneficial for patients unable to tolerate oral medications after they are discharged from the hospital (oral, rectal, IV, IM, transdermal). This would be beneficial for patients with multiple comorbidities or complex medication regimens susceptible to drug interactions. Administering perioperative NSAIDs to women undergoing a greater diversity of breast surgery procedures may optimise patient selection and allow for a greater number of recommendations for use. None of the studies evaluated NSAIDs in women undergoing autologous breast reconstruction, breast reduction, and mastopexy surgery.

Other pain medications administered intraoperatively during anesthesia are likely to impact outcomes associated with NSAIDs. Evaluating NSAIDs along with different anesthesia medications may help to further identify discrepancies between studies. With completion of the ongoing study NCT03535116 2018, we hope it will provide insight into these areas of research. RCTs are required to definitively identify the benefits or non-benefits of NSAIDs in perioperative breast surgery.

ACKNOWLEDGEMENTS

We would like to acknowledge the editorial team of the Cochrane Breast Cancer Group for their assistance preparing this full-text review. Si Jia Zhu (Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China) for her assistance with translation of articles in Chinese. We are grateful for peer-reviewer comments from Professor Patrice Forget, MD, PhD (University of Aberdeen; Epidemiology group; Institute of Applied Health Sciences; School of Medicine, Medical Sciences and Nutrition; NHS Grampian, Department of Anaesthesia; Aberdeen, UK); Linda Bily (Stony Brook Cancer Center, New York, USA); Bonner Cutting (Alamo Breast Cancer Foundation), Susan G Komen (Advocate-in-Science, Texas, USA) and Dr Amalia Karahalios (Monash University, The University of Melbourne, Melbourne, Australia).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bakr 2016

Study characteristics	
Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 20, age 50.9 ± 12.32
	  ○ Type of breast surgery: modified radical mastectomy
	  ○ Breast cancer history
	• Analgesic
	  ○ n = 20, age 46.25 ± 10.42
	  ○ Type of breast surgery: modified radical mastectomy

Bakr 2016 *(Continued)*

	○ Breast cancer history
Interventions	• NSAID versus other analgesic ○ Ketorolac 60 mg IM once at end of surgery versus morphine 5 mg IV once at end of surgery
Outcomes	• Postoperative pain intensity within 24 (± 12) hours of surgery: VAS 1.6 versus 1.5 • Incidence rate or severity of PONV: 0 versus 20 participants • Other side effects of NSAID use: ○ respiratory depression: 0 versus 0 participants
Notes	Authors received no funding and had no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated according to computer-generated randomisation tables into one of 3 groups of 20 patients
Allocation concealment (selection bias)	Low risk	Computer-generated allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed
Selective reporting (reporting bias)	Low risk	Trial registration confirmed all reported outcomes were assessed

Bosek 1996

Study characteristics

Methods	Randomized controlled trial
Participants	• NSAID ○ n = 40, age 55.1 ± 12.9 ○ Type of breast surgery: mastectomy or lumpectomy with axillary lymph node dissection ○ Breast cancer history • Placebo ○ n=20, age 56.4 ± 16 ○ Type of breast surgery: mastectomy or lumpectomy with axillary lymph node dissection ○ Breast cancer history
Interventions	• NSAID versus placebo

Bosek 1996 *(Continued)*

	◦ Ketorolac 30 mg IV or ketorolac 30 mg via Jackson-Pratt drain at end of surgery and every 6 hours postoperatively ◦ 0.9% NaCL IV or Jackson-Pratt drain at end of surgery and every 6 hours postoperatively
Outcomes	• Postoperative pain intensity 18 hours after surgery: VAS 1.15 ± 1.25 versus 1.1 ± 1.4 • Incidence rate or severity of PONV: 16 versus 14 • Opioid use at 18 hours after surgery: 1.7 ± 3.1 mg versus 2.7 ± 3.9 mg morphine
Notes	No declaration of funding or conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Chan 1996

Study characteristics

Methods	Randomized controlled trial
Participants	• NSAID ◦ n = 40, preoperative (n = 20) and postoperative (n = 20), age 37.6 ± 10.55 ◦ Type of breast surgery: breast lump excision ◦ Breast cancer history • No intervention ◦ n = 20, age 40 ± 9.6 ◦ Type of breast surgery: breast lump excision ◦ Breast cancer history
Interventions	• NSAID versus no intervention ◦ Diclofenac 75 mg IM preoperative or postoperative

Chan 1996 *(Continued)*

Outcomes	• Perioperative: postoperative pain intensity at 120 minutes after surgery was VAS 0.25 ± 0.18 versus 0.75 ± 1.18 • Preoperative: postoperative pain intensity at 120 minutes after surgery was VAS 0.375 ± 0.92 versus 0.75 ± 1.18 • Postoperative: postoperative pain intensity at 120 minutes after surgery was VAS 0.125 ± 0.56 versus 0.75 ± 1.18
Notes	No declaration of funding or conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized controlled trial
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Forget 2019

Study characteristics

Methods	Belgian, multicenter, prospective, double-blind, placebo-controlled, parallel assignment, randomized phase III trial in high-risk breast cancer patients

Participants	• NSAID
	  ○ n = 96, age 56.1 ± 14
	  ○ Type of breast surgery: mastectomy (n = 60), breast-conserving surgery (n = 34), missing data (n = 2)
	• Placebo
	  ○ n = 107, age 55.4 ± 13.9
	  ○ Type of breast surgery: mastectomy (n = 59), breast-conserving surgery (n = 48)

Interventions	• NSAID versus placebo
	  ○ Experimental: ketorolac
	  ■ Ketorolac 30 mg IV (single dose) at induction of anesthesia (pre-incision)
	  • Placebo comparator: control
	  • Saline 3 mL IV (single dose) at induction of anesthesia (pre-incision)

Forget 2019 *(Continued)*

Outcomes	• Postoperative pain intensity 24 hours after surgery
	  ○ Verbal simple scale: VAS 3.33 ± 2.2 versus 3.75 ± 2.3
	  ○ Bleeding from any location within 90 days: 1 versus 0 participants
	  ○ Need for blood transfusion: 0 versus 0 participants
	  ○ Other side effects of NSAID use: 8 versus 7 participants
	  ○ Length of hospital stay: 3.9 ± 1.2 days versus 3.7±1 days

Notes	Funded by the Anticancer Fund, the Belgian Society of Anaesthesia and Resuscitation, the Foundation Saint-Luc; the Commission du Patrimoine of the Université catholique de Louvan, St-Luc Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized controlled trial. Randomization of eligible patients was done the day before surgery and used randomisation blocks of 4. There was no stratification factor.
Allocation concealment (selection bias)	Low risk	In each center, a randomisation list was kept accessible exclusively to the pharmacist in charge of the preparation of the study product (ketorolac or placebo). For each patient, a sealed opaque envelope was provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were given one dose of intervention or a matching placebo. Each patient was randomly assigned on a 1:1 ratio to receive either 30 mg of ketorolac or a placebo during the induction of anesthesia (pre-incision). The placebo consisted of NaCl 0.9% (3 mL) and was identically presented to ensure double-blinding. No dose modification was allowed because only one single dose was administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A randomisation list was kept accessible exclusively to the pharmacist in charge of the preparation of the study product.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient with missing data in placebo group for postoperative pain intensity within 24 (± 12) hours of surgery
Selective reporting (reporting bias)	Low risk	Trial registration confirmed all reported outcomes were assessed

Freedman 2006

Study characteristics

Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 50, age 34 ± 8
	  ○ Type of breast surgery: augmentation mammaplasty
	• Analgesic
	  ○ n = 50, age 32 ± 8
	  ○ Type of breast surgery: augmentation mammaplasty

Interventions	• NSAID versus other analgesic

Freedman 2006 *(Continued)*

	○ Celecoxib 400 mg 1 to 2 hours preoperative, then daily for 7 days postoperative ○ Hydrocodone 5 mg as needed postoperative
Outcomes	• Incidence of breast hematoma within 90 days of breast surgery: 0 versus 1 participant • Postoperative pain intensity within 24 (± 12) hours of surgery: Likert pain scale 3.3 ± 1.3 versus 5.1 ± 1.3 • Incidence rate or severity of PONV: 43 versus 91 postoperative days • Opioid use within 24 (± 12) hours of surgery 34 mg ± 22 mg versus 110 mg ± 34 mg morphine
Notes	No declaration of funding or conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized controlled trial
Allocation concealment (selection bias)	Unclear risk	No information was provided regarding method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Legeby 2005

Study characteristics

Methods	Randomized controlled trial
Participants	• NSAID ○ n = 25 ○ Type of breast surgery: elective breast surgery mastectomy and immediate breast reconstruction ○ Breast cancer history • Placebo ○ n = 23 ○ Type of breast surgery: elective breast surgery mastectomy and immediate breast reconstruction ○ Breast cancer history
Interventions	• NSAID versus placebo ○ Diclofenac 50 mg rectally 1 hour before the start of surgery and every 8 hours for 3 days ○ Placebo rectally every 8 hours for 3 days

Legeby 2005 *(Continued)*

Outcomes	• Postoperative pain intensity 21 to 44 hours after surgery: VAS 1.05 ± 1.13 versus 1.87 ± 1.52
	• Incidence rate or severity of PONV: 14 versus 12 participants
	• Other side effects of NSAID use:
	  ○ respiratory depression 0 versus 1
	  ○ opioid use within 20 hours of surgery 26.8 ± 18.1 mg versus 35.9 ± 13.6 mg morphine

Notes	Supported by grants from Karolinska Institute foundations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized controlled trial
Allocation concealment (selection bias)	Low risk	A randomisation table was used to allocate patients to each group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A table of randomisation (each number corresponding to a package of identically shaped suppositories), prepared by the Hospital pharmacy, each patient received suppositories of either diclofenac (group D) or placebo (group P). The randomisation table was kept by the Hospital Pharmacy beyond the evaluation of all effect variables.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of investigators and assessing nurses to group assignment of the patients and outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients were excluded after randomisation from the intervention group, with reason. 6 patients were lost to follow-up in the intervention group and placebo groups
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Oh 2016

Study characteristics

Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 30, age 48 ± 9
	  ○ Type of breast surgery: excisional biopsy, partial mastectomy, total mastectomy, modified radical mastectomy
	  ○ Breast cancer history
	• Analgesic
	  ○ n = 30, age 51 ± 8
	  ○ Type of breast surgery: excisional biopsy, partial mastectomy, total mastectomy, modified radical mastectomy
	  ○ Breast cancer history

Interventions	• NSAID versus other analgesic • Ibuprofen 50 mg to 800 mg IV per postoperative dosing protocol

Oh 2016 *(Continued)*

	• Hydromorphone 0.25 mg to 2 mg IV per postoperative dosing protocol
Outcomes	• Incidence rate or severity of PONV: 0 versus 1 participant
Notes	Authors received no funding and had no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done prospectively to one of the three groups using a computer-generated table and concealed envelopes.
Allocation concealment (selection bias)	Low risk	Computer-generated table and concealed envelopes were used to allocate participants to each group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participants, observers, and assessors of outcomes)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (participants, observers, and assessors of outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed except for two patients in Group IH who were withdrawn from data analysis due to missing data.
Selective reporting (reporting bias)	Low risk	Trial registration confirmed all reported outcomes were assessed

Parsa 2005

Study characteristics	
Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 347
	  ○ Type of breast surgery: subpectoral breast augmentation
	• Placebo
	  ○ n = 348
	  ○ Type of breast surgery: subpectoral breast augmentation

Interventions	• NSAID versus placebo
	  ○ Celecoxib 400 mg orally once 30 minutes preoperative
	  ○ Glucose capsule orally once 30 minutes preoperative

Outcomes	• Incidence rate or severity of PONV: 6 versus 0 participants • Opioid use within 24 (± 12) hours of surgery: 30.5 mg versus 51.5 mg morphine
Notes	Authors received no funding and had no conflicts of interest

Parsa 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized controlled trial
Allocation concealment (selection bias)	Unclear risk	No information was provided regarding method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a blinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	All randomized participants were analyzed, did not report standard deviations with mean opioid use within 24 (± 12) hours of surgery
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Romundstad 2006a

Study characteristics

Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 68, age 28 ± 8
	  ○ Type of breast surgery: augmentation mammaplasty
	• Placebo
	  ○ n = 68, age 29 ± 6
	  ○ Type of breast surgery: augmentation mammaplasty

Interventions	• NSAID versus placebo
	  ○ Parecoxib 40 mg IV once preoperative before the start of sedation
	  ○ 0.9% NaCl IV once preoperative before the start of sedation

Outcomes	• Incidence of breast hematoma within 90 days of breast surgery: 1 versus 1 participant • Incidence rate or severity of PONV: 41 versus 25 participants • Opioid use within 24 (± 12) hours of surgery: 9.9 ± 5.85 mg versus 15.3 ± 6.75 mg morphine
Notes	No declaration of funding or conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement

Romundstad 2006a *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomized, double-blind, single-dose, parallel-group
Allocation concealment (selection bias)	Low risk	Patients randomized the patients in blocks of nine to 1 of 3 groups of equal size using a list of random numbers, according to the Moses-Oakford algorithm
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to all measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were analyzed
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

Sun 2013

Study characteristics	
Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 30, age 50.9 ± 11.2
	  ○ Type of breast surgery: mastectomy
	  ○ Breast cancer history
	• Placebo
	  ○ n = 30, age 48 ± 10.8
	  ○ Type of breast surgery mastectomy: breast cancer history

Interventions	• NSAID versus placebo
	  ○ Flurbiprofen 50 mg IV preoperative and 6 hours later
	  ○ Intralipid 5 mL IV preoperative and 6 hours later

Outcomes	• Postoperative pain intensity within 24 (± 12) hours of surgery: NRS 0 ± 0 versus 0 ± 0
	• Other side effects of NSAID use:
	  ○ peptic ulcer: 0 versus 0
	  ○ liver or renal dysfunction: 0 versus 0
	  ○ respiratory depression: 0 versus 0 participants
	  ○ opioid use within 24 (± 12) hours of surgery: 0.18 ± 0.04 mg versus 0.18 ± 0.03 mg morphine

Notes	No declaration of funding or conflicts of interest
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Sun 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomized control trial
Allocation concealment (selection bias)	Low risk	Computer-generated random number utilized to allocate participants to each group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomization and anesthesia procedure was done by an anesthesiologist, and the follow-up and evaluation after the surgery was done by another anesthesiologist blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

van Helmond 2016

Study characteristics	
Methods	Randomized prospective controlled trial

Participants	• NSAID
	  ○ n = 48, age 51 ± 9
	  ○ Type of breast surgery: lumpectomy, total simple mastectomy or modified radical mastectomy
	  ○ Breast cancer history
	• Placebo
	  ○ n = 46, age 55 ± 11
	  ○ Type of breast surgery: lumpectomy, total simple mastectomy or modified radical mastectomy
	  ○ Breast cancer history

Interventions	• NSAID versus placebo
	  ○ Parecoxib 40 mg IV preoperative 30 minutes before the start of surgery and 6 hours later
	  ○ Celecoxib 200 mg oral daily postoperative day 1 to 5
	• Placebo
	  ○ Injections and tablets

Outcomes	• Incidence of breast hematoma within 90 days of breast surgery: 0 versus 3 participants • Postoperative pain intensity within 24 (± 12) hours of surgery: VAS pain scale 20 mm versus 30 mm
Notes	Funded by Pfizer. Pfizer had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript.
Risk of bias	
Bias	**Authors' judgement**	**Support for judgement**

van Helmond 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Pseudo-randomisation employed using computer-generated blocks of six
Allocation concealment (selection bias)	Unclear risk	A pseudo-random code was computer-generated for the randomisation blocks that had a size of six. Stratified random sampling ensured equal distribution of axillary lymph node dissections over groups.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Observers and personnel involved in patient management were blinded to medication assignment as well as study participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observers and personnel involved in patient management were blinded to medication assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	There was relatively high exclusion rate due to treatment failure (unsuccessful paravertebral block) in 5 patients (2 intervention group and 3 placebo group) and failure of the hospital pharmacy to deliver study drugs to the operating room on time in 30 patients. Consent was withdrawn in 2 patients (1 placebo and 1 intervention). Three patients from each group were excluded due to not meeting inclusion criteria. Study used a modified intention-to-treat analysis for 94 patients included in analysis.
Selective reporting (reporting bias)	Low risk	Trial registration confirmed all reported outcomes were assessed

Wen 2015

Study characteristics	
Methods	Randomized controlled trial

Participants	• NSAID
	  ○ n = 20, age 45.5 ± 9.1
	  ○ Type of breast surgery reconstruction mastectomy
	  ○ Breast cancer history
	• Fentanyl alone
	  ○ n = 20, age 43.9 ± 7.8
	  ○ Type of breast surgery reconstruction: mastectomy
	  ○ Breast cancer history

Interventions	• NSAID versus other analgesic ○ Flurbiprofen 3 mg/kg IV infusion 48 hours postoperative
Outcomes	• Postoperative pain intensity within 24 (± 12) hours of surgery: VAS 2.6 ± 0.66 versus 2.55 ± 0.66 • Incidence rate or severity of PONV: 2 versus 12 participants • Opioid use within 24 (± 12) hours of surgery 26.8 ± 1.8 mg versus 80.7 ± 4.8 mg morphine
Notes	No declaration of funding or conflicts of interest

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Wen 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomized controlled trial
Allocation concealment (selection bias)	Low risk	Secure web-based computer-generated randomisation process that automatically records numbers and assignments. A researcher who did not participate in the clinical trial performed the process of randomising patients.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	No information available for trial registrations or protocols to determine if all reported outcomes were assessed

IM: intramuscular
IV: intravenous
NaCl: sodium chloride
NRS: numerical rating scale
NSAID: nonsteroidal anti-inflammatory drug
PONV: postoperative nausea and vomiting
VAS: visual analog scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12614000507684	Ineligible comparator. The control arm is aromatase inhibitor alone and study arm is aromatase inhibitor plus aspirin
Aristarco 2016	Ineligible intervention. This a placebo-controlled trial to evaluate the activity of exemestane and celecoxib before surgery.
Barker 2018	Ineligible comparator. This is a retrospective review comparing acetaminophen to other analgesics.
Betambeau 2004	Ineligible intervention. This RCT looked at the use of NSAIDs to reduce the incidence of breast cancer.
Blomqvist 1996	Non-RCT
Bosek 1992	Ineligible patient population
Bosek 1994	Ineligible outcomes
Brandao 2013	Preoperative treatment

Study	Reason for exclusion
Bundred 2010	Ineligible outcomes. This study looked only at a decrease in Ki67 between diagnosis and surgical excision.
Cawthorn 2012	Non-RCT
ChiCTR-IPR-14005271	No data available on this study
CTRI/2016/10/007397	Ineligible comparator. This RCT compared pregabalin to placebo
DeOliveira 2018	Ineligible comparators. This RCT compared acetaminophen to placebo
Desmedt 2017	Ineligible outcomes. The full text was not available
EUCTR2012-003774-76-BE	Study protocol. No data available
Filippini 2014	Only long-term pain data available
Forget 2010	A retrospective analysis of patients receiving intraoperative analgesics. It was not possible to differentiate effects from NSAID and other drugs
Forget 2013	Study protocol with no data available
Forget 2014	Ineligible comparators and non-RCT study. This retrospective study looked at the use of ketorolac or diclofenac intraoperatively during breast surgery
Francis 1988	Ineligible indication. Exmined the effect of diclofenac verus placebo on platelet aggregation
Hidar 2007	Ineligible outcomes. This study only looked at postoperative drainage volume as their primary outcome
Himendra 1985	Ineligible indication. A double-blind, randomized, placebo-controlled study was carried out to assess the efficacy of ketoprofen suppositories as a postoperative analgesic in outpatients undergoing extirpation surgery
Hu 2009	Ineligible outcomes. Full text not available
ISRCTN06628870	Protocol only. No data provided for study
ISRCTN86894592	Ineligible intervention. Study only looks at pharmacological therapy and not breast surgery
Kampe 2006	Ineligible comparators. This study compared IV paracetamol to IV dipyrone
Kodaka 2012	Ineligible outcomes. Full text not available
Laisalmi 2001a	Non-RCT
Laisalmi 2001b	Ineligible outcomes. The study only looked at renal effects of the combination of ketorolac and sevoflurane anesthesia versus placebo and sevoflurane anesthesia
Lakdja 1997	Non-RCT
Mahabir 2008	Ineligible comparator. This trial compared placebo to ketorolac and bupivacaine in controlling postoperative pain in breast augmentation patients
Martin 2010	Preoperative treatment

Study	Reason for exclusion
McCrea 2009	Unable to differentiate data of NSAID from that of other drugs
Mitchell 2012	Ineligiblecomparator. This study compared acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine (Tylenol 3) after outpatient breast surgery
Molon 2009	Non-RCT
Morley-Forster 1993	Unable to differentiate breast surgery data from gynecological data
NCT00070057	Ineligible comparator. The study compared celecoxib to surgical intervention
NCT00435747	Duplicate study
NCT00502684	Incorrect comparator. This study compared beta-blocker to COX-2 inhibitor or placebo
NCT01695226	Preoperative treatment
NCT01806259	The study recruitment was active. The current recruitment is unknown
NCT01852955	Ineligible comparators, comparing acetomorphine to placebo
NCT02102555	Ineligible comparators. This study compared acetomorphine to placebo. This study was terminated. The study closed due to difficulty enrolling subjects. No results are available
NCT02141139	Ineligible comparators and outcomes. This study compared NSAID to NSAID
NCT02461056	Duplicate study
NCT03007381	The study was withdrawn due to a lack of funding
NCT03185871	The study was withdrawn due to slow accrual and as a result was excluded from this study
Nguyen 2018a	Non-RCT
Nguyen 2018b	Non-RCT
Ohnesorge 2009	Ineligible comparators. This study compared acetaminophen to metamizol, both of which are not NSAIDs
Parsa 2009	Ineligible comparator. The study looked at NSAID versus an anti-epileptic drug for patients undergoing all types of surgery
Pavlin 2002	It was not possible to differentiate breast data from the study analysis
Priya 2002	This study only compared NSAIDS in both groups
Retsky 2012	Review article
Retsky 2013	Review article
Riest 2006	This study looked at patients scheduled for spine, breast or orthopaedic surgery. It was not possible to assess the data for just breast surgery
Romundstad 2006b	The data presented in this study only looked at long-term pain assessment

Study	Reason for exclusion
Shaashua 2017	Unable to extrapolate the data from NSAID and other drugs
Sharma 2001	Non-RCT, RCTs were available for assessment in this study
Sun 2008	This study looked at consenting patients undergoing major plastic surgery (e.g. breast augmentation, abdominoplasty procedures). It was not possible to differentiate the data for only breast surgery.
Tallian 2014	Ineligible intervention, the study compared patients undergoing intra-abdominal and breast reconstruction surgery receiving no iIV acetaminophen with patients receiving concomitant IV acetaminophen. Furthermore the full text was not available. As a result, sufficient amount of data could not be extrapolated
VanHelmond 2014	The full text was not available as a result sufficiat amount data could not be extrapolated.

IV: intravenous
NSAIDs: nonsteroidal anti-inflammatory drugs
RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT03535116 2018

Study name	The effect of intra-operative ketorolac on hematoma rates in breast reduction surgery
Methods	Double-blind, randomized, controlled, parallel assignment trial of breast reduction patients and their postoperative hematoma rates with the use of ketorolac
Participants	100 female > 18 years of age undergoing breast reduction surgery

Interventions	• NSAID versus placebo
	  ◦ Experimental: ketorolac
	  ◦ Patient receives 30 mg IV ketorolac (single dose) towards the end of the operation
	  • Placebo comparator: control
	  • Patient receives IV saline (single dose) towards the end of the operation

Outcomes	• Primary outcomes
	  ◦ Hematoma (timeframe: 6 weeks)
	  ◦ Postoperative hematoma

Starting date	24 May 2018
Contact information	Geethan Chandran, Assistant Professor, Dr Chandran Medical Prof Corp
Notes	Current recruitment status: not yet recruiting; no declaration of funding or conflicts of interest

IV: intravenous
NSAID: nonsteroidal anti-inflammatory drug

DATA AND ANALYSES

Comparison 1. NSAID versus placebo

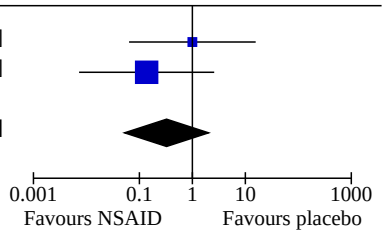
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Breast hematoma	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.02]
1.2 Breast hematoma by timing of drug administration	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Preoperative	1	136	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.66]
1.3 Pain intensity 24 (± 12) hours following surgery	3	310	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.49, -0.03]
1.4 Pain intensity 24 (± 12) hours following surgery by timing of drug administration	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 Preoperative	1	202	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.46, 0.09]
1.4.2 Postoperative	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.50, 0.57]
1.5 Incidence rate or severity of postoperative nausea, vomiting, or both	4	939	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.58, 2.27]
1.6 Incidence rate or severity of postoperative nausea, vomiting, or both by timing of drug administration	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Preoperative	2	831	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.42, 20.64]
1.6.2 Postoperative	1	60	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.36, 0.92]
1.7 Bleeding from any location within 90 days	2	251	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.24]
1.8 Bleeding from any location within 90 days by timing of drug administration	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 Preoperative	1	203	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [0.14, 81.03]
1.9 Need for blood transfusion	1	48	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [0.23, 91.34]
1.10 Need for blood transfusion by timing of administration	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 Preoperative	1	48	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [0.23, 91.34]
1.11 Other side effects of NSAID use	2	251	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.44, 2.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Other side effects of NSAID use by timing of drug administration	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.12.1 Preoperative	1	203	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.48, 3.38]
1.13 Opioid use within 24 (± 12) hours of surgery	4	304	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.85, -0.05]
1.14 Opioid use within 24 (± 12) hours of surgery by timing of drug administration	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 Preoperative	1	136	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-1.20, -0.50]
1.14.2 Postoperative	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.83, 0.25]
1.15 Length of hospital stay	1	203	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.09, 0.46]

Analysis 1.1. Comparison 1: NSAID versus placebo, Outcome 1: Breast hematoma

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Romundstad 2006a	1	68	1	68	21.9%	1.00 [0.06 , 15.66]
van Helmond 2016	0	48	3	46	78.1%	0.14 [0.01 , 2.58]
Total (95% CI)		**116**		**114**	**100.0%**	**0.33 [0.05 , 2.02]**
Total events:	1		4			

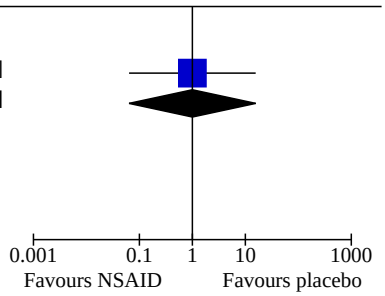
Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: NSAID versus placebo, Outcome 2: Breast hematoma by timing of drug administration

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Preoperative						
Romundstad 2006a	1	68	1	68	100.0%	1.00 [0.06 , 15.66]
Subtotal (95% CI)		**68**		**68**	**100.0%**	**1.00 [0.06 , 15.66]**
Total events:	1		1			

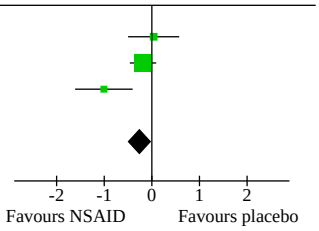
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Analysis 1.3. Comparison 1: NSAID versus placebo, Outcome 3: Pain intensity 24 (± 12) hours following surgery

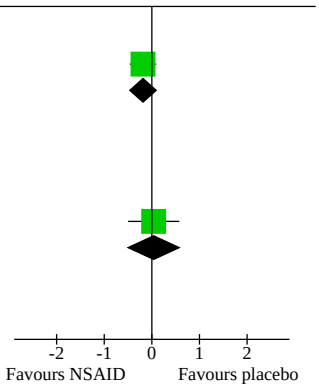
Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bosek 1996	1.15	1.25	40	1.1	1.4	20	18.0%	0.04 [-0.50 , 0.57]
Forget 2019	3.33	2.2	96	3.75	2.3	106	67.8%	-0.19 [-0.46 , 0.09]
Legeby 2005	2.04	1.03	25	3.33	1.47	23	14.2%	-1.01 [-1.61 , -0.40]
Total (95% CI)			**161**			**149**	**100.0%**	**-0.26 [-0.49 , -0.03]**

Heterogeneity: Chi² = 7.34, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: NSAID versus placebo, Outcome 4: Pain intensity 24 (± 12) hours following surgery by timing of drug administration

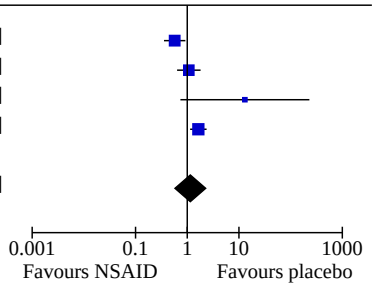
Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.4.1 Preoperative								
Forget 2019	3.33	2.2	96	3.75	2.3	106	100.0%	-0.19 [-0.46 , 0.09]
Subtotal (95% CI)			**96**			**106**	**100.0%**	**-0.19 [-0.46 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
1.4.2 Postoperative								
Bosek 1996	1.15	1.25	40	1.1	1.4	20	100.0%	0.04 [-0.50 , 0.57]
Subtotal (95% CI)			**40**			**20**	**100.0%**	**0.04 [-0.50 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								



Analysis 1.5. Comparison 1: NSAID versus placebo, Outcome 5: Incidence rate or severity of postoperative nausea, vomiting, or both

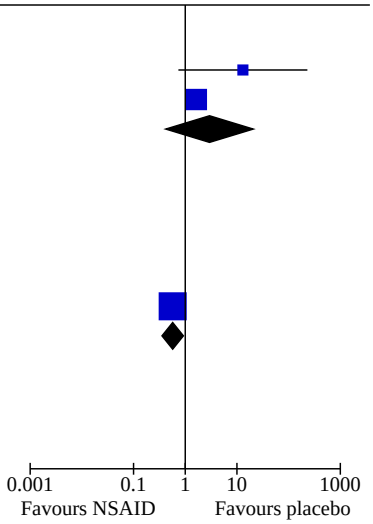
Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bosek 1996	16	40	14	20	31.3%	0.57 [0.36 , 0.92]
Legeby 2005	14	25	12	23	30.4%	1.07 [0.64 , 1.81]
Parsa 2005	6	347	0	348	4.9%	13.04 [0.74 , 230.54]
Romundstad 2006a	41	68	25	68	33.4%	1.64 [1.14 , 2.37]
Total (95% CI)		**480**		**459**	**100.0%**	**1.15 [0.58 , 2.27]**
Total events:	77		51			

Heterogeneity: Tau² = 0.33; Chi² = 15.54, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



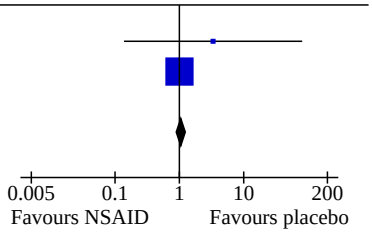
Analysis 1.6. Comparison 1: NSAID versus placebo, Outcome 6: Incidence rate or severity of postoperative nausea, vomiting, or both by timing of drug administration

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Preoperative						
Parsa 2005	6	347	0	348	28.3%	13.04 [0.74 , 230.54]
Romundstad 2006a	41	68	25	68	71.7%	1.64 [1.14 , 2.37]
Subtotal (95% CI)		**415**		**416**	**100.0%**	**2.95 [0.42 , 20.64]**
Total events:	47		25			
Heterogeneity: Tau² = 1.34; Chi² = 2.23, df = 1 (P = 0.14); I² = 55%						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.6.2 Postoperative						
Bosek 1996	16	40	14	20	100.0%	0.57 [0.36 , 0.92]
Subtotal (95% CI)		**40**		**20**	**100.0%**	**0.57 [0.36 , 0.92]**
Total events:	16		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.31 (P = 0.02)						



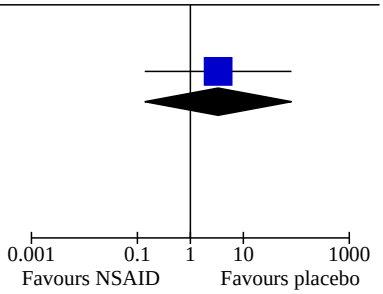
Analysis 1.7. Comparison 1: NSAID versus placebo, Outcome 7: Bleeding from any location within 90 days

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Forget 2019	1	96	0	107	2.0%	3.34 [0.14 , 81.03]
Legeby 2005	24	25	22	23	98.0%	1.00 [0.89 , 1.13]
Total (95% CI)		**121**		**130**	**100.0%**	**1.05 [0.89 , 1.24]**
Total events:	25		22			
Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Test for subgroup differences: Not applicable						



Analysis 1.8. Comparison 1: NSAID versus placebo, Outcome 8: Bleeding from any location within 90 days by timing of drug administration

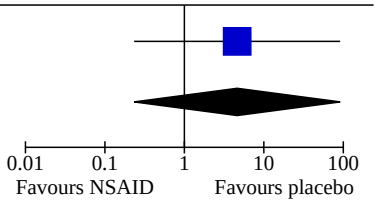
Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Preoperative						
Forget 2019	1	96	0	107	100.0%	3.34 [0.14 , 81.03]
Subtotal (95% CI)		**96**		**107**	**100.0%**	**3.34 [0.14 , 81.03]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						



Analysis 1.9. Comparison 1: NSAID versus placebo, Outcome 9: Need for blood transfusion

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Legeby 2005	2	25	0	23	100.0%	4.62 [0.23 , 91.34]
Total (95% CI)		**25**		**23**	**100.0%**	**4.62 [0.23 , 91.34]**
Total events:	2		0			

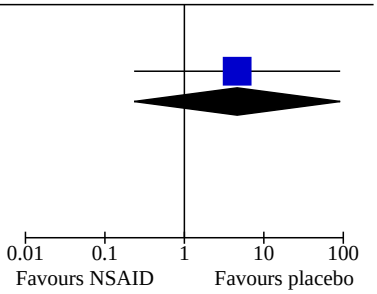
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: NSAID versus placebo, Outcome 10: Need for blood transfusion by timing of administration

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Preoperative						
Legeby 2005	2	25	0	23	100.0%	4.62 [0.23 , 91.34]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**4.62 [0.23 , 91.34]**
Total events:	2		0			

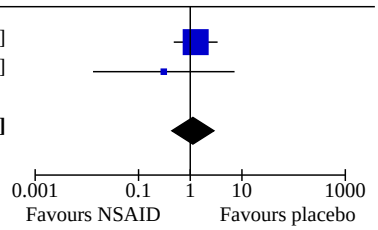
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



Analysis 1.11. Comparison 1: NSAID versus placebo, Outcome 11: Other side effects of NSAID use

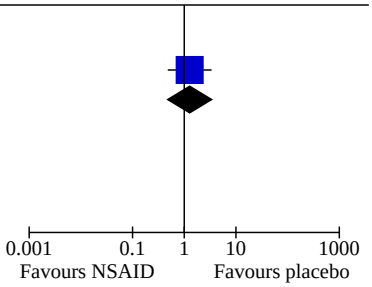
Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Forget 2019	8	96	7	107	91.2%	1.27 [0.48 , 3.38]
Legeby 2005	0	25	1	23	8.8%	0.31 [0.01 , 7.20]
Total (95% CI)		**121**		**130**	**100.0%**	**1.12 [0.44 , 2.86]**
Total events:	8		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



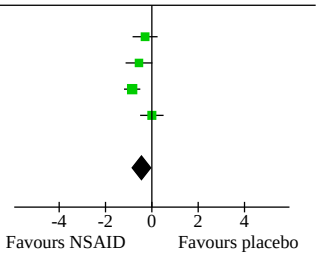
Analysis 1.12. Comparison 1: NSAID versus placebo, Outcome 12: Other side effects of NSAID use by timing of drug administration

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Preoperative						
Forget 2019	8	96	7	107	100.0%	1.27 [0.48 , 3.38]
Subtotal (95% CI)		**96**		**107**	**100.0%**	**1.27 [0.48 , 3.38]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						



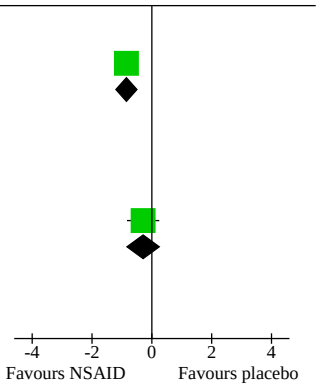
Analysis 1.13. Comparison 1: NSAID versus placebo, Outcome 13: Opioid use within 24 (± 12) hours of surgery

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bosek 1996	1.7	3.1	40	2.7	3.9	20	23.2%	-0.29 [-0.83 , 0.25]
Legeby 2005	26.8	18.1	25	35.9	13.6	23	21.8%	-0.56 [-1.13 , 0.02]
Romundstad 2006a	9.9	5.85	68	15.3	6.75	68	30.6%	-0.85 [-1.20 , -0.50]
Sun 2013	0.18	0.04	30	0.18	0.03	30	24.4%	0.00 [-0.51 , 0.51]
Total (95% CI)			**163**			**141**	**100.0%**	**-0.45 [-0.85 , -0.05]**
Heterogeneity: Tau² = 0.10; Chi² = 8.15, df = 3 (P = 0.04); I² = 63%								
Test for overall effect: Z = 2.20 (P = 0.03)								
Test for subgroup differences: Not applicable								



Analysis 1.14. Comparison 1: NSAID versus placebo, Outcome 14: Opioid use within 24 (± 12) hours of surgery by timing of drug administration

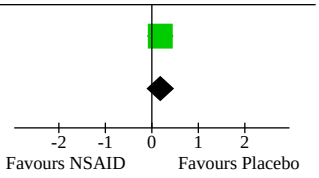
Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 Preoperative								
Romundstad 2006a	9.9	5.85	68	15.3	6.75	68	100.0%	-0.85 [-1.20 , -0.50]
Subtotal (95% CI)			**68**			**68**	**100.0%**	**-0.85 [-1.20 , -0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.74 (P < 0.00001)								
1.14.2 Postoperative								
Bosek 1996	1.7	3.1	40	2.7	3.9	20	100.0%	-0.29 [-0.83 , 0.25]
Subtotal (95% CI)			**40**			**20**	**100.0%**	**-0.29 [-0.83 , 0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								



Analysis 1.15. Comparison 1: NSAID versus placebo, Outcome 15: Length of hospital stay

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Forget 2019	3.9	1.2	96	3.7	1	107	100.0%	0.18 [-0.09 , 0.46]
Total (95% CI)			**96**			**107**	**100.0%**	**0.18 [-0.09 , 0.46]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



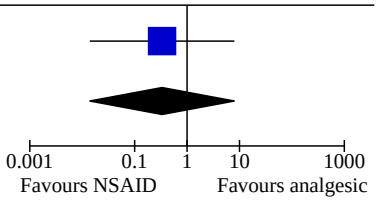
Comparison 2. NSAID versus other analgesic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of breast hematoma within 90 days of breast surgery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
2.2 Pain intensity 24 (± 12) hours following surgery	3	200	Std. Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.97, -0.39]
2.3 Pain intensity 24 (± 12) hours following surgery by timing of drug administration	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Postoperative	2	100	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.51, 0.27]
2.4 Incidence rate or severity of postoperative nausea, vomiting, or both	3	128	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.57]
2.5 Bleeding from any location within 90 days	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
2.6 Other side effects of NSAID use	1	48	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.80]
2.7 Opioid use within 24 (± 12) hours of surgery	3	178	Std. Mean Difference (IV, Random, 95% CI)	-6.87 [-10.93, -2.81]
2.8 Opioid use within 24 (± 12) hours of surgery by timing of drug administration	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 Postoperative	2	78	Std. Mean Difference (IV, Random, 95% CI)	-9.56 [-18.48, -0.64]

Analysis 2.1. Comparison 2: NSAID versus other analgesic, Outcome 1: Incidence of breast hematoma within 90 days of breast surgery

Study or Subgroup	NSAID Events	NSAID Total	Analgesic Events	Analgesic Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freedman 2006	0	50	1	50	100.0%	0.33 [0.01 , 7.99]
Total (95% CI)		**50**		**50**	**100.0%**	**0.33 [0.01 , 7.99]**
Total events:	0		1			

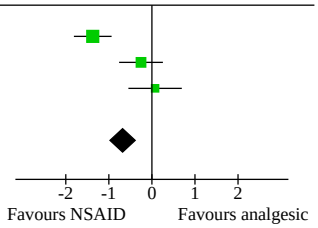
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: NSAID versus other analgesic, Outcome 2: Pain intensity 24 (± 12) hours following surgery

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Analgesic Mean	Analgesic SD	Analgesic Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Freedman 2006	3.3	1.3	50	5.1	1.3	50	44.7%	-1.37 [-1.81 , -0.94]
Oh 2016	6.31	1.7	30	6.8	2.1	30	33.1%	-0.25 [-0.76 , 0.26]
Wen 2015	2.6	0.66	20	2.55	0.66	20	22.2%	0.07 [-0.55 , 0.69]
Total (95% CI)			**100**			**100**	**100.0%**	**-0.68 [-0.97 , -0.39]**

Heterogeneity: Chi² = 18.06, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 4.56 (P < 0.00001)
Test for subgroup differences: Not applicable

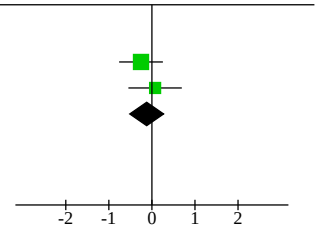


Analysis 2.3. Comparison 2: NSAID versus other analgesic, Outcome 3: Pain intensity 24 (± 12) hours following surgery by timing of drug administration

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Analgesic Mean	Analgesic SD	Analgesic Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
2.3.1 Postoperative								
Oh 2016	6.31	1.7	30	6.8	2.1	30	59.8%	-0.25 [-0.76 , 0.26]
Wen 2015	2.6	0.66	20	2.55	0.66	20	40.2%	0.07 [-0.55 , 0.69]
Subtotal (95% CI)			**50**			**50**	**100.0%**	**-0.12 [-0.51 , 0.27]**

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)

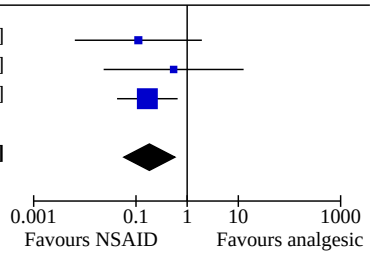
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: NSAID versus other analgesic, Outcome 4: Incidence rate or severity of postoperative nausea, vomiting, or both

Study or Subgroup	NSAID Events	NSAID Total	Analgesic Events	Analgesic Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakr 2016	0	20	4	20	16.1%	0.11 [0.01 , 1.94]
Oh 2016	0	18	1	30	13.2%	0.54 [0.02 , 12.68]
Wen 2015	2	20	12	20	70.7%	0.17 [0.04 , 0.65]
Total (95% CI)		**58**		**70**	**100.0%**	**0.18 [0.06 , 0.57]**
Total events:	2		17			

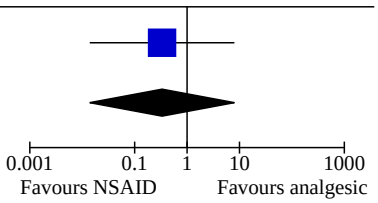
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: NSAID versus other analgesic, Outcome 5: Bleeding from any location within 90 days

Study or Subgroup	NSAID Events	NSAID Total	Analgesic Events	Analgesic Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freedman 2006	0	50	1	50	100.0%	0.33 [0.01 , 7.99]
Total (95% CI)		**50**		**50**	**100.0%**	**0.33 [0.01 , 7.99]**
Total events:	0		1			

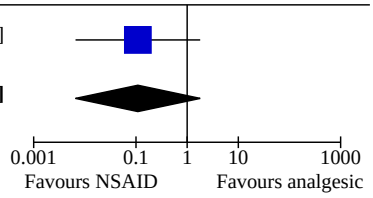
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: NSAID versus other analgesic, Outcome 6: Other side effects of NSAID use

Study or Subgroup	NSAID Events	NSAID Total	Analgesic Events	Analgesic Total	Weight	Risk Ratio M-H, Random, 95% CI
Oh 2016	0	18	7	30	100.0%	0.11 [0.01 , 1.80]
Total (95% CI)		**18**		**30**	**100.0%**	**0.11 [0.01 , 1.80]**
Total events:	0		7			

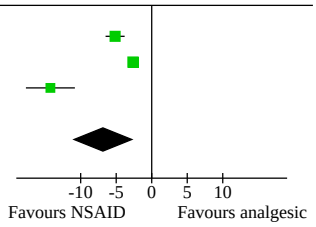
Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



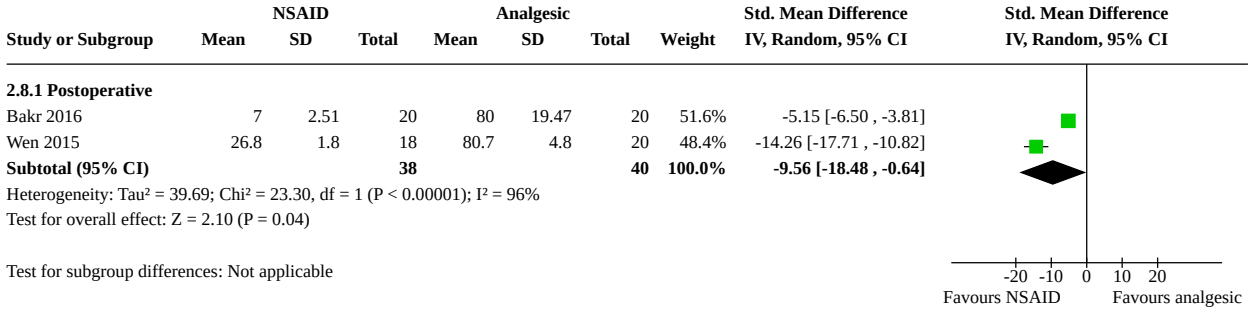
Analysis 2.7. Comparison 2: NSAID versus other analgesic, Outcome 7: Opioid use within 24 (± 12) hours of surgery

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Analgesic Mean	Analgesic SD	Analgesic Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bakr 2016	7	2.51	20	80	19.47	20	35.0%	-5.15 [-6.50 , -3.81]
Freedman 2006	34	22	50	110	34	50	36.2%	-2.63 [-3.17 , -2.09]
Wen 2015	26.8	1.8	18	80.7	4.8	20	28.8%	-14.26 [-17.71 , -10.82]
Total (95% CI)			**88**			**90**	**100.0%**	**-6.87 [-10.93 , -2.81]**

Heterogeneity: Tau² = 11.81; Chi² = 51.94, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.31 (P = 0.0009)
Test for subgroup differences: Not applicable



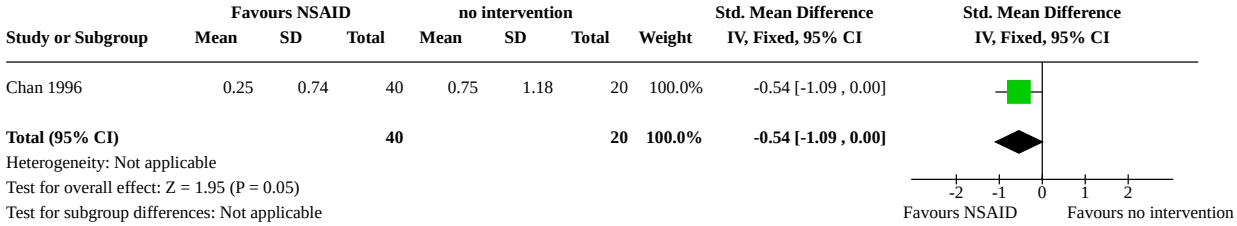
Analysis 2.8. Comparison 2: NSAID versus other analgesic, Outcome 8: Opioid use within 24 (± 12) hours of surgery by timing of drug administration



Comparison 3. NSAID versus no intervention

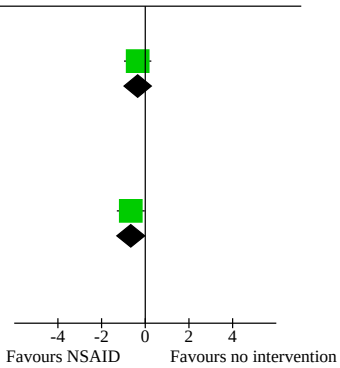
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pain intensity 24 (± 12) hours following surgery	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.09, 0.00]
3.2 Pain intensity 24 (± 12) hours following surgery by timing of drug administration	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2.1 Preoperative	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.97, 0.28]
3.2.2 Postoperative	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.30, -0.02]

Analysis 3.1. Comparison 3: NSAID versus no intervention, Outcome 1: Pain intensity 24 (± 12) hours following surgery



Analysis 3.2. Comparison 3: NSAID versus no intervention, Outcome 2: Pain intensity 24 (± 12) hours following surgery by timing of drug administration

Study or Subgroup	Favours NSAID Mean	SD	Total	no intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.2.1 Preoperative								
Chan 1996	0.375	0.92	20	0.75	1.18	20	100.0%	-0.35 [-0.97 , 0.28]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-0.35 [-0.97 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.09 (P = 0.28)								
3.2.2 Postoperative								
Chan 1996	0.125	0.56	20	0.75	1.18	20	100.0%	-0.66 [-1.30 , -0.02]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-0.66 [-1.30 , -0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.04 (P = 0.04)								



APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near cancer*
#3 breast near neoplasm*
#4 breast near carcinoma*
#5 breast near tumour*
#6 breast near tumor*
#7 breast near malignan*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Breast] explode all trees
#10 breast
#11 #9 or #10
#12 MeSH descriptor: [General Surgery] explode all trees
#13 MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#14 (Surger* or surgical*)
#15 (operation* or operative*)
#16 #12 or #13 or #14 or #15
#17 (#8 or #11) and #16
#18 MeSH descriptor: [Reconstructive Surgical Procedures] explode all trees
#19 MeSH descriptor: [Surgery, Plastic] explode all trees
#20 MeSH descriptor: [Surgical Oncology] explode all trees
#21 #18 or #19 or #20
#22 #11 and #21
#23 MeSH descriptor: [Breast Neoplasms] explode all trees and with qualifier(s): [surgery - SU]
#24 MeSH descriptor: [Mastectomy] explode all trees
#25 (breast near surger*)
#26 MeSH descriptor: [Breast Implants] this term only
#27 MeSH descriptor: [Breast Implantation] this term only
#28 MeSH descriptor: [Mammaplasty] explode all trees
#29 (breast near reconstruct*)
#30 #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 #17 or #22 or #30
#32 MeSH descriptor: [Analgesia] explode all trees
#33 MeSH descriptor: [Analgesics] explode all trees
#34 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#35 NSAID* or non steroidal anti-inflammator*
#36 MeSH descriptor: [Aspirin] explode all trees
#37 aspirin

#38 MeSH descriptor: [Salicylates] explode all trees
#39 MeSH descriptor: [Salicylic Acid] explode all trees
#40 diflusinal or salicylate* or salicylic acid
#41 MeSH descriptor: [Acetaminophen] explode all trees
#42 acetaminophen or paracetamol
#43 MeSH descriptor: [Dipyrone] explode all trees
#44 dipyrone or propyphenazone or Isopropylantipyrine
#45 MeSH descriptor: [Indomethacin] explode all trees
#46 indomethacin or arthrexin or indocid
#47 MeSH descriptor: [Diclofenac] explode all trees
#48 diclofenac or Clonac or Diclohexal or Fenac or Imflac or Viclofen or Voltaren or APO-diclofenac
#49 aceclofenac
#50 MeSH descriptor: [Etodolac] explode all trees
#51 MeSH descriptor: [Ketorolac] explode all trees
#52 MeSH descriptor: [Sulindac] explode all trees
#53 etodolac or ketorolac or ketoral or toradol or sulindac or aclin
#54 MeSH descriptor: [Ibuprofen] explode all trees
#55 ibuprofen or advil or Brufen or Bugesic or Dimotapp or iProfen or Nurofen or Panafen or ProVen or Rafen or Tri-Profen
#56 MeSH descriptor: [Naproxen] explode all trees
#57 naproxen or Aleve or Anaprox or Crysanal or Eazydayz or Inza or Naprosyn or Naprofem or Naprogesic or Proxen
#58 MeSH descriptor: [Fenoprofen] explode all trees
#59 MeSH descriptor: [Flurbiprofen] explode all trees
#60 fenoprofen or flurbiprofen
#61 MeSH descriptor: [Ketoprofen] explode all trees
#62 ketoprofen or Orudis or Oruvail
#63 MeSH descriptor: [Mefenamic Acid] explode all trees
#64 Mefenamic acid or ponstan
#65 MeSH descriptor: [Meclofenamic Acid] explode all trees
#66 Meclofenamic acid or meclofenamate or meclomen
#67 Meloxicam or Meloxibell or Mobic or Movalis or Moxicam#68 MeSH descriptor: [Piroxicam] explode all trees
#69 Piroxicam or Feldene or Feldene-D or Mobilis or Mobilis D
#70 nabumetone
#71 MeSH descriptor: [Celecoxib] explode all trees
#72 celecoxib or celebrex
#73 etoricoxib
#74 nabumetone or etoricoxib or arcoxia or parecoxib or dynastat or rofecoxib or vioxx
#75 MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees
#76 {OR #32-#75}
#77 #31 and #76

Appendix 2. MEDLINE

# ▲	Searches
1	exp Breast Neoplasms/
2	(breast adj6 cancer$).tw.
3	(breast adj6 neoplasm$).tw.
4	(breast adj6 carcinoma$).tw.
5	(breast adj6 tumo?r$).tw.
6	or/1-5
7	exp BREAST/

(Continued)

8	breast.tw.
9	or/7-8
10	exp General Surgery/
11	exp SURGICAL PROCEDURES, OPERATIVE/
12	(Surger* or surgical*).tw.
13	(operation* or operative*).tw.
14	or/10-13
15	(6 or 9) and 14
16	exp Reconstructive Surgical Procedures/
17	exp Surgery, Plastic/
18	exp Surgical Oncology/
19	or/16-18
20	9 and 19
21	exp Breast Neoplasms/su [Surgery]
22	exp Mastectomy/
23	(breast adj6 surger*).tw.
24	Breast Implants/ or Breast Implantation/
25	exp MAMMAPLASTY/
26	(breast adj6 reconstruct*).tw.
27	or/21-26
28	15 or 20 or 27
29	exp ANALGESIA/
30	exp ANALGESICS/
31	exp Anti-Inflammatory Agents, Non-Steroidal/
32	exp ASPIRIN/
33	(aspirin or NSAID* or non-steroidal anti-inflammator*).mp.
34	exp SALICYLATES/
35	exp Salicylic Acid/

(Continued)

36	(diflusinal or salicylate* or salicylic acid).mp.
37	exp ACETAMINOPHEN/
38	(acetaminophen or paracetamol).mp.
39	exp DIPYRONE/
40	(dipyrone or propyphenazone or Isopropylantipyrine).mp.
41	exp INDOMETHACIN/
42	(indomethacin or arthrexin or indocid).mp.
43	exp DICLOFENAC/
44	(diclofenac or Clonac or Diclohexal or Fenac or Imflac or Viclofen or Voltaren or APO-diclofenac).mp.
45	aceclofenac.mp.
46	exp ETODOLAC/
47	exp KETOROLAC/
48	exp SULINDAC/
49	(etodolac or ketorolac or ketoral or toradol or sulindac or aclin).mp.
50	exp IBUPROFEN/
51	(ibuprofen or advil or Brufen or Bugesic or Dimotapp or iProfen or Nurofen or Panafen or ProVen or Rafen or Tri-Profen).mp.
52	exp NAPROXEN/
53	(naproxen or Aleve or Anaprox or Crysanal or Eazydayz or Inza or Naprosyn or Naprofem or Naprogesic or Proxen).mp.
54	exp FENOPROFEN/
55	exp FLURBIPROFEN/
56	(fenoprofen or flurbiprofen).mp.
57	exp KETOPROFEN/
58	(ketoprofen or Orudis or Oruvail).mp.
59	exp Mefenamic Acid/
60	(Mefenamic acid or ponstan).mp.
61	exp Meclofenamic Acid/
62	(Meclofenamic acid or meclofenamate or meclomen).mp.

(Continued)

63	(Meloxicam or Meloxibell or Mobic or Movalis or Moxicam).mp.
64	exp PIROXICAM/
65	(Piroxicam or Feldene or Feldene-D or Mobilis or Mobilis D).mp.
66	nabumetone.mp.
67	exp CELECOXIB/
68	(celecoxib or celebrex).mp.
69	etoricoxib.mp.
70	(nabumetone or etoricoxib or arcoxia or parecoxib or dynastat or rofecoxib or vioxx).mp.
71	exp Cyclooxygenase Inhibitors/
72	or/29-71
73	28 and 72
74	animals/ not humans/
75	73 not 74
76	randomized controlled trial.pt.
77	controlled clinical trial.pt.
78	randomized.ab.
79	placebo.ab.
80	Clinical Trials as Topic/
81	randomly.ab.
82	trial.ti.
83	(crossover or cross-over).tw.
84	Pragmatic Clinical Trials as Topic/
85	pragmatic clinical trial.pt.
86	or/76-85
87	Case-Control Studies/
88	Control Groups/
89	Matched-Pair Analysis/
90	Retrospective Studies/

(Continued)

91	((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
92	or/87-91
93	Cohort Studies/
94	Longitudinal Studies/
95	Follow-Up Studies/
96	Prospective Studies/
97	Retrospective Studies/
98	cohort.ti,ab.
99	longitudinal.ti,ab.
100	prospective.ti,ab.
101	retrospective.ti,ab.
102	or/93-101
103	75 and 86
104	75 and 92
105	75 and 102
106	104 or 105

Appendix 3. Embase

#	**Searches**
1	exp breast/
2	exp breast disease/
3	(1 or 2) and exp neoplasm/
4	exp breast tumor/
5	exp breast cancer/
6	exp breast carcinoma/
7	(breast$ adj5 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).ti,ab.
8	or/3-7

(Continued)

9	breast.tw.
10	1 or 9
11	exp surgery/
12	exp surgical technique/
13	(Surger* or surgical*).tw.
14	(operation* or operative*).tw.
15	or/11-14
16	(8 or 10) and 15
17	exp reconstructive surgery/
18	exp plastic surgery/
19	exp surgical oncology/
20	exp cancer surgery/
21	or/17-20
22	10 and 21
23	exp breast tumor/su [Surgery]
24	exp breast cancer/su [Surgery]
25	exp mastectomy/
26	exp breast surgery/
27	exp breast implant/
28	exp breast augmentation/
29	exp breast reconstruction/
30	(breast adj6 reconstruct*).tw.
31	(breast adj6 surger*).tw.
32	or/23-31
33	16 or 22 or 32
34	exp analgesia/
35	exp analgesic agent/
36	exp nonsteroid antiinflammatory agent/

(Continued)

37	(NSAID* or non-steroidal anti-inflammator*).mp.
38	exp acetylsalicylic acid/
39	aspirin.mp.
40	exp salicylic acid/
41	(diflusinal or salicylate* or salicylic acid).mp.
42	exp paracetamol/
43	(acetaminophen or paracetamol).mp.
44	exp dipyrone/
45	exp propyphenazone/
46	exp indometacin/
47	(dipyrone or propyphenazone or Isopropylantipyrine or indomethacin or arthrexin or indocid).mp.
48	exp diclofenac/
49	(diclofenac or Clonac or Diclohexal or Fenac or Imflac or Viclofen or Voltaren or APO-diclofenac).mp.
50	exp aceclofenac/
51	exp etodolac/
52	exp ketorolac/
53	exp sulindac/
54	(etodolac or ketorolac or ketoral or toradol or sulindac or aclin).mp.
55	exp ibuprofen/
56	(ibuprofen or advil or Brufen or Bugesic or Dimotapp or iProfen or Nurofen or Panafen or ProVen or Rafen or Tri-Profen).mp.
57	exp naproxen/
58	(naproxen or Aleve or Anaprox or Crysanal or Eazydayz or Inza or Naprosyn or Naprofem or Naprogesic or Proxen).mp.
59	exp fenoprofen/
60	exp flurbiprofen/
61	(fenoprofen or flurbiprofen).mp.
62	exp ketoprofen/
63	(ketoprofen or Orudis or Oruvail).mp.

(Continued)

64	exp mefenamic acid/
65	(Mefenamic acid or ponstan).mp.
66	exp meclofenamic acid/
67	(Meclofenamic acid or meclofenamate or meclomen).mp.
68	exp meloxicam/
69	(Meloxicam or Meloxibell or Mobic or Movalis or Moxicam).mp.
70	exp piroxicam/
71	(Piroxicam or Feldene or Feldene-D or Mobilis or Mobilis D).mp.
72	exp nabumetone/
73	exp celecoxib/
74	(celecoxib or celebrex).mp.
75	exp etoricoxib/
76	(etoricoxib or arcoxia).mp.
77	exp parecoxib/
78	(parecoxib or dynastat).mp.
79	exp rofecoxib/
80	(rofecoxib or vioxx).mp.
81	exp prostaglandin synthase inhibitor/
82	Cyclooxygenase Inhibitor*.mp.
83	((COX-1 or COX-2) and inhibitor*).mp.
84	or/34-83
85	33 and 84
86	limit 85 to (human and (conference abstracts or embase))
87	Randomized controlled trial/
88	Controlled clinical study/
89	Random$.ti,ab.
90	randomization/
91	intermethod comparison/

(Continued)

92	placebo.ti,ab.
93	(compare or compared or comparison).ti.
94	(open adj label).ti,ab.
95	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
96	double blind procedure/
97	parallel group$1.ti,ab.
98	(crossover or cross over).ti,ab.
99	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
100	(assigned or allocated).ti,ab.
101	(controlled adj7 (study or design or trial)).ti,ab.
102	(volunteer or volunteers).ti,ab.
103	trial.ti.
104	or/87-103
105	exp case control study/
106	case control study.ti,ab.
107	((case control or case base or case matched or retrospective) adj1 (analys* or design* or evaulation* or research or stud* or survey* or trial*)).ti,ab.
108	or/105-107
109	exp retrospective study/
110	exp prospective study/
111	((cohort or concurrent or incidence or longitudinal or followup or 'follow up' or prospective or retrospective) adj1 (analys* or design* or evaluation* or research or stud* or survey* or trial*)).ti,ab.
112	or/109-111
113	86 and 104
114	86 and 108
115	86 and 112
116	114 or 115

Appendix 4. WHO ICTRP

Basic search:

1. non-steroidal anti-inflammatory AND breast cancer
2. non-steroidal anti-inflammatory AND breast surgery
3. NSAID and breast cancer
4. NSAID and breast surgery

Advanced search:

1. Condition: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention: non-steroidal anti-inflammatory drug

2. Condition: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention: aspirin OR salicylic acid OR diflunisal OR paracetamol OR acetaminophen

3. Condition: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention: dipyrone OR propyphenazone OR indomethacin OR diclofenac OR aceclofenac OR etodolac OR ketorolac

4. Condition: breast surgery or mastectomy or mammaplasty
Intervention: Sulindac

5. Condition: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention: ibuprofen OR naproxen OR fenoprofen OR flurbiprofen OR ketoprofen OR mefenamic acid OR meclofenamate

6. Condition: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention: meloxicam OR piroxicam OR nabumetone OR celecoxib OR etoricoxib OR parecoxib OR rofecoxib

Appendix 5. ClinicalTrials.gov

Basic search:

1. Condition or disease: breast cancer or breast surgery
Other terms: NSAID

2. Condition or disease: breast cancer or breast surgery
Other terms: non-steroidal anti-inflammatory

Advanced search:

1. Condition or disease: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention/treatment: NSAID
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

2. Condition or disease: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention/treatment: aspirin OR salicylic acid OR diflunisal OR paracetamol OR acetaminophen
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

3. Condition or disease: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention/treatment: dipyrone OR propyphenazone OR indomethacin OR diclofenac OR aceclofenac OR etodolac OR ketorolac
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

4. Condition or disease: breast cancer or breast surgery or mastectomy or mammaplasty
Intervention/treatment: Sulindac
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

5. Condition or disease: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention/treatment: ibuprofen OR naproxen OR fenoprofen OR flurbiprofen OR ketoprofen OR mefenamic acid OR meclofenamate
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

6. Condition or disease: breast cancer OR breast surgery or mastectomy or mammaplasty
Intervention/treatment: meloxicam OR piroxicam OR nabumetone OR celecoxib OR etoricoxib OR parecoxib OR rofecoxib
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

HISTORY

Protocol first published: Issue 3, 2019

CONTRIBUTIONS OF AUTHORS

1. Drafting the full text: KMK, AE, RP
2. Selecting studies: KMK, AE
3. Extracting data from studies: KMK, AE
4. Entering data into RevMan 5: KMK
5. Carrying out the analysis: KMK, AE
6. Interpreting the analysis: KMK, AE
7. Drafting the final review: KMK, AE
8. Resolving disagreements: GDR
9. Updating the review: KMK, AE, RP, CMC, MAM, GDR

DECLARATIONS OF INTEREST

KMK: none known.
AE: none known. AE has received funding from Health Research Board (Ireland) under the HRB Cochrane Ireland Fellowship Scheme to undertake a Cochrane Review (grant number CTF-2016-1863).
RP: none known.
CMC: none known. CC is a co-inventor of MileMarkerTM (a web-based assessment software that helps drive efficiencies in medical training), and the Operative Entrustability Assessment (OEA). She is the vice-president, an advisor, and an equity holder for EduMD LLC (a start-up company that designs and develops application software to improve medical training programs).
MAM: none known.
GDR: none related to this review topic. GDR has licensed IP to Aegeria Soft Tissue, LLC (Baltimore, MD). GDR's institution has received educational grants and/or grants for investigator-initiated studies pertaining to peripheral nerve surgery, microsurgical outcomes and/or breast reconstruction outcomes from TEI Bioschiences, LifeCell, Mentor, Sienta and AxoGen, and consulted on peripheral nerve surgery for AxoGen.

The co-authors acknowledge the following institutional support: the Johns Hopkins Department of Plastic Surgery receives/received research support from LifeCell Corp (Branchburg, NJ) and AxoGen Inc (Alachua, FL). The Johns Hopkins Department of Plastic Surgery receives/received educational support from LifeCell Corp (Branchburg, NJ), Mentor Corp (Santa Barbara, CA), Integra LifeSciences (Plainsboro, NJ) and Sientra (Santa Barbara, CA). Products sold by these companies may be discussed in generic or brand name format, as appropriate.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Paracetamol, acetaminophen, and dipyrone were not classified as a NSAID.
- The seven outcomes selected for the summary of findings table in the protocol changed; that is, 'breast hematoma' outcomes were covered by 'incidence of breast hematoma within 90 days of breast surgery (requiring reoperation, interventional drainage, or no treatment)', 'postoperative pain' was updated to 'pain intensity following surgery', and 'other side effects of NSAIDs' and 'opioid use' were added.
- Non-randomized studies were not included in our review due to available RCTs, so we did not extract data on the following: methods used to control for confounders, adjusted and unadjusted outcome measures, list of variables authors have included in analyses for adjusted estimates. Use of the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was not necessary to assess bias in non-randomized studies (Sterne 2016).
- Preoperative, intraoperative and postoperative NSAID use was assessed for all outcomes of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [adverse effects]; *Breast Neoplasms [surgery]; Ketorolac [therapeutic use]; Pain, Postoperative [drug therapy]; *Pharmaceutical Preparations

MeSH check words

Female; Humans