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Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain (Review)

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TABLE OF CONTENTS

[Intervention Review]

Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain

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ABSTRACT

Background

Despite multi-modal analgesic techniques, acute postoperative pain remains an unmet health need, with up to three quarters of people undergoing surgery reporting significant pain. Liposomal bupivacaine is an analgesic consisting of bupivacaine hydrochloride encapsulated within multiple, non-concentric lipid bi-layers offering a novel method of sustained-release analgesia.

Objectives

To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain.

Search methods

On 13 January 2016 we searched CENTRAL, MEDLINE, MEDLINE In-Process, Embase, ISI Web of Science and reference lists of retrieved articles. We obtained clinical trial reports and synopses of published and unpublished studies from Internet sources, and searched clinical trials databases for ongoing trials.

Selection criteria

Randomised, double-blind, placebo- or active-controlled clinical trials in people aged 18 years or over undergoing elective surgery, at any surgical site, were included if they compared liposomal bupivacaine infiltration at the surgical site with placebo or other type of analgesia.

Data collection and analysis

Two review authors independently considered trials for inclusion, assessed risk of bias, and extracted data. We performed data analysis using standard statistical techniques as described in the Cochrane Handbook for Systematic Reviews of Interventions, using Review Manager 5.3. We planned to perform a meta-analysis and produce a 'Summary of findings' table for each comparison however there were insufficient data to ensure a clinically meaningful answer. As such we have produced two 'Summary of findings' tables in a narrative format. Where possible we assessed the quality of evidence using GRADE.

Main results

We identified nine studies (10 reports, 1377 participants) that met inclusion criteria. Four Phase II dose-escalating/de-escalating trials, designed to evaluate and demonstrate efficacy and safety, presented pooled data that we could not use. Of the remaining five parallel-arm studies (965 participants), two were placebo controlled and three used bupivacaine hydrochloride local anaesthetic infiltration as a control. Using the Cochrane tool, we judged most studies to be at unclear risk of bias overall; however, two studies were at high risk of selective reporting bias and four studies were at high risk of bias due to size (fewer than 50 participants per treatment arm).

Three studies (551 participants) reported the primary outcome cumulative pain intensity over 72 hours following surgery. Compared to placebo, liposomal bupivacaine was associated with a lower cumulative pain score between the end of the operation (0 hours) and 72 hours (one study, very low quality). Compared to bupivacaine hydrochloride, two studies showed no difference for this outcome (very low quality evidence), however due to differences in the surgical population and surgical procedure (breast augmentation versus knee arthroplasty) we did not perform a meta-analysis.

No serious adverse events were reported to be associated with the use of liposomal bupivacaine and none of the five studies reported withdrawals due to drug-related adverse events (moderate quality evidence).

One study reported a lower mean pain score at 12 hours associated with liposomal bupivacaine compared to bupivacaine hydrochloride, but not at 24, 48 or 72 hours postoperatively (very low quality evidence).

Two studies (382 participants) reported a longer time to first postoperative opioid dose compared to placebo (low quality evidence).

Two studies (325 participants) reported the total postoperative opioid consumption over the first 72 hours: one study reported a lower cumulative opioid consumption for liposomal bupivacaine compared to placebo (very low quality evidence); one study reported no difference compared to bupivacaine hydrochloride (very low quality evidence).

Three studies (492 participants) reported the percentage of participants not requiring postoperative opioids over initial 72 hours following surgery. One of the two studies comparing liposomal bupivacaine to placebo demonstrated a higher number of participants receiving liposomal bupivacaine did not require postoperative opioids (very low quality evidence). The other two studies, one versus placebo and one versus bupivacaine hydrochloride, found no difference in opioid requirement (very low quality evidence). Due to significant heterogeneity between the studies (I^2 = 92%) we did not pool the results.

All the included studies reported adverse events within 30 days of surgery, with nausea, constipation and vomiting being the most common. Of the five parallel-arm studies, none performed or reported health economic assessments or patient-reported outcomes other than pain.

Using GRADE, the quality of evidence ranged from moderate to very low. The major limitation was the sparseness of data for outcomes of interest. In addition, a number of studies had a high risk of bias resulting in further downgrading.

Authors' conclusions

Liposomal bupivacaine at the surgical site does appear to reduce postoperative pain compared to placebo, however, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. There were no reported drug-related serious adverse events and no study withdrawals due to drug-related adverse events. Overall due to the low quality and volume of evidence our confidence in the effect estimate is limited and the true effect may be substantially different from our estimate.

PLAIN LANGUAGE SUMMARY

Liposomal bupivacaine at the site of surgery to treat pain

Bottom Line

Liposomal bupivacaine administered at the site of surgery appears to reduce postoperative pain when compared to placebo (salt water). At present there is limited evidence as to how effective it is compared to other painkillers, such as bupivacaine hydrochloride. Further large studies are required to see if there is a role for liposomal bupivacaine in this area.

Background

Despite painkillers, three in four people report pain following surgery. One method to treat pain is for the surgeon to inject a painkiller at the site of surgery to block the nerves that send pain signals to the brain. A new drug called liposomal bupivacaine has been developed which has been designed to release the painkiller over a much longer time and provide prolonged pain relief. This review has been designed to look at how good liposomal bupivacaine injected at the site of surgery is at treating pain and also to look at whether there are any risks associated with its use.

Study characteristics and key results

In January 2016, we found nine studies (10 reports) involving 1377 people that assessed liposomal bupivacaine following five different types of operation: total knee replacement; haemorrhoidectomy; inguinal hernia repair; bunionectomy and breast augmentation. The results suggested that compared to placebo (salt water) liposomal bupivacaine was better at reducing pain when injected at the site of surgery and also reduced both the overall requirement for, and duration before needing, additional, opiate-based (strong), painkillers. However, the limited evidence did not suggest that liposomal bupivacaine was better than the currently used painkiller bupivacaine hydrochloride. Overall across all the included studies no-one dropped out due to drug-related side effects.

Quality of the evidence

Due to the small number of studies and some limitations in the quality of these trials, we ranked the quality of evidence as moderate to very low. Further research is required to evaluate the role of liposomal bupivacaine infiltration at the surgical site to treat pain after surgery.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: liposomal bupivacaine vs placebo

Liposomal bupivacaine infiltration at the surgical site compared with placebo for the management of postoperative pain

Patient or population: aged 18 years and older undergoing elective surgery at any surgical site

Settings: inpatient

Intervention: surgical site infiltration of liposomal bupivacaine

Comparison: surgical site infiltration of placebo

Outcomes	Impact	Number of participants (number of studies)	Quality of the evidence (GRADE)
Cumulative pain score from the end of operation (0 hours) to 72 hours (NRS 0 to 10)	A reduction in cumulative pain score associated with the use of liposomal bupivacaine was reported in one study. The mean cumulative pain score from the end of operation to 72 hours (NRS 0 to 10) in the placebo control group was 202.5 points with the mean cumulative pain score from the end of operation to 72 hours in the liposomal bupivacaine intervention group being 60.7 points lower (90.4 lower to 31.1 lower).	189 participants (1 study)	⊕⊖⊖⊖ **very low[a]**
Serious adverse events	No reported drug-related serious adverse events, no study withdrawals due to drug-related adverse events	382 participants (2 studies)	⊕⊕⊖⊖ **low[b]**
Mean pain score at 12, 24, 48, 72 and 96 hours following surgery (NRS 0 to 10)	No data reported	No studies	
Time to first postoperative opioid dose over initial 72 hours	A longer time to first postoperative opioid dose associated with the use of liposomal bupivacaine was reported in two studies. In the placebo control group the time to first postoperative opioid was 4.3 and 1.2 hours compared to 7.2 and 14.3 hours in the liposomal bupivacaine groups respectively. The distribution of data was not reported.	382 participants (2 studies)	⊕⊕⊖⊖ **low[c]**
Total postoperative opioid consumption over first 72 hours	A reduction in total postoperative opioid consumption over first 72 hours associated with the use of liposomal bupivacaine was reported in one study. In the placebo control group the mean cumulative parenteral morphine equivalent dose over the first 72 hours was 29.1 mg and was 6.8 mg lower (12.8 mg lower to 0.9 mg lower) in the liposomal bupivacaine intervention group.	189 participants (1 study)	⊕⊖⊖⊖ **very low[d]**
Percentage of participants not requiring postoperative opioids over initial 72 hours	One study reported a higher proportion of participants not requiring postoperative opioids over initial 72 hours associated with the use of liposomal bupivacaine (RR 0.82; 95% CI 0.72 to 0.94), and one study found no difference (RR 0.99; 95% CI 0.95 to 1.03).	382 participants (2 studies)	⊕⊖⊖⊖ **very low[e]**

Incidence of adverse events within 30 days of surgery	The incidence of cardiac events and wound complications within 30 days of surgery were not reported in any study Adverse events within 30 days of surgery were reported in all studies with nausea, constipation and vomiting being the most common.	382 participants (2 studies)	⊕⊕⊖⊖ **low**[f]

CI: confidence interval; NRS: numeric rating scale; RR: risk ratio

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

[a]We downgraded the quality of this evidence due to the sparseness of data (-1), indirectness (-1) and risk of bias (-1) due to the unclear risk of bias due to the sample size (50-199).
[b]We downgraded the quality of this evidence one level due to the sparseness of data and a further level due the high risk of bias due to Golf 2011 being subject to a risk of performance bias as well as the unclear risk of bias due to the sample size (50-199) of the two studies.
[c]We downgraded the quality of this evidence one level due to the sparseness of data and a further level due to Golf 2011 being subject to a high risk of performance bias (as well as the unclear risk of bias due to the sample size (50-199) of the two studies). No meta-analysis was carried out because time to first postoperative opioid dose follows a skewed distribution and hence meta-analysis isn't recommended. Additionally there was expected heterogeneity due population characteristics (bunionectomy vs haemorrhoidectomy).
[d]We downgraded the quality of this evidence due to the sparseness of data (-1), indirectness (-1) and risk of bias (-1) due to the unclear risk of bias due to the sample size (50-199).
[e]We downgraded the quality of this evidence one level due to the to the sparseness of data, one level due to inconsistency, and a further level due to Golf 2011 being subject to a high risk of performance bias as well as the unclear risk of bias due to the sample size (50-199) of the two studies.
[f]We downgraded the quality of this evidence one level due to the sparseness of data and a further level due the high risk of bias due to Golf 2011 being subject to a risk of performance bias as well as the unclear risk of bias due to the sample size (50-199) of the two studies.

Summary of findings 2. Summary of findings: liposomal bupivacaine vs bupivacaine hydrochloride

Liposomal bupivacaine infiltration at the surgical site compared with bupivacaine hydrochloride for the management of postoperative pain

Patient or population: aged 18 years and older undergoing elective surgery at any surgical site

Settings: inpatient

Intervention: surgical site infiltration of liposomal bupivacaine

Comparison: surgical site infiltration of bupivacaine hydrochloride

Outcomes	Impact	Number of participants (number of studies)	Quality of the evidence (GRADE)
Cumulative pain score from the end of operation (0 hours) to 72 hours (NRS 0 to 10)	No difference in cumulative pain score was reported in two studies. In one study the mean cumulative pain score from the end of operation to 72 hours (NRS 0 to 10) in the active control group was 335.0 points and 24.0 points higher (5.7 lower to 53.7 higher) in the liposomal bupivacaine intervention group. In the oth-	379 participants (2 studies)	⊕⊖⊖⊖ **very low**[a]

	er study the mean cumulative pain score from the end of operation to 72 hours (NRS 0 to 10) in the active control group was 468.2 points and 26.7 points lower (91.3 lower to 37.9 higher) in the liposomal bupivacaine intervention group. Data were not pooled as differences in outcomes were expected due to differences in surgical interventions between studies.		
Serious adverse events	No reported drug-related serious adverse events, no study withdrawals due to drug-related adverse events	583 participants (3 studies)	⊕⊕⊕⊖ **moderate[b]**
Mean pain score at 12, 24, 48, 72 and 96 hours following surgery (NRS 0 to 10)	A reduction in mean pain score at 12 hours, but not 24, 48 or 72 hours, associated with the use of liposomal bupivacaine was reported in one study. Mean pain score at these time points were not reported in other studies. In the study that reported mean pain score (NRS 0 to 10) at 12 hours in the active control group it was 6.9 points and 1.3 points lower (2.4 lower to 0.2 lower) in the liposomal bupivacaine intervention group at this time point.	134 participants (1 study)	⊕⊖⊖⊖ **very low[c]**
Time to first postoperative opioid dose over initial 72 hours	No data reported	No studies	
Total postoperative opioid consumption over first 72 hours	No difference in cumulative parenteral morphine equivalent dose over first 72 hours was reported in one study though no estimate of variance was provided and as such estimates of effect could not be calculated.	134 participants (1 study)	⊕⊖⊖⊖ **very low[d]**
Percentage of participants not requiring postoperative opioids over initial 72 hours	No difference in the percentage of participants not requiring postoperative opioids over initial 72 hours was reported in one study (RR 0.95; 95% CI 0.86 to 1.05).	134 participants (1 study)	⊕⊖⊖⊖ **very low[e]**
Incidence of adverse events within 30 days of surgery	The incidence of cardiac events and wound complications within 30 days of surgery were not reported in any study Adverse events within 30 days of surgery were reported in all studies with nausea, constipation and vomiting being the most common.	583 participants (3 studies)	⊕⊕⊕⊖ **moderate[f]**

CI: confidence interval; NRS: numeric rating scale; RR: risk ratio

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

[a]We downgraded the quality of this evidence one level due to the sparseness of data, a further level because Smoot 2012 was subject to a high risk of bias due to the risk of performance bias and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)), and a further level due to inconsistency. We did not pool of results as we predicted that participant characteristics, as well as nature of postoperative pain, would be different following breast augmentation and knee replacement. As such we expected there to be heterogeneity of the results due to population characteristics, not due to intervention characteristics.

[b]We downgraded the quality of this evidence one level due the high risk of bias due to Smoot 2012 being subject to a risk of performance and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)).
[c]We downgraded the quality of this evidence one level due to the sparseness of data, and a further level because Smoot 2012 was subject to a high risk of bias due to the risk of performance bias and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)), and by a further level due to indirectness due to the limitations in interpreting data from a single study.
[d]We downgraded the quality of this evidence one level due to the sparseness of data, a further level because Smoot 2012 was subject to a high risk of bias due to the risk of performance bias and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)) and by a further level due to indirectness due to the limitations in interpreting data from a single study.
[e]We downgraded the quality of this evidence one level due to the sparseness of data, and a further level because Smoot 2012 was subject to a high risk of bias due to the risk of performance bias and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)), and by a further level due to indirectness due to the limitations in interpreting data from a single study.
[f]We downgraded the quality of this evidence one level due the high risk of bias due to Smoot 2012 being subject to a risk of performance and attrition bias due to early termination of the study (as well as the unclear risk of bias due to the sample size (50-199)).

BACKGROUND

Description of the condition

The treatment of acute postoperative pain remains an unmet health need. Despite the development of guidelines to assist clinicians and allied health professionals to recognise and treat the so-called 'fifth vital sign', it has been reported that up to three quarters of surgical patients receive inadequate pain relief (Apfelbaum 2003; Gan 2014; Lorentzen 2012; Nimmaanrat 2007). Optimising postoperative pain management, and reducing the requirement for systemic analgesia, in particular opiates, through the use of multi-modal analgesia has many benefits. These include patient benefits, such as reduced morbidity and mortality, as well as benefits to the healthcare system through enhanced patient satisfaction and reduced healthcare-associated costs including a reduced postoperative length of stay. Furthermore, there is increasing evidence that optimising perioperative and postoperative analgesia reduces the incidence of chronic post-surgical pain as well as enhancing long-term patient-reported functional outcomes (Kehlet 2006).

Description of the intervention

The concept of multi-modal analgesia was introduced over 20 years ago and its use has expanded to many surgical specialties (Kehlet 1993). Multi-modal analgesia employs a range of techniques all aiming to inhibit the multiple pathways of nociceptive stimuli along their path, from the site of surgical injury, passing through the peripheral nervous system to the central nervous system. Using paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, as well as local and regional anaesthetic techniques, the need for oral or parenteral opioids in the postoperative period, and as a consequence their side effects, is reduced. Local anaesthetic incisional infiltration, where local anaesthetic is infiltrated at the site of the surgical incision at the time of surgery, and local anaesthetic peripheral nerve blocks are commonly used as part of a multi-modal regime with the view that modification of pain stimuli at their origin will reduce the transmission of nociceptive stimuli, thereby reducing downstream organ dysfunction and pain and stress responses, including centrally mediated changes in the spinal cord or cerebral cortex (Kehlet 2006). The use of liposomal bupivacaine for peripheral nerve blockade will be the subject of a separate review (Hamilton 2016).

Local anaesthetic incisional infiltration is used in a wide range of operations. The local anaesthetic can be administered prior to wound incision as pre-emptive analgesia, during surgery, or immediately following wound closure. Bupivacaine hydrochloride is the most commonly used local anaesthetic for local infiltration, however its duration of action is a major limiting factor. Despite the addition of drugs such as epinephrine and clonidine to enhance the duration of action many people report significant rebound pain when the effect of the local anaesthetic wears off (Apfelbaum 2003). As such, there has been a great deal of interest in sustained-release local anaesthetics such as liposomal bupivacaine, which are administered in the same manner but have been reported to have an effect that lasts significantly longer than currently used drugs (Grant 2004).

The adverse effects of bupivacaine and liposomal bupivacaine administered at the surgical site are typical of those associated with other amide-type local anaesthetics. A major cause of adverse reactions to these drugs is high plasma levels, which may be due to overdosage, rapid absorption from the injection site, diminished tolerance, accidental intravascular injection or slow metabolic degradation. Side effects that require immediate treatment are related to neurological and cardiovascular toxicity, which can cause fits and cardiac arrest resistant to standard treatment. These reactions are generally dose-related and due to excessively high plasma levels. Other side effects include gastrointestinal symptoms (nausea, vomiting, constipation), nervous system side effects (peri-oral tingling, dizziness, headache, syncope, somnolence), skin side effects (pruritus), fungal infections and pyrexia. In addition, for liposomal bupivacaine the potential exists for local adverse effects due to the liposomal component, which is known to undergo slow lipid degradation and clearance at the injection site.

How the intervention might work

Liposomal bupivacaine consists of bupivacaine hydrochloride encapsulated within multiple, non-concentric lipid bi-layers. This encapsulation technique produces vesicles of a diameter of 10 to 20 micrometres that contain the active drug, which offers a novel method of sustained release (Spector 1996). Release of the active drug from these multi-vesicular liposomes is via three mechanisms, membrane breakdown, membrane reorganisation and diffusion (Mantripragada 2002). The relative importance of each mechanism is not known.

Following its release from the liposome vesicles, the active component bupivacaine hydrochloride, an amide local anaesthetic, binds to the intracellular portion of voltage-gated sodium channels thereby preventing depolarisation of the nerve cell and thus conduction of nociceptive stimuli. Bupivacaine hydrochloride is subsequently metabolised, primarily in the liver via a microsomal cytochrome P450 3A4 mediated pathway to pipecoloxylidide, with 5% undergoing renal excretion and around 15% being excreted unchanged (Gantenbein 2000). The multi-vesicular liposome component of liposome bupivacaine undergoes a slow process of lipid degradation and clearance; studies have demonstrated that a significant proportion of the liposome component is detectable at the injection site at periods exceeding 21 days following administration (Mantripragada 2002).

Why it is important to do this review

Regional anaesthetic techniques using local anaesthetics have an established role as part of a multi-modal technique across a wide range of surgical specialties. Currently their duration of action is a major limiting factor with patients reporting rebound pain. Liposomal bupivacaine is a new therapy utilising a novel mechanism to provide sustained release of local anaesthetic at the origin of pain, which has the potential to address this limitation. At present there are a limited number of trials evaluating liposomal bupivacaine for the management of postoperative pain. This independent review has been designed to critically appraise the current literature on liposomal bupivacaine administered at the surgical site in people aged 18 years and over undergoing elective surgery to evaluate its clinical and cost effectiveness in managing postoperative pain.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included prospective randomised and quasi-randomised controlled trials (including cluster-randomised trials) that compared liposomal bupivacaine infiltration against placebo or other types of analgesia. We included data from clinical trials registries and clinical trial records in the review. We included studies irrespective of publication status or language.

Types of participants

We included all trials with participants aged 18 years and older undergoing elective surgery at any surgical site, without restriction on any co-morbidities.

Types of interventions

We included all double-blind randomised controlled trials (RCTs) that compared the effects of a single dose of liposomal bupivacaine infiltrated at the surgical site against placebo or other types of analgesia delivered systemically, via local infiltration, perineural injection, or epidural or subarachnoid (spinal) routes. We considered studies reporting on pre-emptive, intraoperative and postoperative wound infiltration eligible for inclusion provided the drug was administered not earlier than 30 minutes prior to the procedure or later than 30 minutes after wound closure.

Types of outcome measures

We included patient-reported outcome measures of pain, use of supplementary opiate analgesia (incidence of supplementary analgesia, time to supplementary analgesia, mean and total opiate consumption, opiate or other analgesia-related adverse events) and measures of cost effectiveness. We included withdrawals from the trials and adverse events.

Primary outcomes

- Cumulative pain intensity assessed on a 100 mm visual analogue scale (VAS) over the initial 72 hours following surgery, at rest or with activity. However, we considered all types of pain scales with standardisation of pain intensity data described by other means than a 100 mm VAS, where possible.
- Serious adverse events, specifically incidence of cardiac events and incidence of wound complications within 30 days of surgery.

Secondary outcomes

- Mean pain score, at rest or with activity, assessed on a 100 mm VAS at 12, 24, 48, 72 and 96 hours following surgery. We considered all types of pain scales with standardisation of pain intensity data described by other means than a 100 mm VAS, where possible.
- Time to first postoperative opioid dose over initial 72 hours.
- Total postoperative opioid consumption over first 72 hours.
- Percentage of participants not requiring postoperative opioids over initial 72 hours.
- Health economics assessed using a recognised health economic technique.
- Incidence of adverse events within 30 days of surgery.
- Patient-reported outcomes, using validated outcome scores, at any time point following surgery.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- CENTRAL (in the Cochrane Library) Issue 1, 2016;
- MEDLINE (Ovid) 1946 to 13 January 2016;
- Embase (Ovid) 1974 to 13 January 2016;
- Web of Science (ISI Web of Knowledge) 1945 to 13 January 2016;

We used MeSH or equivalent and text word terms with no language restrictions. We tailored searches to individual databases. The search strategies used are shown in Appendix 1.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.isrctn.com/page/mrct) (4 January 2016), clinicaltrials.gov (www.clinicaltrials.gov) (4 January 2016) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) (4 January 2016) for ongoing trials. In addition, we searched reference lists of reviews and retrieved articles for additional studies and citation searches performed on key articles. We contacted study authors where necessary for additional information.

Data collection and analysis

Selection of studies

We assessed studies independently and in duplicate for eligibility (TWH, VA). In the first instance, we selected studies from the title and abstract. For those deemed relevant, we obtained the full text. Different pairs of authors (TWH, VA, LHS) assessed the full text according to the eligibility criteria. We resolved disagreement by consensus with input from the senior author (HP). We have presented a summary of the search strategy yield and study selection as a PRISMA flowchart (Liberati 2009). We retrieved the full texts of eligible studies and collated data where there were multiple publications of individual studies.

Data extraction and management

Two authors (TWH, VA) extracted data independently and in duplicate and recorded them onto a pre-tested, standardised, electronic data collection form. We resolved inconsistency in data collection by discussion with input of a third author (LHS). Where additional information was required we contacted the study authors and study sponsors.

Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that were randomised and double blind as a minimum.

Two authors (TWH, VA) also independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a) and adapted from those used by Cochrane Pregnancy and Childbirth, with any disagreements resolved by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We excluded studies that were not double blind.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved). Studies where outcome assessment was not blinded were excluded.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or used ‘baseline observation carried forward’ analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Selective outcome reporting. We compared outcomes of interest published in the protocol, clinical trials registry entry and methods section against those published in the study report. Where all outcomes of interest were reported then we considered these studies as at low risk of bias. Where there was incomplete outcome data reporting we considered these studies as at high risk of bias.
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at: low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

A lack of data prevented a quantitative assessment of the efficacy of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. For dichotomous data we planned to calculate the risk ratio (RR) and for continuous data the standardised mean difference (SMD), along with 95% confidence intervals (95% CI) (RevMan 2014). We planned, where possible, for efficacy outcomes, to calculate the numbers needed to treat for a beneficial outcome (NNTB) and harmful outcome (NNTH) for adverse events.

Unit of analysis issues

We assessed outcomes at the patient level and proposed to analyse studies involving multiple treatment arms by dividing the sample size of the control group into the appropriate number of groups depending on the number of arms of the trial.

Dealing with missing data

We contacted study authors and sponsors to request further information in the event of missing data. We did not attempt data imputation because of the controversies associated with imputing data from multiple scoring schemes, especially due to possible small sample sizes per scoring scale (Sterne 2009).

Assessment of heterogeneity

We examined the heterogeneity of included studies, where possible, using the I^2 statistic (Higgins 2003) as described in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). Where there was substantial heterogeneity (that is I^2 greater than 85%) we did not attempt pooled analysis. Had it been possible to perform meta-analysis, as we expected a degree of variability among the eligible studies in terms of the measurement scale used and the subjectivity of the outcome, we planned to use a random-effects model.

Assessment of reporting biases

We assessed for publication bias, due to non-reporting of negative studies, by contacting the principal investigators of unpublished trials registered as completed on trial registries. As there were fewer than 10 studies included we did not explore publication bias by means of a funnel plot.

Data synthesis

A lack of data prevented a quantitative assessment of the efficacy of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain and as such we did not perform meta-analysis. In future updates of this review, where outcome data are found to be of sufficient quality, and participants, interventions, comparisons and outcomes judged to be sufficiently similar to ensure an answer that is clinically meaningful, then we will perform a meta-analysis.

Quality of the Evidence

We planned to assess the quality of the evidence for each of the primary and secondary outcomes independently in duplicate

(TH, LS) using the GRADE system for all of the primary and secondary outcomes assessed. However, this was not possible for all outcomes due to the lack of data available.

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome.

The GRADE system uses the following criteria for assigning grade of evidence.

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

The grade is decreased if:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

Further information on the use of the GRADE System and GRADEprofiler Guideline Development Tool software can be found in Chapter 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions (GRADEPro GDT 2015; Schünemann 2011).

'Summary of findings' table

Due to the lack of data we have produced two 'Summary of findings' tables as a narrative to present the main findings in a transparent and simple tabular format. In future updates, we will update these depending on data availability.

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analysis due to lack of sufficient data. In future updates of this review we will carry out subgroup analysis for different doses (based on the licensed recommendations for dosage) of liposomal bupivacaine administered and different surgical sites. The indications for these subgroup analyses are that in basic science studies it has been demonstrated that a dose response curve is seen and, as such, the dose of liposomal bupivacaine may have an effect on outcome. Furthermore, different surgeries will have different pain profiles and, in addition, the release pattern of bupivacaine hydrochloride from liposomal bupivacaine may be altered by the local environment and therefore different efficacies may be observed at different surgical sites.

Sensitivity analysis

We planned to perform sensitivity analysis based on the following domains from the Cochrane tool for assessing risk of bias: blinding of outcome assessment and incomplete outcome data. Due to lack of sufficient data, we did not perform sensitivity analysis.

RESULTS

Description of studies

Results of the search

Using electronic searches we identified 179 possible studies for inclusion. We identified an additional 43 possible studies, 40 by searches of clinical trials registers and three by searching reference lists of included studies. After removal of duplicates, we screened the titles of 127 records and excluded 59 studies as these were irrelevant. We explored the full text of 68 studies. We excluded 21 studies (see Excluded studies) and identified 37 ongoing studies, leaving nine studies (10 reports) for inclusion in the review (see Characteristics of included studies). For a flowchart of the study selection process, please see Figure 1.

Figure 1. Study flow diagram

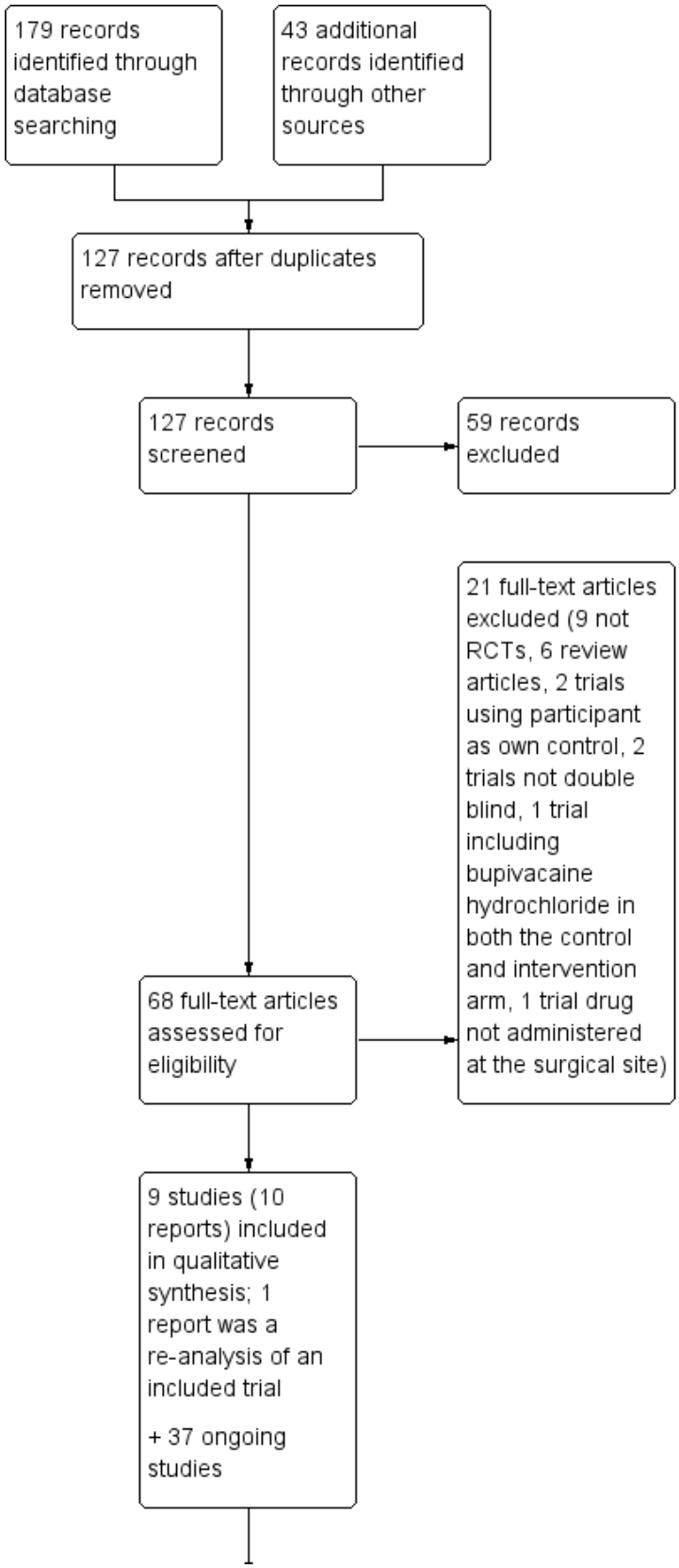
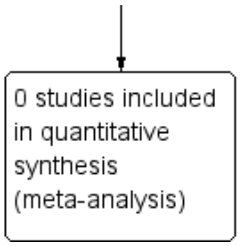


Figure 1. (Continued)



Included studies

We identified nine studies (10 reports) involving 1377 participants that met inclusion criteria, with 780 participants randomised to receive liposomal bupivacaine infiltration at the surgical site. All studies were conducted in the inpatient setting. In the control group, two studies used placebo (0.9% sodium chloride) at the surgical site (one haemorrhoidectomy Gorfine 2011 (results of this study also reported by Schmidt 2012 (secondary reference of Gorfine 2011)), one bunionectomy (Golf 2011)) and seven studies used bupivacaine hydrochloride at the surgical site (Bramlett 2012; Haas 2012; Langford 2008; NCT 00744848; NCT 00745290; Smoot 2012 (long-term follow-up of this study reported by Minkowitz 2012 (secondary reference of Smoot 2012); White 2009).

Studies were conducted across five surgical sites including:

- total knee replacement; two studies, 383 participants (Bramlett 2012; NCT 00745290);
- haemorrhoidectomy; three studies, 493 participants (Gorfine 2011; Haas 2012; NCT 00744848);
- inguinal hernia repair; two studies, 174 participants (Langford 2008; White 2009);
- bunionectomy; one study, 193 participants (Golf 2011);
- breast augmentation, one study, 134 participants (Smoot 2012).

The dose of liposomal bupivacaine in included studies ranged from 66 mg to 532 mg. The timing of administration of liposomal bupivacaine or control varied between studies. In one study it was administered in a staged fashion, starting after dissection (Bramlett 2012), in three studies it was administered intra-operatively but the timing was not specified (Golf 2011; NCT 00745290; White 2009) and in five studies it was administered at the end of surgery (Gorfine 2011; Haas 2012; Langford 2008; NCT 00744848; Smoot 2012). We identified five simultaneous parallel-arm studies (Golf 2011; Gorfine 2011; NCT 00744848; NCT 00745290; Smoot 2012) and four Phase II adaptive trials, where the dose was escalating/de-escalating (Bramlett 2012; Haas 2012; Langford 2008; White 2009). The adaptive trials randomised sequential cohorts of participants to control or intervention arms, with the dose of liposomal bupivacaine in the intervention arm increased or decreased conditional on the efficacy and safety of the previous cohort. We have discussed the results of the simultaneous parallel-arm and adaptive-design studies separately.

We have given details of randomisation schedule and interventions, together with details of all eligible studies, in the Characteristics of included studies tables. Outcomes of interest were not investigated in all studies or not reported (reporting bias), or reported in an idiosyncratic manner in adaptive trial designs. As such we were not able to include data from every study in all analyses.

Excluded studies

We excluded 21 studies as:

- nine were not RCTs;
- six were review papers;
- two trials, both assessing liposomal bupivacaine for bilateral breast augmentation, used the patient as own control preventing inclusion of these data;
- two trials were not appropriately blinded, with the outcome assessors or participants, or both, not blinded to treatment allocation;
- one trial did not assess liposomal bupivacaine at the surgical site;
- one included bupivacaine hydrochloride, at different doses, in both the control and intervention arm.

The study that included bupivacaine hydrochloride, at different doses in both the control and intervention arm, was an RCT evaluating the efficacy of liposomal bupivacaine at the surgical site for the management of pain following total knee replacement. This trial compared 266 mg liposomal bupivacaine mixed with 75 mg bupivacaine hydrochloride against an active control arm of 150 mg bupivacaine hydrochloride. At the time of writing the trial protocol it was not advised to mix liposomal bupivacaine with other drugs, in particular bupivacaine, due the risk of premature de-encapsulation of liposomal bupivacaine. As such we excluded this study from the analysis. However, it must be noted that in December 2015, an amendment to the FDA-licensed indication was made which approved admixing liposomal bupivacaine with bupivacaine, including co-administration in the same syringe, as it has been proposed that admixing with bupivacaine hydrochloride enhances early postoperative analgesia. Whilst excluded from this analysis, in future updates of this review we will include studies evaluating liposomal bupivacaine admixed with bupivacaine hydrochloride. We have given details of excluded studies in the Characteristics of excluded studies tables.

We also identified 37 ongoing studies, details of which are given in the Characteristics of ongoing studies tables.

Risk of bias in included studies

A summary of the risk of bias assessment using the Cochrane tool can be seen in Figure 2 and Figure 3.

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

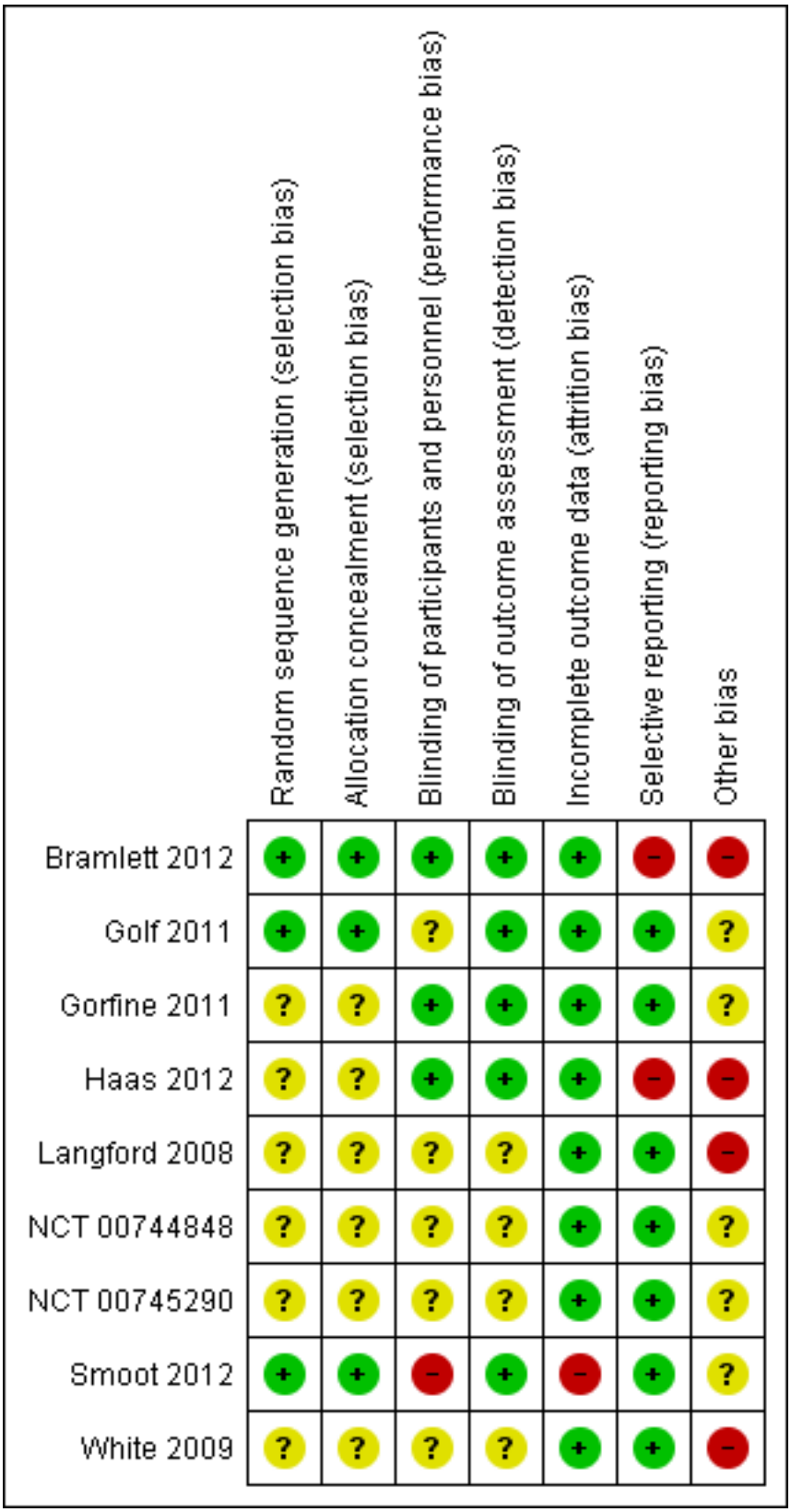
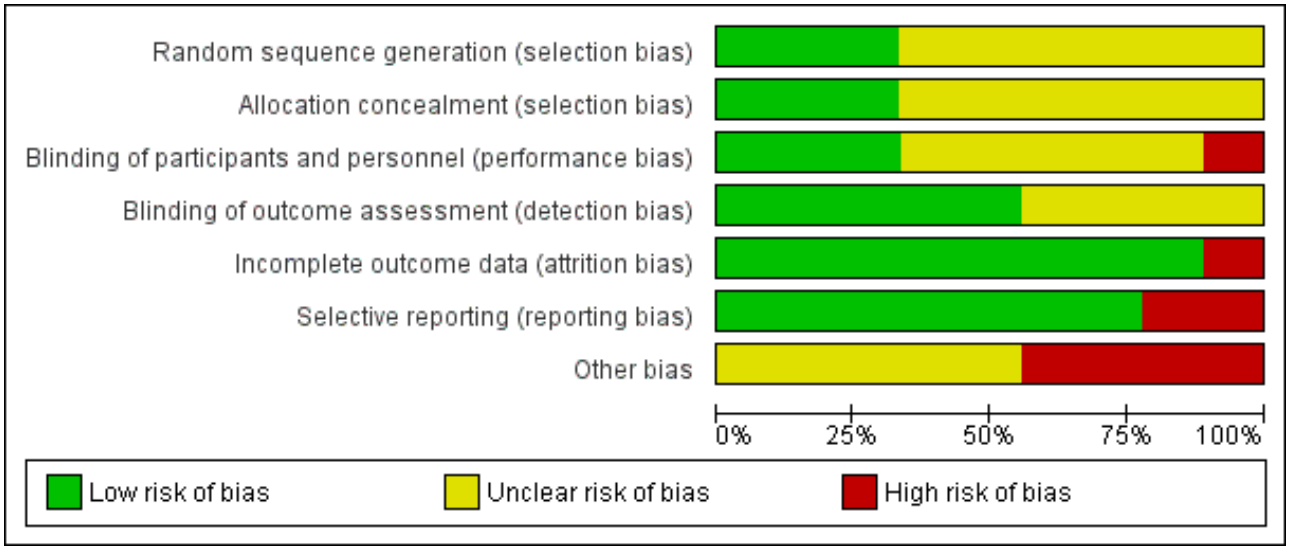


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



On the five-point Oxford Scale (Jadad 1996) addressing randomisation, blinding, and withdrawals, five studies scored three points (Langford 2008; NCT 00744848; NCT 00745290; Smoot 2012; White 2009), three studies scored four points (Golf 2011; Gorfine 2011; Haas 2012), and one study scored five points (Bramlett 2012), with studies scoring three or more points considered unlikely to be subject to major systematic bias (Khan 1996).

Allocation

Three studies clearly described the method of randomisation (computer-generated randomisation) and allocation concealment (central-allocation) and we assigned them a low risk of bias for selection bias (Bramlett 2012; Golf 2011; Smoot 2012).

Six studies (two conference abstracts (Langford 2008; White 2009), two clinical trials registry entries (NCT 00744848; NCT 00745290) and two complete manuscripts (Gorfine 2011; Haas 2012)), did not describe the method of random sequence generation or allocation concealment and as such presented an unclear risk of selection bias.

Blinding

Blinding of participants and personnel (performance bias)

Liposomal bupivacaine is cloudy and has a different visual appearance to both normal saline and bupivacaine hydrochloride. Furthermore liposomal bupivacaine is more viscous than both normal saline and bupivacaine hydrochloride. As such there is a risk of performance bias by the surgeon who administers drug at the time of surgery. To reduce the risk of performance bias the injection technique was standardised in three trials (Bramlett 2012; Gorfine 2011; Haas 2012) and we regarded these as presenting a low risk of performance bias.

Five studies (two conference abstracts (Langford 2008; White 2009), two clinical trials registry entries (NCT 00744848; NCT 00745290) and one manuscript (Golf 2011), did not state whether the injection technique was standardised, presenting an unclear risk of performance bias.

One study (Smoot 2012), left the injection technique at the discretion of the operating surgeon, presenting a high risk of performance bias. Both the participant and outcome assessor remained blinded and as such we considered this study double-blind and included it in this review.

Blinding of outcome assessment (detection bias)

Five studies blinded participants and staff involved in assessment of outcome measures to the treatment allocation (Bramlett 2012; Golf 2011; Gorfine 2011; Haas 2012; Smoot 2012), presenting a low risk of detection bias.

Four studies (two conference abstracts (Langford 2008; White 2009) and two clinical trials registry entries (NCT 00744848; NCT 00745290), did not state whether the participants and staff were blinded, presenting an unclear risk of detection bias.

Incomplete outcome data

We assessed one study as having a high risk of attrition bias (Smoot 2012), as it was terminated early by the study sponsor for "administrative reasons". We assessed all other studies as having a low risk of attrition bias with greater than 95% follow-up of randomised participants.

Selective reporting

We assessed seven of the nine studies as having a low risk of reporting bias. As each included study investigated a number of outcome measures, often at multiple time points, outcome measures were commonly reported as being non-significant without other measures of variance being reported. We assessed two studies as having a high risk of reporting bias (Bramlett 2012; Haas 2012), as cumulative pain scores other than that of the primary endpoint were not reported.

Other potential sources of bias

As the majority of trials were drug development trials, that is, Phase II and Phase III, the sample size of the treatment and control groups was small. We considered four of the included trials at

high risk of bias due to having fewer than 50 participants per treatment arm (Bramlett 2012; Haas 2012; Langford 2008; White 2009), with the remainder considered at unclear risk of bias due to sample sizes of between 50 and 199 participants per treatment arm (Golf 2011; Gorfine 2011; NCT 00744848; NCT 00745290; Smoot 2012). All studies were commissioned, funded or published by Pacira Pharmaceuticals Incorporated, manufacturer of liposomal bupivacaine, presenting an unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: liposomal bupivacaine vs placebo; **Summary of findings 2** Summary of findings: liposomal bupivacaine vs bupivacaine hydrochloride

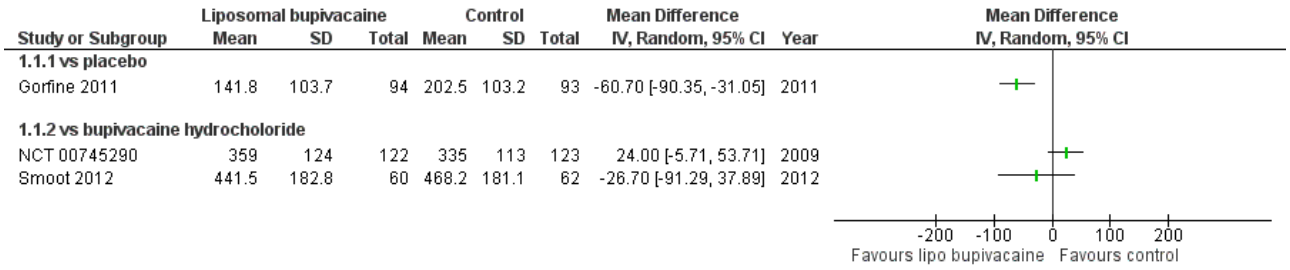
Results of simultaneous parallel-arm studies

The five simultaneous parallel-arm studies reported the following outcomes (Golf 2011; Gorfine 2011; NCT 00744848; NCT 00745290; Smoot 2012).

Cumulative pain intensity over 72 hours following surgery

- Three studies with 551 participants assessed cumulative pain intensity over 72 hours following surgery (Gorfine 2011; NCT 00745290; Smoot 2012). One study assessing liposomal bupivacaine 266 mg in participants undergoing excisional haemorrhoidectomy, was placebo controlled (Gorfine 2011), and two studies using liposomal bupivacaine 532 mg, in total knee replacement and breast augmentation respectively, used bupivacaine hydrochloride 200 mg as a control (NCT 00745290; Smoot 2012). They recorded pain scores on an 11-point Numeric Rating Scale (NRS; 0 to 10) with cumulative pain intensity over 72 hours calculated using a windowed worst observation carried forward, plus last observation carried forward method in two studies (Gorfine 2011; Smoot 2012) (Appendix 2). One study did not specify the method of calculation (NCT 00745290).
- We have reported the results of these studies in Analysis 1.1 (Figure 4).
- One placebo-controlled study demonstrated a significant reduction in cumulative pain score over 72 hours associated with the use of liposomal bupivacaine (Gorfine 2011). Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, a further level due to indirectness and concerns about the generalisability of limited data presented to the population undergoing elective surgery, and one level due to the unclear risk of bias presented by the sample size of the included study (Summary of findings for the main comparison). Overall we judged the evidence to be of very low quality, meaning that we have very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.
- The two studies that used bupivacaine hydrochloride as a control did not demonstrate a difference in cumulative pain scores from 0 to 72 hours associated with the use of liposomal bupivacaine (NCT 00745290; Smoot 2012). Whilst both studies did not demonstrate a difference in cumulative pain score, we decided not to pool the data as we predicted that participant characteristics, as well as the nature of postoperative pain, would be different following breast augmentation and knee replacement, and as such a pooled analysis would not be appropriate. Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, a further level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study (as well as an unclear risk of bias due to the sample size), and by a further level due to indirectness and concerns about the generalisability of limited data presented to the population undergoing elective surgery (Summary of findings 2). Overall we judged the evidence to be of very low quality, meaning that we have very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.

Figure 4. Forest plot of comparison: 1 Liposomal bupivacaine vs control, outcome: 1.1 Cumulative pain score 0 to 72 hours



Serious adverse events

- There were no serious adverse events reported to be associated with the use of liposomal bupivacaine and none of the five studies (Golf 2011; Gorfine 2011; NCT 00744848; NCT 00745290; Smoot 2012), 964 participants, reported withdrawals due to drug-related adverse events.
- Compared to placebo, 2 studies, 382 participants, using GRADE, we downgraded the quality of this evidence one level due sparseness of the data and one level due to Golf 2011 being subject to a high risk of performance bias and both studies presenting an unclear risk of bias due to their sample size (50-199). Overall we judged the evidence to be of low quality, meaning our confidence in the effect estimate is limited and that the true effect may be substantially different from the estimate of the effect.
- Compared to bupivacaine hydrochloride, 3 studies, 583 participants, using GRADE, we downgraded the quality of this evidence one level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study. Overall we judged the evidence to be of moderate quality, meaning we were moderately confident in the effect

estimate and that the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Mean pain score at 12, 24, 48, 72 and 96 hours following surgery

- The mean pain score using an 11-point NRS (0 to 10) at 12, 24, 48 and 72 hours following breast augmentation surgery was reported by Smoot 2012, 136 participants, who found a significantly lower pain score at 12 hours in those participants receiving liposomal bupivacaine 532 mg compared to bupivacaine hydrochloride 200 mg (P = 0.014; Figure 5) with no difference in mean pain score (mean NRS not reported) found at 24, 48 or 72 hours.
- The other simultaneous parallel-arm studies did not report mean pain score at 12, 24, 48, 72 or 96 hours following surgery.
- Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data; a further level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study; and by a further level due to indirectness and the limitations in interpreting data from a single study. Overall we judged the evidence to be of very low quality, meaning we had very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.

Figure 5. Table of results for included simultaneous parallel-arm trials

				Cumulative pain score	Mean Pain Score					Time to first opioid	Cumulative opioid use	Patients not requiring post-operative opioids 0-72h
				0 to 72 hours	12 hours	24 hours	48 hours	72 hours	96 hours	0 to 96 hours	0 to 72 hours	
				Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Median (Range) hours	Mean (SD) mg	n (%)
Study	Arm	Intervention	Participants									
5.1 Liposomal bupivacaine *vs* placebo												
Golf 2011	I_1	LB 106mg	97							7.2 (NR)		2 (2%)
	C	NaCl 0.9%	96							4.3 (NR)		1 (1%)
Gorfine 2011	I_1	LB 266mg	95	141.8 (104.3)						14.3	22.3 (21.0)	24 (26%)
	C	NaCl 0.9%	94	202.5 (103.7)						1.2	29.1 (20.7)	9 (10%)
5.2 Liposomal bupivacaine *vs* Bupivacaine hydrochloride												
NCT 00744848	I_1	LB 266mg	101									
	C	BHCl 100mg	103									
NCT 00745290	I_1	LB 532mg	122	359 (124)								
	C	BHCl 200mg	123	335 (113)								
Smoot 2012	I_1	LB 532mg	66	441.5 (163)	5.6 (3.2)						13.5 (NR)	6 (10%)
	C	BHCl 200mg	70	468.2 (181)	6.9 (3.1)						20.4 (NR)	3 (5%)

LB = Liposomal bupivacaine; BHCl = Bupivacaine hydrochloride; FNB = Femoral Nerve Block; RHCl = Ropivacaine hydrochloride; NR = Not reported; pain score at rest reported by Gorphine 2011 and with activity NCT 00745290 and Smoot 2012; = not reported

Time to first postoperative opioid dose over initial 72 hours

- Two studies, 382 participants, reported the median time to first opioid dose following bunionectomy and haemorrhoidectomy respectively with both studies finding the time to first postoperative opioid dose to be significantly longer (P < 0.0001) in those participants receiving liposomal bupivacaine (106 mg and 266 mg respectively) compared to placebo (Golf 2011; Gorfine 2011). We did not pool the data as they were not normally distributed and in addition participant characteristics, as well as the nature of postoperative pain, would be different

following bunionectomy and haemorrhoidectomy; as such, a pooled analysis would not be appropriate.
- The other simultaneous parallel-arm studies did not report time to first postoperative opioid dose.
- Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data and a further level due to Golf 2011 being subject to a high risk of performance bias. Overall we judged the evidence to be of low quality, meaning that our confidence in the effect estimate was limited and the true effect may be substantially different from our estimate of effect.

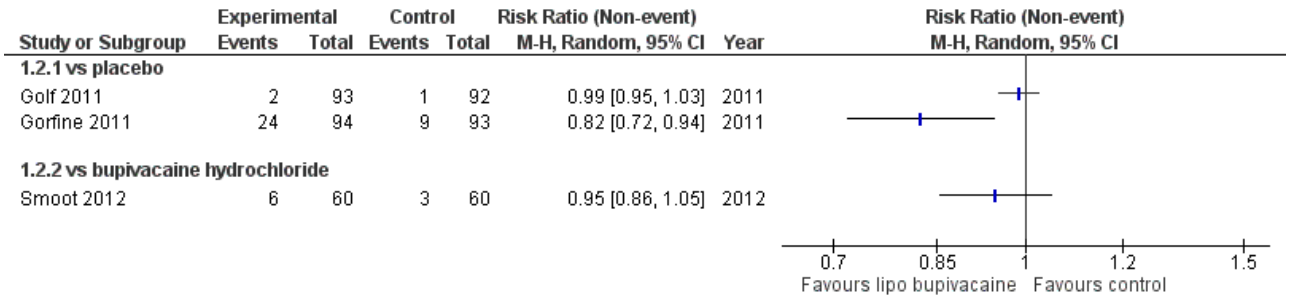
Total postoperative opioid consumption over first 72 hours

- Two studies with 325 participants reported the total postoperative opioid consumption over the first 72 hours (Gorfine 2011; Smoot 2012).
- One study compared liposomal bupivacaine 266 mg with placebo (Gorfine 2011) in participants undergoing haemorrhoidectomy and reported a reduction in cumulative parenteral morphine equivalent dose of 6.8 mg (95% CI (-12.8 mg to -0.9 mg) for the liposomal bupivacaine arm. Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, a further level due to indirectness due to the limitations in interpreting data from a single study, and a further level due to the unclear risk of bias due the sample size of the included study (50-199). Overall we judged the evidence to be of very low quality, meaning we had very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.
- One trial compared liposomal bupivacaine 532 mg with bupivacaine hydrochloride 200 mg (Smoot 2012) in participants undergoing breast augmentation and found no difference in cumulative parenteral morphine equivalent dose (Figure 5). Using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, a further level due to indirectness due to the limitations in interpreting data from a single study and a further level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study. Overall we judged the evidence to be of very low quality, meaning we had very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.

Percentage of participants not requiring postoperative opioids over initial 72 hours

- Three studies with 492 participants reported the percentage of participants not requiring postoperative opioids over initial 72 hours following surgery (Golf 2011; Gorfine 2011; Smoot 2012). Two studies were placebo controlled (Gorfine 2011; Golf 2011), and one study used bupivacaine hydrochloride as a control (Smoot 2012). One of the two studies comparing liposomal bupivacaine with placebo demonstrated a higher number of participants receiving liposomal bupivacaine did not require postoperative opioids. The other two studies, one versus placebo, one versus bupivacaine hydrochloride, found no difference in opioid requirement. Due to significant heterogeneity between the studies ($I^2 = 92\%$) we have not shown the pooled result (Figure 6). Possible reasons for heterogeneity could be due to differences in pain response after different surgical procedures or differences in pain response between patient groups undergoing specific surgeries.
- Compared to placebo, 2 studies, 382 participants, using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, one level due to inconsistency of data, and a further level due to Golf 2011 being subject to a high risk of performance bias and unclear risk of bias due to the sample size (50-199). Overall we judged the evidence to be of very low quality, meaning we had very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.
- Compared to bupivacaine hydrochloride, 1 study, 134 participants, using GRADE, we downgraded the quality of this evidence one level due to the sparseness of data, a further level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study and by a further level due to indirectness and the limitations in interpreting data from a single study. Overall we judged the evidence to be of very low quality, meaning we had very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.

Figure 6. Forest plot of comparison: 1 Liposomal bupivacaine vs control, outcome: 1.2 Participants not requiring postoperative opioids



Health economics assessment

- None of the included studies presented a health economic assessment.

Incidence of adverse events within 30 days of surgery

- None of the included studies reported the incidence of cardiac events and wound complications within 30 days of surgery.

- All the included studies reported adverse events within 30 days of surgery, with nausea, constipation and vomiting being the most common.
- Nausea was reported in 38% of participants receiving placebo (Golf 2011), 31% to 58% of those receiving bupivacaine hydrochloride (NCT 00744848; NCT 00745290; Smoot 2012) and 44% to 62% of those participants receiving liposomal bupivacaine (Golf 2011; NCT 00744848; NCT 00745290; Smoot 2012).
- Constipation was reported in between 9% and 38% of participants receiving bupivacaine hydrochloride (NCT 00744848; NCT 00745290; Smoot 2012) and between 16% and 46% of participants receiving liposomal bupivacaine (NCT 00744848; NCT 00745290; Smoot 2012).
- Vomiting was reported in 18% of participants receiving placebo (Golf 2011), 20% to 34% of those receiving bupivacaine hydrochloride (NCT 00745290; Smoot 2012) and 15% to 31% of participants receiving liposomal bupivacaine (Golf 2011; NCT 00745290; Smoot 2012).
- We decided not to pool the data as we predicted that participant characteristics, as well as the nature of adverse events, would be different following different surgical procedures and, as such, a pooled analysis would not be appropriate.
- Compared to placebo, 2 studies, 382 participants, using GRADE, we downgraded the quality of this evidence one level due sparseness of the data and one level due to Golf 2011 being subject to a high risk of performance bias and both studies presenting an unclear risk of bias due to their sample size (50-199). Overall we judged the evidence to be of low quality, meaning our confidence in the effect estimate is limited and that the true effect may be substantially different from the estimate of the effect.
- Compared to bupivacaine hydrochloride, 3 studies, 583 participants, using GRADE, we downgraded the quality of this evidence one level due to Smoot 2012 being subject to a high risk of performance bias and attrition bias due to early termination of the study. Overall we judged the evidence to be of moderate quality, meaning we were moderately confident in the effect estimate and that the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Patient-reported outcomes

- None of the included studies reported patient-reported outcomes (outside of pain), using validated outcome scores, at any time point following surgery.

Results of adaptive-design trials

We identified four dose-escalating/de-escalating studies (Bramlett 2012; Haas 2012; Langford 2008; White 2009). Dose-escalating/de-escalating studies are designed to evaluate efficacy and safety. An illustrative example of a typical adaptive-design trial is shown in Figure 7. In the four Phase II adaptive-design studies (Bramlett 2012; Haas 2012; Langford 2008; White 2009), the results from the control groups of all dose-escalating steps in the randomisation process were reported collectively as a single population. Data from adaptive-design trials cannot be included in meta-analysis for a number of reasons: a) the decision to escalate or de-escalate a dose is conditional on the failure of the previous dose on either the efficacy, or safety, or cost-effectiveness of the intervention, introducing bias in any pooled analysis, and b) the randomisation ratio is altered with each escalation/de-escalation while the control group population is typically reported cumulatively for all dose levels. We therefore have decided to report the information from these studies as a narrative and we have included it in Figure 8. In hindsight, due to the role of adaptive-design trials in identifying an efficient and safe dose for further exploration of the intervention in larger scale trials, and the limitations imposed in including such data in meta-analyses, we may consider excluding trials of this design from the definition in Types of studies in future updates of this review.

Figure 7. Illustrative example of an adaptive-design trial. The decision to escalate, or de-escalate a dose is conditional on the failure of the previous dose on the efficacy, or safety, or cost-effectiveness of the intervention, introducing bias in any pooled analysis. The randomisation ratio is altered with each escalation/de-escalation while the control group population is typically reported cumulatively for all dose levels

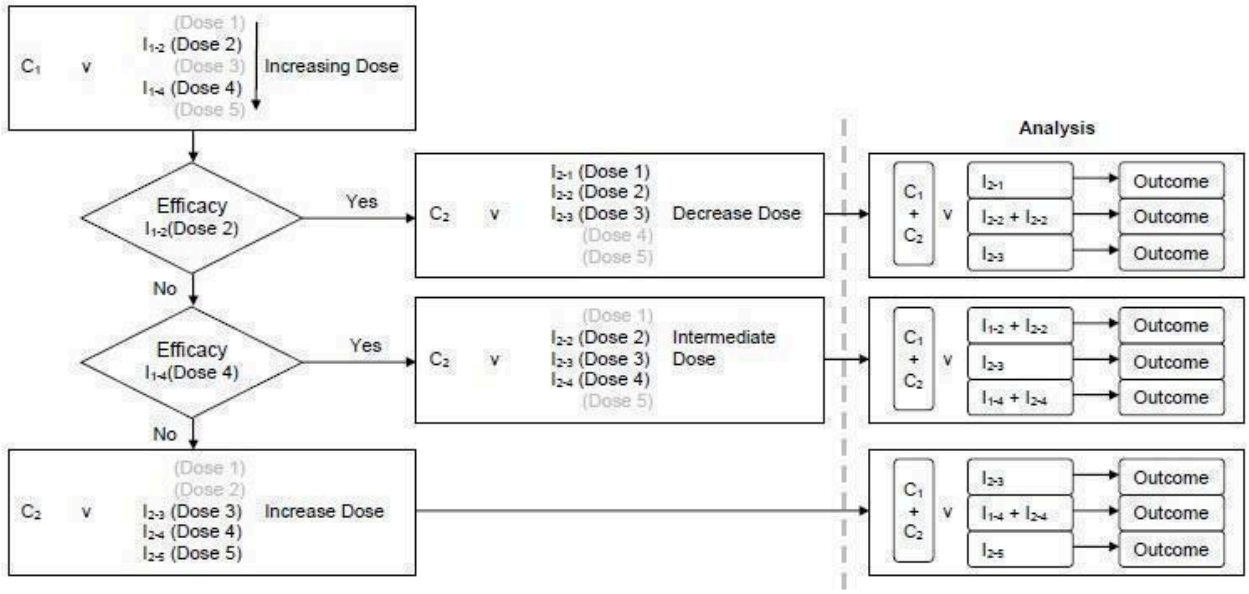


Figure 8. Table of results for adaptive-design trials

				Cumulative pain score	Mean Pain Score					Time to first opioid	Cumulative opioid use	Patients not requiring post-operative opioids
				0 to 72 hours	12 hours	24 hours	48 hours	72 hours	96 hours	0 to 96 hours	0 to 72 hours	
				Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Median (Range) hours	Mean (SD) mg	n (%)
Study	Arm	Intervention	Participants									
Bramlett 2012	I_1	LB 133mg	27	9.3 (NR)		3.8 (2.2)	5.2 (2.1)	3.9 (2.8)	3.4 (2.9)			
	I_2	LB 266mg	25	8.1 (NR)		3.1 (2.4)	4.7 (2.3)	3.4 (2.4)	2.9 (2.4)			
	I_3	LB 399mg	26	7.9 (NR)		3.6 (2.1)	4.1 (2.2)	3.4 (2.1)	3.0 (2.0)			
	I_4	LB 532mg	25	6.5 (NR)		2.4 (2.4)	4.2 (2.1)	2.9 (2.3)	1.9 (2.3)			
	C	BHCl 150mg	35	9.2 (NR)		4.3 (3.3)	4.8 (2.4)	3.8 (2.3)	3.0 (2.7)			
Haas 2012	I_1	LB 66mg	24	224 (162)						9 (0.1 to 96.0)	44 (NR)	
	I_2	LB 199mg	25	171 (175)						11 (0.2 to 96.0)	21 (NR)	
	I_3	LB 399mg	24	176 (175)						19 (0.1 to 96.0)	12 (NR)	
	C	BHCl 75mg	26	331 (178)						8 (0.3 to 96.0)	29 (NR)	
Langford 2008	I_1	LB 175mg	12		26.4 (21.2)	27.2 (23.5)	33.4 (30.2)	23.8 (20.2)	15.5 (15.5)		5.5 (NR)	10 (83.3)
	I_2	LB 225mg	12		21.4 (19.2)	29.8 (18.6)	31.6 (27.5)	24.1 (23.6)	14.4 (16.3)		1.1 (NR)	9 (75)
	I_3	LB 300mg	12		22.0 (17.0)	20.8 (18.6)	28.5 (24.6)	16.8 (14.8)	16.1 (18.5)		13.4 (NR)	9 (75)
	I_4	LB 350mg	14		24.6 (19.0)	29.9 (24.2)	27.5 (24.9)	21.7 (23.1)	15.1 (20.0)		11.1 (NR)	10 (71.4)
	C	BHCl 100mg	26		48.0 (18.0)	48.7 (20.1)	39.4 (20.8)	35.7 (22.5)	24.0 (20.1)		15.4 (NR)	13 (50)
White 2009	I_1	LB 93mg	25	286.9 (146.4)								
	I_2	LB 160mg	24	274.6 (115.4)								
	I_3	LB 306mg	25	274.4 (253.4)								
	C	BHCl 105mg	24	298.1 (136.6)								

LB = Liposomal bupivacaine; BHCl = Bupivacaine hydrochloride; NR = Not reported; pain score at rest reported by Bramlett 2012 and Haas 2012 and with activity Langford 2008 and White 2009; = not reported

DISCUSSION

Summary of main results

We identified nine studies that met inclusion criteria for this review. Four Phase II dose-escalating/de-escalating studies (Bramlett 2012; Haas 2012; Langford 2008; White 2009), designed to evaluate and demonstrate efficacy and safety, presented pooled data which could not be used in this analysis. Of the remaining five studies two were placebo controlled (Golf 2011; Gorfine 2011) and three used bupivacaine hydrochloride as a control (NCT 00744848; NCT 00745290; Smoot 2012).

Compared to placebo one study (Gorfine 2011) reported a lower cumulative pain score 0 to 72 hours after surgery, two studies reported a longer time to first postoperative opioid (Golf 2011;

Gorfine 2011), and one study reported a lower cumulative opioid consumption 0 to 72 hours after surgery associated with the used of liposomal bupivacaine (Gorfine 2011). Compared to bupivacaine hydrochloride two studies found no difference in the cumulative pain score 0 to 72 hours after surgery associated with the use of liposomal bupivacaine (NCT 00745290; Smoot 2012), and one study reported a lower mean pain score at 12 hours, but not at 24, 48 or 72 hours postoperatively (Smoot 2012). Three studies reported the number of participants not requiring postoperative opioids (Golf 2011; Gorfine 2011; Smoot 2012), however significant heterogeneity (I^2 = 92%) was observed, limiting further analysis. Data comparing liposomal bupivacaine with femoral nerve block were not available for inclusion in the analysis.

Of the five parallel-arm studies which did not have an adaptive design assessing liposomal bupivacaine against either placebo or bupivacaine hydrochloride, no studies reported health economic assessments or patient-reported outcomes other than pain (Golf 2011; Gorfine 2011; NCT 00744848; NCT 00745290; Smoot 2012). Nausea, constipation and vomiting were the most commonly reported adverse events. Data regarding cardiac events and wound complications were not reported. No withdrawals were reported to be due to drug-related adverse events.

Using GRADE we considered the quality of evidence to be very low to moderate with further research considered very likely to have an important impact on our confidence in the estimate of effect. This assessment of quality was predominantly due to sparseness of data as well as a high risk of bias in some of the included studies.

Liposomal bupivacaine does appear to have efficacy in reducing postoperative pain compared to placebo when infiltrated at the surgical site, but, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. Due to the low quality and volume of evidence our confidence in the effect estimate is limited and the true effect may be substantially different from our estimate.

Overall completeness and applicability of evidence

The main limitations of this review are the small number of studies, incomplete outcome data reporting and significant heterogeneity observed between studies. The use of adaptive-design dose-escalating/de-escalating Phase II studies is necessary to evaluate and demonstrate efficacy and safety of a novel drug, however, when the decision to escalate/de-escalate is conducted in a conditional manner this can lead to the introduction of bias as well as leading to imbalance in the randomisation ratio (where the control group is reported cumulatively). This review found four of the nine included studies to be of an adaptive design, and we decided to exclude these from the analysis. Assessing the five remaining studies, these were conducted across four surgical sites (bunionectomy, haemorrhoidectomy, knee replacement and breast augmentation) with differences in pain profiles, as well as differences in the way that people report pain at these surgical sites being a possible explanation for the heterogeneity seen in this review.

Quality of the evidence

The quality of evidence ranged from moderate to very low across the different outcomes. The major limitation in quality was the sparseness of data for the outcomes of interest. In addition, we assessed a number of included studies as at high risk of bias resulting in further downgrading of the quality assessment. As such our confidence in the effect estimate was limited and the true effect may be substantially different from our estimates of effect.

Potential biases in the review process

Liposomal bupivacaine is a relatively new drug and has been recently licensed. As such many studies investigating its efficacy and safety are currently underway. Our review identified 37 ongoing studies (See Characteristics of ongoing studies) which will report over the next few years. Whilst every effort has been made to minimise bias in this review, new evidence will continue to emerge in this field that may impact on the conclusions drawn. Methods used to minimise the possibility of bias in this review included the use of a comprehensive broad search strategy based on previous Cochrane Reviews for RCTs in postoperative pain, such that we could identify all relevant studies. Additionally, we searched reference lists of potentially relevant studies and reviews, and searched trials registries.

Agreements and disagreements with other studies or reviews

The results of this meta-analysis disagree with previous meta-analyses performed by Bergese 2012a and Dasta 2012 which reported the use of liposomal bupivacaine to be associated with lower cumulative pain scores between 0 and 72 hours after the end of the operation, longer time to first opioid and lower cumulative postoperative opioid usage between 0 and 72 hours postoperatively compared to bupivacaine hydrochloride control. There are several reasons for the disagreement seen between ours and the previous meta-analyses. Firstly, previous meta-analyses included the results of adaptive-design studies, which, as discussed, we do not believe is valid. Secondly, previous meta-analyses pooled data from a range of different surgical procedures in which patient demographics and postoperative pain profiles would be expected to be different; and finally both previous meta-analyses were performed in collaboration with Pacira Pharmaceuticals Inc. who manufacture the drug and funded the drug development studies, and as such had privileged access to the complete set of data for each of the studies.

AUTHORS' CONCLUSIONS

Implications for practice

General Implications

Liposomal bupivacaine does appear to have efficacy in reducing postoperative pain compared to placebo when infiltrated at the surgical site, however, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. We assessed the quality of the evidence as moderate to very low and as such our confidence in the effect estimate is limited and the true effect may be substantially different from our estimates.

For people with postoperative pain

The current data do not support or refute the use of liposomal bupivacaine infiltration at the surgical site to reduce postoperative pain.

For clinicians

Further evidence as the clinical and cost effectiveness of liposomal bupivacaine infiltration at the surgical site is required as, due to the quality of evidence, the current data do not support or refute the use of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain.

For policymakers

The current data do not permit firm estimates of effect size due to the low quantity and quality. As such the current data do not support or refute the use of liposomal bupivacaine infiltration at the surgical site to reduce postoperative pain. Further evidence of clinical, as well as cost-effectiveness, is required.

For funders of the intervention

Currently the limited evidence does not demonstrate superiority to bupivacaine hydrochloride, however due to the quality of the evidence our confidence in the effect estimate is limited and the true effect may be substantially different from our estimates. The current data do not support or refute the use of liposomal bupivacaine infiltration at the surgical site to reduce postoperative pain and further evidence of clinical, as well as cost-effectiveness, is required.

Implications for research

General implications

Good quality, large, active comparator randomised controlled studies are required to establish the clinical and cost effectiveness of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. Studies should be conducted across a range of surgical sites with the results stratified and interpreted by site. Studies should be focused on surgeries that are known to be associated with significant postoperative pain, particularly surgeries where improved pain control may deliver significant clinical benefits through reduced morbidity, or cost-effectiveness benefits through faster rehabilitation and discharge (i.e. total knee replacement).

Design

Future studies should be parallel-arm, active comparator randomised controlled trials with broad inclusion criteria, such that results are applicable to the general population. Studies should be well designed and adequately powered, involving more than 200 participants per arm, to reduce the risk of bias.

Measurement (end points)

This review focuses on the management of postoperative pain however it is important to note that recovery following surgery is multi-factorial, with patients highly valuing the absence of nausea and sedation as well the ability to mobilise and perform self-care, as well as other factors. A gold standard outcome measure for postoperative recovery following surgery has yet to be established however it is prudent that in addition to the clinical outcome measures of pain scores and opioid usage, future studies should also evaluate patient-reported functional outcome measures, which are likely to be surgery-specific, as these outcome measures will provide further information about the effectiveness of any intervention from the patient perspective.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bramlett 2012

Methods	Phase II dose-ranging randomised controlled study, participant and assessor blinded. 5 parallel groups. Participants enrolled into 3 consecutive cohorts based on efficacy and safety results of previous cohort. • Cohort 1: randomised 1:1:1 to control (Arm 1) or liposomal bupivacaine 133 mg (Arm 2) or liposomal bupivacaine 266 mg (Arm 3) • Cohort 2: randomised 2:2:2:5 to control (Arm 1) or liposomal bupivacaine 133 mg (Arm 2) or liposomal bupivacaine 266 mg (Arm 3) or (Arm 4) liposomal bupivacaine 399 mg • Cohort 3: randomised 2:5 to control (Arm 1) or liposomal bupivacaine 532 mg (Arm 5) Liposomal bupivacaine or control administered in a staged fashion starting after dissection but before prostheses insertion with the final injections administered before wound closure
Participants	People undergoing primary unilateral total knee replacement under general anaesthesia (n = 138) Age 18-75 years ASA 1-3 Location: 10 centres (USA and Czech Republic) Dates: October 2007-November 2008
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration using a standardised technique Control: • Arm 1: bupivacaine hydrochloride 150 mg with epinephrine 1:200,000 (n = 35) Intervention: • Arm 2: liposomal bupivacaine 133 mg (n = 27) • Arm 3: liposomal bupivacaine 266 mg (n = 25) • Arm 4: liposomal bupivacaine 399 mg (n = 26)

Bramlett 2012 *(Continued)*

	• Arm 5: liposomal bupivacaine 532 mg (n = 25)
Outcomes	Primary outcome • Cumulative pain score (AUC) with activity (maximum active knee flexion) 0-96 h Secondary outcomes • Cumulative pain score (AUC) with rest and activity 0 to: 24, 48, 72, 96 and 120 h • Mean pain score (NRS 0 to 10) at: 24, 48, 72, 96 and 120 h • Total rescue opioid consumption (mg) 24, 48, 72, 96 and 120 h • Cumulative opioid consumption (mg) 48, 72, 96 and 120 h • Blinded care providers' satisfaction with postoperative analgesia (day 8) • Time to resumption of work or daily activities • Adverse events (vital signs, wound healing, scarring, electrocardiogram results) day 0 to day 36 • Drug pharmacokinetics
Notes	Clinical Trials reference: NCT 00485693

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated via computer randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation separate to trial sites
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded. Personnel preparing and administering the study drug and control (who were not involved in post-operative assessments) were not blinded but the injection technique was specified to decrease the risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff performing post operative assessment were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate, 6 of 138 participants did not complete the study
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes of interest as stated in study methods
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - funding provided by Pacira Pharmaceuticals as well as 2 authors were employees or consultants for Pacira

Golf 2011

Methods	Phase III RCT, participant and assessor blinded. 2 parallel groups. Liposomal bupivacaine or control administered intra-operatively (timing not specified)

Golf 2011 *(Continued)*

Participants	People undergoing primary first metatarsal bunionectomy under midazolam and/or propofol sedation followed by a Mayo block (n = 193) Age 18 years and older Location: 1 centre (USA) Dates: April 2000-August 2009
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration. The infiltration technique was not specified Control: • Arm 1: sodium chloride 0.9% (n = 96) Intervention: • Arm 2: liposomal bupivacaine 106 mg (n = 97)
Outcomes	Primary outcome • Cumulative pain score (AUC) at rest 0-24 h Secondary outcomes • Cumulative pain score (AUC) at rest 0 to: 36, 48, 60 and 72 h • Pain score (NRS 0-10) at: 2, 4, 8, 12, 24, 36, 48, 60 and 72 h • Total rescue opioid consumption (mg) 0 to 72 h • Cumulative opioid consumption (mg) 0 to: 24, 36, 48, 60 and 72 h • Time to first rescue opioid • Proportion of participants pain free (NRS ≤ 1) at: 2, 4, 8, 12, 24, 36, 48, 60 and 72 h • Patient satisfaction with postoperative analgesia 24 and 72 h + 8 • Adverse events (vital signs, wound healing) day 0-day 30
Notes	Clinical Trials reference: NCT 00890682

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated via computer randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation separate to trial sites
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not stated whether the surgeon was blinded and no standard injection technique was specified presenting a risk of performance bias. As such we considered this study to have an unclear risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff performing post operative assessment were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data exist for all randomised participants

Golf 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	All stated outcomes of interest reported
Other bias	Unclear risk	Unclear risk of bias - sample size 50-199 participants/arm Funding provided by Pacira Pharmaceuticals as well as author was employee of Pacira

Gorfine 2011

Methods	Phase III RCT, participant and assessor blinded. 2 parallel groups. Liposomal bupivacaine or control administered at the end of surgery
Participants	People undergoing excisional haemorrhoidectomy (Miller-Morgan technique) under general anaesthesia (n = 189) Age 18 years and older ASA 1-3 Location: 13 centres (Republic of Georgia, Poland and Serbia) Dates: May 2009-August 2009
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration using a standardised technique Control: • Arm 1: sodium chloride 0.9% (n = 94) Intervention: • Arm 2: liposomal bupivacaine 266 mg (n = 95)
Outcomes	Primary outcome • Cumulative pain score (AUC) 0-72 h Secondary outcomes • Cumulative opioid consumption (mg) 12, 24, 36, 48, 60 and 72 h • Time to first rescue opioid • Proportion of participants not requiring rescue opioid 0 to: 12, 24, 36, 48, 60 and 72 h • Brief Pain Inventory (BPI) Assessment 24 and 72 h and 30 d • Blinded care providers satisfaction with wound healing (day 30) • Patient satisfaction with postoperative analgesia 24 and 72 h + 8 • Adverse events (vital signs, clinical and laboratory assessments) day 0-day 30
Notes	Clinical Trials reference: NCT 00890721 Trial also reported by Schmidt 2012 (Secondary reference of Gorfine 2011)

Risk of bias

Bias	Authors' judgement	Support for judgement

Gorfine 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded as were personnel involved in administering the study drug and control. Furthermore, the injection technique was specified to decrease the risk of performance bias due to the risk of unbinding due to differences in appearance and viscosity of the trial drug with the control.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and the study team performing post-operative assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate, 3 of 189 participants did not complete the study
Selective reporting (reporting bias)	Low risk	All stated outcomes of interest reported
Other bias	Unclear risk	Unclear risk of bias - sample size 50-199 participants/arm Funded by Pacira Pharmaceuticals

Haas 2012

Methods	Phase II dose-ranging RCT, participant and assessor blinded. 4 parallel groups Participants enrolled into 2 consecutive cohorts based on efficacy and safety results of previous cohort: • Cohort 1: randomised 1:1:1 to control (Arm 1) or liposomal bupivacaine 66 mg (Arm 2) or liposomal bupivacaine 199 mg (Arm 3) • Cohort 2: randomised 1:1:1:2.5 to control (Arm 1) or liposomal bupivacaine 66 mg (Arm 2) or liposomal bupivacaine 199 mg (Arm 3) or liposomal bupivacaine 266 mg (Arm 4) Liposomal bupivacaine or control administered at the end of surgery
Participants	People undergoing 2 or 3 column excisional haemorrhoidectomy (incision length > 3 cm) under general anaesthesia (n = 100) Age 18 years and older ASA 1-3 Location: 9 centres (USA and Republic of Georgia) Dates: July 2007-January 2008
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration using a standardised technique Control: • Arm 1: bupivacaine hydrochloride 75 mg with epinephrine 1:200,000 (n = 26) Intervention:

Haas 2012 *(Continued)*

- Arm 2: liposomal bupivacaine 66 mg (n = 24)
- Arm 3: liposomal bupivacaine 199 mg (n = 25)
- Arm 4: liposomal bupivacaine 266 mg (n = 25)

Outcomes	Outcomes • Cumulative pain score (AUC) 0 to: 12, 24, 36, 48, 60, 72, 84 and 96 h • Pain score (NRS) with bowel movement 0-96 h • Time to first bowel movement • Cumulative opioid consumption (mg) 0 to: 72 and 96 h • Time to first rescue opioid through 96 h • Proportion of participants not requiring rescue opioids • Blinded care providers' satisfaction with analgesia through 96 h • Quality of Life (EuroQol, EQ-5D) • Time to resumption of work or daily activities through day 30 • Readiness for discharge using the modified Postanesthesia Discharge Scoring System • Adverse events day 0-day 30
Notes	Clinical Trials reference: NCT 00529126

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To reduce the risk of performance bias, drugs were dispensed by sheathed syringe by study members not involved with postoperative assessment. Furthermore the injection technique specified to further reduce the risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All staff members involved in study related evaluation remained blinded throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate, 97 of 100 of participants completed the study
Selective reporting (reporting bias)	High risk	Incomplete reporting of: all time point NRS, discharge readiness and EQ5D
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - support in preparation of the manuscript was provided by Peloton Advantage, supported by Pacira Pharmaceuticals

Langford 2008

Methods	Phase II dose-ranging parallel group RCT, participant and assessor blinded

Langford 2008 *(Continued)*

	Participants enrolled into 4 consecutive cohorts based on efficacy and safety results of previous cohort • Cohort 1: randomised 1:1 to control (Arm 1) or liposomal bupivacaine 155 mg (Arm 2) • Cohort 2: randomised 1:3 to control (Arm 1) or liposomal bupivacaine 199 mg (Arm 3) • Cohort 3: randomised 1:3 to control (Arm 1) or liposomal bupivacaine 266 mg (Arm 4) • Cohort 4: randomised 1:3 to control (Arm 1) or liposomal bupivacaine 310 mg (Arm 5) Liposomal bupivacaine or control administered at the end of surgery before wound closure
Participants	People undergoing unilateral inguinal hernia repair (tension-free technique) under general anaesthesia (n = 76) Age 18 years and older ASA 1-2 Location: not specified Dates: December 2004-December 2006
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration. The infiltration technique was not specified Control: • Arm 1: bupivacaine hydrochloride 100 mg with epinephrine 1:200,000 (n = 26) Intervention: • Arm 2: liposomal bupivacaine 155 mg (n = 12) • Arm 3: liposomal bupivacaine 199 mg (n = 12) • Arm 4: liposomal bupivacaine 266 mg (n = 12) • Arm 5: liposomal bupivacaine 310 mg (n = 14)
Outcomes	Primary outcome • Time to use of supplemental rescue medication (opioid or non-opioid) through 96 h Secondary outcomes • Mean pain score (NRS 0-10) at rest and with activity (undefined): 4, 8, 12, 24, 48, 72 and 96 h • Cumulative opioid consumption (mg) through 96 h • Proportion of participants requiring supplemental rescue medication (opioid or non-opioid) through 96 h • Patient satisfaction with postoperative analgesia through 96 h • Adverse events (serious AEs, wound healing, application site reaction, clinical laboratory values, electrocardiogram results) day 0-day 36 • Drug pharmacokinetics
Notes	Clinical Trials reference: NCT 01203644

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified

Langford 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is stated that the participant was blinded to treatment, however it is not specified whether the surgeon administering the treatment was blinded presenting an unclear risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated that the participant and the outcome assessor were blinded to treatment, however it is not clear whether other staff involved in the participants care were blinded presenting an unclear risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Low risk	All outcomes specified reported
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - funding received from Pacira Pharaceuticals

NCT 00744848

Methods	Phase III RCT, participant and assessor blinded. 2 parallel groups. Liposomal bupivacaine or control administered at the end of surgery
Participants	People undergoing 2 or 3 column excisional haemorrhoidectomy under general anaesthesia (n = 204) Age 18 years and older ASA 1-4 Location: 20 centres (SA) Dates: August 2008-February 2009
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration using a standardised technique Control: • Arm 1: bupivacaine hydrochloride 100 mg with epinephrine 1:200,000 (n = 103) Intervention: • Arm 2: liposomal bupivacaine 266 mg (n = 101)
Outcomes	Primary outcome • Cumulative pain score (AUC) at rest 0-96 h Secondary outcomes • Adverse events through 96 h • Serious adverse events through 30 d
Notes	Clinical Trials reference: NCT 00744848

NCT 00744848 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not stated whether the surgeon was blinded or whether a standard injection technique was specified. As such we considered this study to have an unclear risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated that the participant and the outcome assessor were blinded to treatment, however it is not clear whether other staff involved in the participants care were blinded presenting an unclear risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Low risk	All outcomes specified on clinical trials registry reported
Other bias	Unclear risk	Unclear risk of bias - sample size 50-199 participants/arm Funded by Pacira Pharmaceuticals

NCT 00745290

Methods	Phase III RCT, participant and assessor blinded. 2 parallel groups. Liposomal bupivacaine or control administered intra-operatively (timing not specified)
Participants	People undergoing primary unilateral total knee replacement under general anaesthesia (n = 245) Age 18 years and older ASA 1-4 Location: 19 centres (USA) Dates: August 2008-January 2009
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration. The infiltration technique was not specified Control • Arm 1: bupivacaine hydrochloride 200 mg with (n = 123) Intervention • Arm 2: liposomal bupivacaine 532 mg (n = 122)
Outcomes	Primary outcome

NCT 00745290 *(Continued)*

	• Cumulative pain score (AUC) with activity (maximum active knee flexion) 0-72 h Secondary outcomes • Adverse events through 96 h • Serious adverse events through 30 d
Notes	Clinical Trials reference: NCT 00745290

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is stated that the participant was blinded to treatment, however it is not specified whether the surgeon administering the treatment was blinded presenting an unclear risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated that the participant and the outcome assessor were blinded to treatment, however it is not clear whether other staff involved in the participants' care were blinded presenting an unclear risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Low risk	All outcomes specified on clinical trials registry reported
Other bias	Unclear risk	Unclear risk of bias - sample size 50-199 participants/arm Funded by Pacira Pharmaceuticals

Smoot 2012

Methods	Phase III RCT, participant and assessor blinded. 2 parallel groups. Liposomal bupivacaine or control administered at the end of surgery
Participants	Women undergoing primary bilateral cosmetic submuscular breast augmentation under general anaesthesia (n = 134) Age 18 years and older ASA 1-4 Location: 11 centres (USA) Dates: November 2008-February 2009
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration. The infiltration technique was not specified

Smoot 2012 *(Continued)*

	Control • Arm 1: bupivacaine hydrochloride 200 mg (100 mg per breast pocket) with epinephrine 1:200,000 (n = 70) Intervention • Arm 2: liposomal bupivacaine 532 mg (266 mg per breast pocket) (n = 64)
Outcomes	Primary outcome • Cumulative pain score (AUC) with activity (raising both hands above the head and holding for 5 s) 0-72 h Secondary outcomes • Cumulative pain score (AUC) with rest and activity 0 to: 24, 48, 72 and 96 h • Pain score (NRS 0-10) at: 4, 8, 12, 24, 36, 48, 72 and 96 h • Cumulative opioid consumption (mg) through 96 h • Proportion of participants receiving no rescue opioid medication • Patient satisfaction with postoperative analgesia through 72 h • Time to first bowel movement • Brief Pain Inventory (BPI) Assessment 24, 48, 72 and 96 h • Integrated Rank Assessment (incorporating pain score and concurrent opioid use) • Blinded care providers' satisfaction with postoperative analgesia (day 8) • Time to resumption of work or daily activities • Adverse events (nausea and vomiting, vital signs, wound healing, wound scarring) day 8 and day 30
Notes	Clinical Trials reference: NCT 00813111 Long-term follow-up reported by Minkowitz 2012 (Secondary reference of Smoot 2012)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated via computer randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation separate to trial sites
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff and participants were blinded to treatment. However there was a high risk of performance bias with respect to the injection technique as no standard injection technique was specified with injections administered "by the surgeon's preferred technique" presenting a high risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff performing outcome assessments blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Trial terminated by study sponsor due to "administrative reasons"
Selective reporting (reporting bias)	Low risk	All outcomes specified reported
Other bias	Unclear risk	Unclear risk of bias - sample size 50-199 participants/arm

Smoot 2012 *(Continued)*

	Funding received from Pacira Pharmaceuticals

White 2009

Methods	Phase II dose-ranging RCT, participant and assessor blinded. 4 parallel groups Timing of liposomal bupivacaine or control administration not specified
Participants	People undergoing primary open inguinal hernia repair under general anaesthesia (n = 98) Age 18 years and over ASA 1-3 Location: 7 centres (USA) Dates: June 2007-August 2008
Interventions	A single dose of the control or intervention drug was administered at the time of operation via wound infiltration. The infiltration technique was not specified. Control • Arm 1: bupivacaine hydrochloride 105 mg (n = 24) Intervention • Arm 2: liposomal bupivacaine 93 mg (n = 25) • Arm 3: liposomal bupivacaine 160 mg (n = 24) • Arm 4: liposomal bupivacaine 306 mg (n = 25)
Outcomes	Primary outcome • Cumulative pain score (AUC) with activity (sitting from supine) 0-72 h Secondary outcomes • Adverse events through 96 h • Serious adverse events through 30 d
Notes	Clinical Trials reference: NCT 00485433 This conference abstract also reported the outcomes of the study reported by Langford 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is stated that the participant was blinded to treatment, however it is not specified whether the surgeon administering the treatment was blinded presenting an unclear risk of performance bias.

White 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated that the participant and the outcome assessor were blinded to treatment, however it is not clear whether other staff involved in the participants' care were blinded presenting an unclear risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Low risk	All outcomes specified on clinical trials registry reported
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - 2 authors were linked to Pacira Pharmaceutical

AE – Adverse Events
ASA – American Society of Anaesthesiologists Score
AUC – Area Under Curve
BPI – Brief Pain Inventory
NRS – Numeric Rating Scale
RCT - randomised controlled trial

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

Study	Reason for exclusion
Bagsby 2014	Open label sequential cohort study
Barrington 2015	Open label sequential cohort study
Baxter 2013	Review paper evaluating wound healing following liposomal bupivacaine at the surgical site
Bergese 2012	Review paper evaluating the cardiac safety of liposomal bupivacaine after surgical site infiltration
Bergese 2012a	Review paper evaluating the efficacy of liposomal bupivacaine when infiltrated at the surgical site
Cohen 2012	Open label sequential cohort study
Cohen 2014	Open label sequential cohort study
Collis 2015	RCT evaluating the efficacy of liposomal bupivacaine at the surgical site during total knee replacement. Study excluded as not double blind with the outcome assessors not blinded to randomisation
Dasta 2012	Review paper evaluating the efficacy of liposomal bupivacaine when infiltrated at the surgical site
Edwards 2015	Open label sequential cohort study
Hu 2013	Review paper evaluating the pharmacokinetics of liposomal bupivacaine at the surgical site
Knight 2015	RCT evaluating the efficacy of liposomal bupivacaine at the laparoscopic port site during laparoscopic urologic surgery. Study excluded as liposomal bupivacaine assessed was not administered at the surgical site (kidney/renal tract/prostate)
Marcet 2013	Open label sequential cohort study

Study	Reason for exclusion
McKeown 2014	Open label sequential cohort study
Nadeau 2015	Women undergoing bilateral breast augmentation. Each participant was used as their own control and as such we excluded this study the review
NCT 01206608	Women undergoing bilateral breast augmentation. Each participant was used as their own control and as such we excluded this study from the review
Schroer 2015	RCT evaluating the efficacy of liposomal bupivacaine at the surgical site for the management of pain following total knee arthroplasty. This trial compared 266 mg liposomal bupivacaine mixed with 75 mg bupivacaine hydrochloride against an active control arm of 150 mg bupivacaine hydrochloride. At the time of writing the trial protocol it was not advised to mix liposomal bupivacaine with other drugs, in particular bupivacaine, due to the risk of premature de-encapsulation of liposomal bupivacaine. As such studies evaluating liposomal bupivacaine with another drug were excluded from this review. In December 2015 an amendment to the FDA-licensed indication was made which approved admixing liposomal bupivacaine with bupivacaine, including co-administration in the same syringe. This amendment was made as it has been proposed that admixing with bupivacaine hydrochloride enhances early postoperative analgesia. As such in future updates of this review trials evaluating liposomal bupivacaine with bupivacaine hydrochloride will be included
Surdam 2015	RCT evaluating the efficacy of liposomal bupivacaine at the surgical site compared with femoral nerve block for total knee replacement. Study excluded as participants in the femoral nerve block group who had persistent quadriceps inhibition after day 0 were also treated with a knee immobiliser which would be expected to impact on outcomes recorded (pain scores, opioid usage, range of movement). Additionally the trial was not double blind with the participants not blinded to randomisation.
Viscusi 2014	Review paper evaluating the safety of liposomal bupivacaine at the surgical site
Vogel 2013	Open label sequential cohort study
White 2015	Open label sequential cohort study

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

NCT01907191

Trial name or title	Ultrasound guided local infiltration analgesia for hip arthroscopy
Methods	Parallel-arm RCT
Participants	Participants undergoing hip arthroscopy
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Opioid consumption Pain scores
Starting date	July 2013
Contact information	ClinicalTrials.gov/show/NCT01907191

NCT01907191 *(Continued)*

Notes	Currently recruiting

NCT02011464

Trial name or title	Evaluation Exparel delivered in knee replacement
Methods	Parallel-arm RCT
Participants	Participants undergoing knee replacement
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Subjective pain Analgesic use Subject satisfaction
Starting date	Dec-13
Contact information	ClinicalTrials.gov/show/NCT02011464
Notes	Yet to recruit

NCT02044302

Trial name or title	A prospective trial to reduce postoperative pain in implant based breast reconstruction
Methods	Parallel-arm RCT
Participants	Participants undergoing breast reconstruction
Interventions	Liposomal bupivacaine vs placebo vs bupivacaine hydrochloride vs botulinum toxin vs bupivacaine hydrochloride plus botulinum toxin
Outcomes	Pain score questionnaire
Starting date	April 2014
Contact information	ClinicalTrials.gov/show/NCT02044302
Notes	Currently recruiting

NCT02052180

Trial name or title	Early postoperative pain control following wrist operations
Methods	Parallel-arm RCT
Participants	Participants undergoing carpometacarpal arthroplasty or proximal row carpectomy operation

NCT02052180 *(Continued)*

Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Changes in pain
Starting date	May 2013
Contact information	ClinicalTrials.gov/show/NCT02052180
Notes	Currently recruiting

NCT02052557

Trial name or title	The effect of Exparel on post operative pain and narcotic use after colon surgery
Methods	Parallel-arm RCT
Participants	Participants undergoing elective colon resection (laparoscopic, robotic or open)
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	PCA (patient controlled analgesia) usage Oral pain medications Total IV (intravenous) narcotic used Total oral narcotic used Length of stay Return of bowel function Readmission Toradol Use Nausea medication Foley catheter removal Postoperative pain Postoperative satisfaction Home oral narcotic use
Starting date	February 2013
Contact information	ClinicalTrials.gov/show/NCT02052557
Notes	Trial completed. Results not yet available - contacted 29 January 2016

NCT02060591

Trial name or title	Comparison of two periarticular injection medications for adjunctive pain management following total knee arthroplasty (TKA)

NCT02060591 *(Continued)*

Methods	Parallel-arm RCT
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Measure pain intensity score (pre and postoperatively) by visual analogue scale (VAS)
Starting date	January 2014
Contact information	ClinicalTrials.gov/show/NCT02060591
Notes	Currently recruiting

NCT02104414

Trial name or title	Efficacy of rectal infiltration of Exparel for analgesic benefit following hemorrhoidectomy
Methods	Parallel-arm RCT
Participants	Participants undergoing haemorrhoidectomy
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Postoperative pain control Postoperative opioid consumption Postoperative nausea and vomiting Frequency of and pain during postoperative bowel movements Incidence of urinary retention
Starting date	April 2014
Contact information	ClinicalTrials.gov/show/NCT02104414
Notes	Currently recruiting

NCT02111746

Trial name or title	PAIN - Postoperative Analgesia INvestigation
Methods	Parallel-arm RCT
Participants	Participants undergoing sternotomy, thoracotomy, laparotomy or mini-thoracotomy
Interventions	Liposomal bupivacaine vs bupivacine hydrochloride
Outcomes	Change in postoperative pain Overall opioid use

NCT02111746 *(Continued)*

	Mean length of hospital stay
	Change from baseline in quality of life
Starting date	November 2014
Contact information	ClinicalTrials.gov/show/NCT02111746
Notes	Currently recruiting

NCT02128646

Trial name or title	Liposomal bupivacaine (Exparel) for postoperative pain control for open and laparoscopic abdominal hernia repair
Methods	Parallel-arm RCT
Participants	Participants undergoing open or laparoscopic abdominal hernia repair
Interventions	Liposomal bupivacaine vs standard care
Outcomes	Patient satisfaction with pain management after surgery Total length of time in post-anaesthesia care unit (PACU) Change in postsurgical opioid consumption
Starting date	April 2014
Contact information	ClinicalTrials.gov/show/NCT02128646
Notes	Currently recruiting

NCT02189317

Trial name or title	Liposomal bupivacaine for pain control following anterior cruciate ligament reconstruction
Methods	Parallel-arm RCT
Participants	Participants undergoing anterior cruciate ligament reconstruction
Interventions	Liposomal bupivacaine vs no treatment
Outcomes	Postoperative pain Pain medication use Patient satisfaction with analgesia
Starting date	August 2014
Contact information	clinicaltrials.gov/ct2/show/NCT02189317
Notes	Trial completed. Results not yet available - contacted 29 January 2016

NCT02197273

Trial name or title	Liposomal bupivacaine versus standard analgesia in TJA
Methods	Parallel-arm RCT
Participants	Participants undergoing total joint arthroplasty (shoulder, hip, knee)
Interventions	Liposomal bupivacaine vs standard care
Outcomes	Length of stay in hospital (days) Time to postoperative rescue opioids (minutes) Readmission or ED visit due to pain control within 30 days
Starting date	July 2014
Contact information	ClinicalTrials.gov/show/NCT02197273
Notes	Currently recruiting

NCT02214810

Trial name or title	A study of postsurgical pain control for lower extremity fractures
Methods	Parallel-arm RCT
Participants	Participants undergoing surgical fixation of a lower extremity fracture
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Change in pain visual analogue scale (VAS) Pain management satisfaction
Starting date	January 2015
Contact information	ClinicalTrials.gov/show/NCT02214810
Notes	Currently recruiting

NCT02219087

Trial name or title	Liposomal bupivacaine versus standard of care in total knee surgery
Methods	Parallel-arm RCT
Participants	Participants undergoing total knee replacement
Interventions	Liposomal bupivacaine vs standard of care
Outcomes	Number physical therapy sessions required

NCT02219087 *(Continued)*

	Visual analog scale (VAS) pain scores during admission (0-10 scale)
	Length of stay
	Opioid consumption
	Incidence of opioid-related adverse events
Starting date	August 2014
Contact information	ClinicalTrials.gov/show/NCT02219087
Notes	Currently recruiting

NCT02242201

Trial name or title	THA lumbar plexus versus periarticular
Methods	Parallel-arm RCT
Participants	Participants undergoing total hip arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride vs lumbar plexus block
Outcomes	Pain control comparison
	Pain management assessment 0-3 months
Starting date	September 2014
Contact information	ClinicalTrials.gov/show/NCT02242201
Notes	Currently recruiting

NCT02274870

Trial name or title	Liposomal bupivacaine for post operative pain after knee replacement surgery
Methods	Parallel-arm RCT
Participants	Participants undergoing knee replacement
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Number physical therapy sessions required
	Visual analog scale (VAS) pain scores during admission (0-10 scale)
	Length of stay (LOS, in days)
	Opioid consumption in oral morphine equivalents (OMEs, in milligrams)
	Incidence of opioid-related adverse events (ORAEs) during admission
	Total cost of care (dollars)

NCT02274870 *(Continued)*

	Hospital readmission
Starting date	August 2014
Contact information	ClinicalTrials.gov/show/NCT02274870
Notes	Currently recruiting

NCT02287246

Trial name or title	Efficacy of extended-release liposomal bupivacaine for postoperative urogynecologic surgery
Methods	Parallel-arm RCT
Participants	Participants undergoing urogynecologic surgery
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Cumulative postoperative pain control Evaluate vaginal pain on postoperative day 7
Starting date	October 2014
Contact information	ClinicalTrials.gov/show/NCT02287246
Notes	Currently recruiting

NCT02296099

Trial name or title	Trial liposomal bupivacaine following retropubic suburethral sling for stress urinary incontinence
Methods	Parallel-arm RCT
Participants	Participants undergoing retropubic suburethral sling for stress urinary incontinence
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Pain on postoperative day 1 Pain upon discharge from post-anaesthesia care unit (PACU) Pain upon discharge from same day surgery Pain at 4 h after discharge home Total narcotic consumption Satisfaction with pain control at 1 week postoperative visit
Starting date	November 2014
Contact information	ClinicalTrials.gov/show/NCT02296099

NCT02296099 *(Continued)*

Notes	Currently recruiting

NCT02299349

Trial name or title	Bupivacaine liposome suspension versus a concentrated multi drug periarticular injection
Methods	Parallel-arm RCT
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride
Outcomes	Pain scores Morphine sulphate equivalent dose
Starting date	August 2013
Contact information	clinicaltrials.gov/show/NCT02299349
Notes	Trial completed. Results not yet available - contacted 29 January 2016

NCT02352922

Trial name or title	Randomized trial of wound infiltration with extended-release bupivacaine before laparoscopic or robotic hysterectomy
Methods	Parallel-arm RCT
Participants	Participants undergoing laparoscopic or robotic hysterectomy
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	Numerical Rating Scale (NRS) postoperative pain score on postoperative day 1 (POD1) NRS Pain score at 2 h NRS Pain score at 4 h NRS Pain score at 8 h NRS Pain score at 16 h NRS Pain score post-op day 2 NRS Pain score post-op day 3 NRS Pain score post-op day 14 Quality of life as measured by the Brief Pain Inventory (BPI) Total opioid use prior to hospital discharge Total opioid use end of post-op day 3 Total NSAID use end of post-op day 3

NCT02352922 *(Continued)*

	Total opioid use at post-op day 14
	Total NSAID use at post-op day 14
	Adverse events
Starting date	July 2015
Contact information	ClinicalTrials.gov/show/NCT02352922
Notes	Currently recruiting

NCT02369523

Trial name or title	Multimodal pain management following primary TKA
Methods	Parallel-arm RCT
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride vs continuous femoral nerve block
Outcomes	Time to discharge readiness
Starting date	September 2014
Contact information	ClinicalTrials.gov/show/NCT02369523
Notes	Currently recruiting

NCT02381353

Trial name or title	Exparel injection for postoperative orbital pain
Methods	Parallel-arm RCT
Participants	Participants undergoing enucleation or evisceration of the eye
Interventions	Liposomal bupivacaine vs bupivacine hydrochloride
Outcomes	Postoperative orbital pain
	Postoperative nausea and vomiting
	Quantity of oral narcotics used for postoperative pain control
	Patient satisfaction
	Postoperative complications
Starting date	February 2015
Contact information	ClinicalTrials.gov/show/NCT02381353

NCT02381353 *(Continued)*

Notes	Currently recruiting

NCT02426164

Trial name or title	Liposomal bupivacaine in total knee arthroplasty
Methods	Parallel-arm RCT
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs bupivacine hydrochloride
Outcomes	Mean visual analogue scale (VAS) pain scores Day 0, 1, 2 and 3 Complications
Starting date	June 2015
Contact information	ClinicalTrials.gov/show/NCT02426164
Notes	Not yet recruiting

NCT02444533

Trial name or title	EXPAREL® for pain after tonsillectomy
Methods	Parallel-arm RCT
Participants	Participants undergoing tonsillectomy
Interventions	Liposomal bupivacaine vs no intervention
Outcomes	Pain score (pain scores on a 0/10 scale) Pain medication usage (milligrams used) Oral intake (patient-recorded oral intake) Patient complication (allergic reaction, swallowing dysfunction, hospital admission related to the study drug) Post-tonsillectomy bleeding rate
Starting date	May 2015
Contact information	ClinicalTrials.gov/show/NCT02444533
Notes	Currently recruiting

NCT02449915

Trial name or title	Improvement of pain following robotic sacrocolpopexy and rectocele repair for pelvic organ prolapse
Methods	Parallel-arm RCT
Participants	Participants undergoing robotic sacrocolpopexy and rectocele repair for pelvic organ prolapse
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Global visual analogue score (VAS) for pain
Starting date	March 2014
Contact information	ClinicalTrials.gov/show/NCT02449915
Notes	Currently recruiting

NCT02472314

Trial name or title	Exparel for postoperative pain management in shoulder surgery
Methods	Parallel-arm RCT
Participants	Participants undergoing surgery for fractures of the shoulder and upper arm
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride (peripheral nerve block)
Outcomes	Quality of analgesia Time to discharge home Time to return to work Postoperative American Shoulder and Elbow surgeons (ASES) Subjective shoulder value (SSV) Constant score Incidence of nerve injury Postoperative opioid consumption
Starting date	June 2015
Contact information	ClinicalTrials.gov/show/NCT02472314
Notes	Yet to recruit

NCT02473198

Trial name or title	Femoral Nerve Block Compared to Exparel in Total Knee Replacement
Methods	Parallel-arm RCT

NCT02473198 *(Continued)*

Participants	Participants undergoing total knee replacement
Interventions	Liposomal bupivacaine vs femoral nerve block
Outcomes	Pain Score (VAS) Functional Outcome (Knee Society Score)
Starting date	January 2014
Contact information	https://ClinicalTrials.gov/show/NCT02473198
Notes	Recruiting

NCT02480621

Trial name or title	Liposomal bupivacaine with bupivacaine in ankle fracture ORIF
Methods	Parallel-arm RCT
Participants	Participants undergoing ankle fracture open reduction internal fixation
Interventions	Liposomal bupivacaine plus bupivacaine hydrochloride vs no treatment
Outcomes	Pain levels on a visual analog scale (VAS)
Starting date	December 2014
Contact information	ClinicalTrials.gov/show/NCT02480621
Notes	Currently recruiting

NCT02499575

Trial name or title	Pericapsular Exparel for pain relief in bunionectomy and related procedures
Methods	Parallel-arm RCT
Participants	Participants undergoing outpatient first metatarsophalangeal (MTP) joint procedure (bunionectomy, 1st MTP fusion, or cheilectomy)
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride
Outcomes	Opioid use as measured by questionnaire Pain relief measured by Defense and Veterans Pain Scale
Starting date	July 2015
Contact information	ClinicalTrials.gov/show/NCT02499575
Notes	Currently recruiting

NCT02515851

Trial name or title	A randomized, double-blind controlled trial of bupivacaine extended-release liposome injection for postsurgical analgesia in patients undergoing open-reduction internal fixation of the distal radius
Methods	Parallel-arm RCT
Participants	Participants undergoing open-reduction internal fixation of the distal radius
Interventions	Liposomal bupivacaine vs placebo
Outcomes	Pain medication usage
Starting date	August 2015
Contact information	ClinicalTrials.gov/show/NCT02515851
Notes	Currently recruiting

NCT02517905

Trial name or title	Evaluation of EXPAREL for prolonged postsurgical analgesia in subjects undergoing third molar extraction
Methods	Parallel-arm RCT
Participants	Participants undergoing third molar extraction
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Area under the curve (AUC) of the numeric rating scale (NRS) at rest (NRS-R) pain intensity scores through 48 h Treatment-emergent adverse events Maximum plasma concentration Time to maximum plasma concentration Area under the plasma concentration-versus-time curve Apparent terminal elimination half-life
Starting date	August 2015
Contact information	ClinicalTrials.gov/show/NCT02517905
Notes	Currently recruiting

NCT02542956

Trial name or title	Comparison of local anesthetic infusion pump versus DepoFoam bupivacaine for pain management

NCT02542956 *(Continued)*

Methods	Parallel-arm RCT
Participants	Participants undergoing abdominoplasty
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride (continuous infiltration pump)
Outcomes	Recurrence of pain
Starting date	October 2014
Contact information	ClinicalTrials.gov/show/NCT02542956
Notes	Currently recruiting

NCT02543801

Trial name or title	A clinical trial of two periarticular multimodal drug injections in total hip arthroplasty
Methods	Parallel-arm RCT
Participants	Participants undergoing total hip arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride vs bupivacaine hydrochloride
Outcomes	Pain score Narcotic consumption Length of stay
Starting date	January 2016
Contact information	ClinicalTrials.gov/show/NCT02543801
Notes	Currently recruiting

NCT02571283

Trial name or title	Peri-articular injection utilizing a pain cocktail with and without Exparel
Methods	Parallel-arm RCT
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride
Outcomes	The visual pain scale from 1-10 will be used to determine changes in pain control at 3, 12, 24, and 48 hour time intervals postoperatively
Starting date	October 2015
Contact information	ClinicalTrials.gov/show/NCT02571283

NCT02571283 *(Continued)*

Notes	Yet to recruit

NCT02591888

Trial name or title	Impact of liposomal bupivacaine administered following placement of a transobturator suburethral sling
Methods	Parallel-arm RCT
Participants	Participants undergoing transobturator suburethral sling
Interventions	Liposomal bupivacaine vs placebo (NaCl 0.9%)
Outcomes	Visual analogue scale (VAS) Numeric rating scale (NRS) Likert scale to rate their level of satisfaction with their postoperative pain control
Starting date	February 2015
Contact information	ClinicalTrials.gov/show/NCT02591888
Notes	Currently recruiting

NCT02606448

Trial name or title	Exparel infiltration in anterior cruciate ligament reconstruction
Methods	Parallel-arm RCT
Participants	Participants undergoing anterior cruciate ligament reconstruction
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride (femoral nerve block)
Outcomes	Pain levels Morphine equivalents
Starting date	May 2014
Contact information	ClinicalTrials.gov/show/NCT02606448
Notes	Yet to recruit

NCT02616367

Trial name or title	Comparison of ropivacaine and liposomal bupivacaine for total knee arthroplasty
Methods	Parallel-arm RCT

NCT02616367 *(Continued)*

Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine vs ropivacaine hydrochloride
Outcomes	Pain control measure on pain scale of 1-10 Decreased maximal pain on pain scale of 1-10
Starting date	December 2015
Contact information	ClinicalTrials.gov/show/NCT02616367
Notes	Yet to recruit

NCT02659501

Trial name or title	Liposomal bupivacaine in implant based breast reconstruction
Methods	Parallel-arm RCT
Participants	Participants undergoing breast reconstruction
Interventions	Liposomal bupivacaine vs bupivacaine hydrochloride
Outcomes	The effect of liposomal bupivacaine on average postoperative pain levels on postoperative day 1, 2, 3, 4, 5, 6 and 7 The effect of liposomal bupivacaine on postoperative opioid consumption The effect of liposomal bupivacaine on length of hospital stay The effect of liposomal bupivacaine on patient satisfaction with postoperative pain control The effect of liposomal bupivacaine on overall patient satisfaction The effect of liposomal bupivacaine on opioid-related adverse events
Starting date	July 2015
Contact information	clinicaltrials.gov/ct2/show/NCT02659501
Notes	Currently recruiting

ASA – American Society of Anaesthesiologists Score
ASES - American Shoulder and Elbow surgeons
AUC – Area Under Curve
BPI - Brief Pain Inventory
BPI – Brief Pain Inventory
ED – Emergency Department
IV - Intravenous
LOS – Length of Stay
MTP - Metatarsophalangeal
NRS – Numeric Rating Scale
NSAID – Non Steroidal Anti Inflammatory Drug
OME - Oral Morphine Equivalents
ORAE – Opioid Related Adverse Event

ORIF – Open Reduction Internal Fixation
PACU - Post Anaesthesia Care Unit
PCA - Patient Controlled Analgesia
POD1 – Post Operative Day 1
RCT - randomised controlled trial
SSV - Subjective Shoulder Value
THA – Total Hip Arthroplasty
TJA – Total Joint Arthroplast
TKA – Total Knee Arthroplasty
TSA – Total Shoulder Arthroplasty
VAS – Visual Analogue Scale

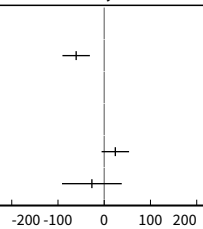
DATA AND ANALYSES

Comparison 1. Liposomal bupivacaine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cumulative pain score 0 to 72 hours	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 vs placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 vs bupivacaine hydrocholoride	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participants not requiring postoperative opioids	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 vs placebo	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 vs bupivacaine hydrochloride	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Liposomal bupivacaine vs control, Outcome 1 Cumulative pain score 0 to 72 hours.

Study or subgroup	Liposomal bupivacaine N	Liposomal bupivacaine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.1.1 vs placebo						
Gorfine 2011	94	141.8 (103.7)	93	202.5 (103.2)		-60.7[-90.35,-31.05]
1.1.2 vs bupivacaine hydrocholoride						
NCT 00745290	122	359 (124)	123	335 (113)		24[-5.71,53.71]
Smoot 2012	60	441.5 (182.8)	62	468.2 (181.1)		-26.7[-91.29,37.89]



Analysis 1.2. Comparison 1 Liposomal bupivacaine vs control, Outcome 2 Participants not requiring postoperative opioids.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.2.1 vs placebo				
Golf 2011	2/93	1/92		0.99[0.95,1.03]
Gorfine 2011	24/94	9/93		0.82[0.72,0.94]
1.2.2 vs bupivacaine hydrochloride				
Smoot 2012	6/60	3/60		0.95[0.86,1.05]
		Favours control	1	Favours lipo bupivacaine

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1(Liposom* near/5 bupivacaine) or (depo* near/5 bupivacaine):ti,ab,kw (Word variations have been searched)
#2exparel or SKY0402:ti,ab,kw (Word variations have been searched)
#3#1 or #2
#4MeSH descriptor: [Pain, Postoperative] this term only
#5((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or ("post-operative analgesi*")):ti,ab,kw (Word variations have been searched)
#6((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)):ti,ab,kw (Word variations have been searched)
#7("pain-relief after surg*" or "pain following surg*" or "pain control after"):ti,ab,kw (Word variations have been searched)
#8(("post surg*" or post-surg*) and (pain* or discomfort)):ti,ab,kw (Word variations have been searched)
#9((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)
#10((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)
#11#4 or #5 or #6 or #7 or #8 or #9 or #10
#12#3 and #11

MEDLINE

1. (Liposom* adj5 bupivacaine).mp. or (depo* adj5 bupivacaine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

2. exparel.mp. or SKY0402.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. Pain, Postoperative/

4. ((postoperative adj4 pain*) or (postoperative adj4 pain*) or postoperative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (postoperative adj4 analgesi*) or "postoperative analgesi*").mp.

5. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.

6. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.

7. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.

8. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

9. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.

10. or/3-9

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. randomized.ab.

14. placebo.ab.

15. drug therapy.fs.

16. randomly.ab.

17. trial.ab.

18. or/11-17

19. exp animals/ not humans.sh.

20. 18 not 19

21. 1 or 2

22. 10 and 20 and 21

Embase

1. (Liposom* adj5 bupivacaine).mp. or (depo* adj5 bupivacaine).tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2. exparel.mp. or SKY0402.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. Pain, Postoperative/

4. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.

5. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.

6. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.

7. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.

8. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

9. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.

10. or/3-9

11. 1 or 2

12. 10 and 11

13. random$.tw.

14. factorial$.tw.

15. crossover$.tw.

16. cross over$.tw.

17. cross-over$.tw.

18. placebo$.tw.

19. (doubl$ adj blind$).tw.

20. (singl$ adj blind$).tw.

21. assign$.tw.

22. allocat$.tw.

23. volunteer$.tw.

24. Crossover Procedure/

25. double-blind procedure.tw.

26. Randomized Controlled Trial/

27. Single Blind Procedure/

28. or/13-27

29. (animal/ or nonhuman/) not human/

30. 28 not 29

31. 12 and 30

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#16 #15 AND #11

#15 #14 OR #13 OR #12

#14 TOPIC: ((((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))))

#13 TOPIC: (((controlled clinical trial OR controlled trial OR clinical trial OR placebo)))

#12 TOPIC: (((randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial)))

#11 #10 AND #3

#10 #9 OR #8 OR #7 OR #6 OR #5 OR #4

#9 TOPIC: (((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")))

#8 TOPIC: (((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")))

#7 TOPIC: ((("post surg*" or post-surg*) and (pain* or discomfort)))

#6 TOPIC: (("pain-relief after surg*" or "pain following surg*" or "pain control after"))

#5 TOPIC: (((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)))

#4 TOPIC: (((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or ("post-operative analgesi*")))

#3 #2 OR #1

#2 TOPIC: (exparel or SKY0402)

#1 TOPIC: ((Liposom* near/5 bupivacaine) or (depo* near/5 bupivacaine))

Appendix 2. Cumulative pain intensity calculation

We calculated cumulative pain over 72 hours using the trapezoidal method to measure the mean area under the curve (AUC). To account for the use of rescue analgesia the windowed worst-observation-carried- forward + last-observation-carried-forward (wWOCF+LOCF) imputation method was used. The wWOCF+LOCF accounts for the effect of a rescue analgesia by replacing pain scores recorded within one half life of rescue medication administration (6 hours for oxycodone/acetaminophen or ketorolac) with the pain score recorded prior to rescue medication administration.)

Where pain scores were missing we replaced them in one of three ways.

- Where the missing score occurred before any pain scores were recorded we used the median score from other participants at the same time point in the same treatment group
- Where the missing score occurred between two non-missing scores linear interpolation was performed.
- Where the missing score occurred after the last non-missing score the last observation was carried forward.

WHAT'S NEW

Date	Event	Description
18 February 2020	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

Thomas Hamilton wrote the protocol with input from Vassilis Athanassoglou. Statistical and methodological advice were provided by Marialena Trivella. The search strategy was designed by Joanne Abbott with input from Thomas Hamilton. Other authors provided general advice on the protocol. Future updates of this review will be performed by Thomas Hamilton.

DECLARATIONS OF INTEREST

- TWH is an orthopaedic registrar and manages patients with peri-operative and postoperative pain. TWH receives funding from the National Institute for Health Research (NIHR).
- VA: none known; VA is a consultant anaesthetist and manages patients with peri-operative and postoperative pain.
- SM none known.
- LHS: none known; LHS is a nurse and surgical assistant and manages patients with perioperative and post-operative pain.
- MT: none known.
- DM is a consultant orthopaedic surgeon and manages patients with perioperative and postoperative pain. DM receives funding from Zimmer Biomet (1998 to present) who manufacture orthopaedic implants, including knee replacements.
- HGP is a consultant orthopaedic surgeon and manages patients with peri-operative and postoperative pain. HGP receives funding from Zimmer Biomet (2015 to present) who manufacture orthopaedic implants, including knee replacements.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK, Other.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In line with current Cochrane guidance, we have added selective outcome reporting and blinding of participants and personnel (performance bias) to the 'Risk of bias' assessment and also completed a GRADE assessment for all included studies. These were not included in the protocol but have been included in this review and will be included in subsequent updates. In our protocol we stated we would assess for adverse events as both a primary and secondary outcome. To avoid duplication we have assessed the incidence of serious adverse events including the incidence of cardiac events and incidence of wound complications as a primary outcome, and incidence of adverse events as a secondary outcome.

NOTES

We updated the searches in full in October 2019, and while we did identify some potentially relevant studies, none were likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in 2022. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthetics, Local [*administration & dosage] [adverse effects]; Arthroplasty, Replacement, Knee; Bupivacaine [*administration & dosage] [adverse effects]; Liposomes; Mammaplasty; Pain Measurement; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans