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[Intervention Review]

Pain relief for the removal of femoral sheath after percutaneous coronary intervention

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ABSTRACT

Background

This is an updated version of the original Cochrane Review published in Issue 4, 2008 of *The Cochrane Library*. There is variation in the use of pain relief for managing pain or discomfort of femoral sheath removal. The efficacy of pain relief to promote comfort during this procedure or to reduce the incidence of vascular and procedural complications has not been established.

Objectives

To assess the efficacy of pain relief used to manage pain of femoral sheath removal in adults after interventional cardiology.

To determine if pain relief influences rates of complications associated with this procedure.

Search methods

We brought the search up to date by searching the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, CINAHL, Australasian Medical Index, Web of Knowledge and Digital Dissertations up to June 2011.

Selection criteria

Randomised studies comparing opioid, local anaesthetic, anxiolytic, no treatment or placebo administered for alleviation of pain or discomfort of the femoral sheath removal procedure.

Data collection and analysis

Two review authors assessed study quality and extracted data. We calculated mean differences (MD) where meta-analysis was feasible. We collected adverse effects information.

Main results

Four studies involving 971 participants were included. All results were reported using a zero to 10 pain scale. Three studies (four treatment arms) involving 498 participants compared subcutaneous lignocaine with control with no significant difference between pain scores; MD 0.12 (95% confidence interval (CI) -0.46 to 0.69). Two studies (three treatment arms) involving 399 participants compared intravenous pain regimens with control. A significant reduction in pain score was observed with intravenous opioid and anxiolytic; MD -0.90 (95% CI -1.54 to

-0.27). One study involving 60 participants compared levobupivacaine with placebo. Longer-acting local anaesthetic significantly lowered the pain score by a MD of -1.10 (95% CI -1.26 to -0.94). The data are insufficient to identify any influence of pain regimens on vascular and procedural complication rates. No studies reported appropriate blinding for all treatment arms. The largest study, comprising 661 participants, was unblinded with a quality score of two out of five.

Authors' conclusions

No new studies have been found since the last version of this review and the conclusions therefore remain the same. Intravenous pain regimens and levobupivacaine may have greater efficacy when compared to control for the management of pain related to femoral sheath removal. However, a definitive study is still required because the clinical difference is small. There is no evidence to support the use of subcutaneous lignocaine. There is insufficient evidence to determine if pain relief influences the rate of complications. One new study has been included as a 'study awaiting assessment' as we await further information from the study authors.

PLAIN LANGUAGE SUMMARY

Pain relief for removal of femoral sheath after cardiac procedures

Procedures for the non-surgical management of coronary heart disease include balloon angioplasty (mechanically widening a narrowed or obstructed blood vessel) and intracoronary stenting (a device to support the blood vessel to keep it open). At the start of each procedure an introducer sheath is inserted through the skin (percutaneously) into an artery, frequently a femoral artery in the groin. This allows the different catheters used for the procedure to be exchanged easily without causing trauma to the skin. At the end of the procedure the sheath is removed and, if the puncture site is not 'sealed' using a device closure, firm pressure is required over the site for 30 minutes or more to control any bleeding and reduce vascular complications. Removing the sheath and the firm pressure required to control bleeding can cause pain, although this is generally mild. Some centres routinely give pain relief before removal, such as intravenous morphine, or an injection of a local anaesthetic in the soft tissue around the sheath (called a subcutaneous injection). Adequate pain control during sheath removal is also associated with a reduced incidence of a vasovagal reaction, a potentially serious complication involving a sudden drop of blood pressure and a slowed heart rate.

In this systematic review of randomised controlled trials four studies were reviewed. Three studies involving 498 participants compared subcutaneous lignocaine, a short-acting local anaesthetic, with a control group (participants received either no pain relief or an inactive substance known as a placebo). Two studies involving 399 people compared intravenous opioids (fentanyl or morphine) and an anxiolytic (midazolam) with a control group. One study involving 60 people compared subcutaneous levobupivacaine, a long-acting local anaesthetic, with a control group. Intravenous pain regimens and subcutaneous levobupivacaine appear to reduce the pain experienced during femoral sheath removal. However, the size of the reduction was small. A significant reduction in pain was not experienced by participants who received subcutaneous lignocaine or who were in the control group. There were insufficient data to determine a correlation between pain relief administration and either adverse events or complications. Some patients may benefit from routine pain relief using levobupivacaine or intravenous pain regimens. Identifying who may potentially benefit from pain relief requires clinical judgement and consideration of patient preference. The mild level of pain generally experienced during this procedure should not influence the decision as some people can experience moderate levels of pain with the conventional wound care.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 4, 2008) on 'Pain relief for the removal of femoral sheath in interventional cardiology adult patients' (Wensley 2008).

Description of the condition

Percutaneous Coronary Intervention (PCI) is accepted management for coronary heart disease and includes coronary revascularisation procedures such as balloon angioplasty and intracoronary stenting (Levine 2003). During PCI, catheters needed to dilate or stent the stenosed artery are inserted into the coronary artery via an introducer sheath. The sheath is inserted percutaneously into the femoral, brachial or radial artery and provides support at the site, reducing potential trauma as catheters are exchanged. Introducer sheaths are frequently located in the femoral artery and are removed after the procedure, at which time haemostasis at the percutaneous access site is achieved. The arterial site can be 'sealed' using a collagen plug, internal suturing device or liquid synthetic thrombin instillations (Davis 1997). Frequently, haemostasis is achieved by firm compression of the femoral artery using manual or assisted manual pressure, such as the C-Clamp or Femo-Stop, to control bleeding.

Pain or discomfort with femoral sheath removal is experienced by virtually all non-medicated and most medicated patients to some degree (Benson 2005; Fulton 2000; Lambert 1996; Puntillo 2001). This is likely to be caused by a combination of the discomfort of the removal of the sheath and the firm pressure required to achieve haemostasis. Pain intensity scores indicate that the amount of procedural distress caused by femoral sheath removal is relatively mild (Benson 2005; Bowden 1995; Fulton 2000; Lambert 1996; Puntillo 2001; Wadas 1998). For example, using a Numeric Rating Score (zero to 10), with higher numbers meaning greater pain intensity, patients rated femoral sheath removal with mean pain intensity scores of 2.7 ± 3.0 (Puntillo 2001). Pre-procedure 30% (775 out of 2574) had received lignocaine before sheath removal and 25.2% (651 out of 2574) received opioids pre-procedure. However, in another study, 8% of patients (11/130) required rescue analgesia for breakthrough pain despite some of these patients having received pain relief before the procedure (Fulton 2000).

Description of the intervention

Internationally, analgesic regimens for the relief of pain or discomfort of femoral sheath removal have varied considerably. A 2004 survey of current practice for patients undergoing PCI across Australia and New Zealand reported 17 variations in analgesic regimens administered before sheath removal (Sanders 2005). Commonly used pain relief includes intravenous morphine, midazolam, diazepam, fentanyl and subcutaneous lignocaine infiltrated at the femoral site with or without intravenous morphine. Some regimens also include small doses of antiemetics or atropine, or both, to prevent vasovagal reactions which may accompany the pain associated with removal and compression (Botti 2000; Bowden 1995; Fulton 2000; Lambert 1996; Puntillo 2001; Wadas 1998; Vish 2001). Some centres do not routinely administer pain relief (Botti 2000; Bowden 1995; Sanders 2005; Smith 2001; Wadas 1998).

How the intervention might work

Inadequate pain control during sheath removal is associated with increased risk of vascular complications and, in addition to promoting patient comfort, the prevention of vascular complications is frequently cited as rationale for the administration of analgesia. Complications associated with femoral sheath removal include bleeding, haematoma and pseudoaneurysm (Fulton 2000; Lambert 1996; Mager 1994; O'Grady 2002; Peet 1995; Rubin 1996; Timlin 2005; Vish 2001). The impact of pain relief on moderating these complications is unclear but pain relief is believed to increase the patient's tolerance to firm groin compression so that risk is reduced. Known risk factors for vascular complications include increased age, female gender, high anticoagulant use, catheter size greater than 8 French and prolonged sheath time in the groin (Davis 1997).

Pain and anxiety states are associated with increased vagal tone and consequently common opinion has been that the pain of sheath removal can trigger a vasovagal reaction in some patients (Lambert 1997; O'Grady 2002). This reaction consists of symptomatic bradycardia, hypotension, nausea and vomiting (Boss 1988; Mager 1994; Rama 1997). Although usually self limiting, vasovagal reactions can have severe consequences in patients undergoing PCI including serious arrhythmias, severe hypotension, abrupt closure of the dilated artery, and myocardial ischaemia or infarction (Ilia 1997; Mager 1994; Rama 1997). The use of vagolytic medication after angioplasty, particularly in patients at risk, has been supported (Mager 1994; Rama 1997). The documented incidence of a vasovagal reaction following femoral sheath removal is variable. Fulton 2000 established that 6% (8/130) of patients experienced a vasovagal event and 8% (10/130) had nausea or vomiting during the sheath procedure.

Why it is important to do this review

As with all medications, analgesic regimens currently used for femoral sheath removal can have adverse outcomes and currently the risks versus the benefits of pain relief for femoral sheath removal are unclear. Even in therapeutic doses, side effects of morphine include nausea, vomiting, drowsiness and confusion (MIMS 2004). Adverse allergic reactions to local anaesthetic are frequently reported (Berkun 2003; Gall 1996), although evaluation at allergy clinics indicates that true allergies are rare (Macy 2003). Accidental intravascular administration of local anaesthetic can be a serious complication, resulting in cardiovascular toxicity if large amounts are absorbed (Achar 2002). Unbuffered subcutaneous lignocaine is associated with reports of stinging (Lambert 1996; Vish 2001). Repeated injections are associated with discomfort as well as the increased risk of infection (Lambert 1996). However, a competent technique can minimise the discomfort of infiltration (Achar 2002) and we have found no literature to support the association of infection with lignocaine infiltration. As with all medication, analgesic regimens incur costs associated with the expense of the medication as well as preparation and administration time.

The relatively mild pain associated with femoral sheath removal, with or without pain relief, is a consistent finding across a number of studies (Benson 2005; Bowden 1995; Fulton 2000; Puntillo 2001; Wadas 1998; Vish 2001). Perceptions of and responses to procedural pain, such as with sheath removal, have a psychological and physiological basis (Puntillo 2001). Thorough patient preparation,

including preparation about expected sensations and pre-procedural administration of analgesia, may assist in keeping pain intensity scores low. Certainly the sheath removal procedure is frequently protocol-driven and associated with a high level of operator education and preparation (O'Grady 2002; Smith 2001). Additionally, as a one-off procedure the discomfort of sheath removal has no cumulative effect unlike repetitive painful procedures such as wound care, which have been associated with higher pain scores (Puntillo 2001).

The practice variation observed in analgesia use for femoral sheath removal is likely to continue until the efficacy of analgesia, and its impact on complications associated with this procedure, is better understood. The initial review concluded that there was evidence of efficacy with intravenous pain regimens and levobupivacaine, when compared to control, but the clinical significance was small and definitive studies were required. There was insufficient evidence to determine if pain relief influences the rate of complications. It is important that this review is updated to ensure that its conclusions and practice recommendations reflect all relevant research.

OBJECTIVES

- To assess the efficacy of pain relief used to manage the pain or discomfort of femoral sheath removal in adults after interventional cardiology.
- To determine if pain relief influences the rate of vascular and procedural complications associated with this procedure.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), published or unpublished, comparing pain regimens or against placebo administered before femoral sheath removal after percutaneous coronary intervention.

Types of participants

Patients with coronary artery disease aged 18 years or over undergoing femoral sheath removal following percutaneous coronary intervention.

Types of interventions

Interventions considered will be any form of opioid, local anaesthetic or anxiolytic pain relief (at any dose or route), or any combination of these, compared with any form of opioid, anaesthetic, anxiolytic pain relief (at any dose or route), no treatment, placebo or saline injection (subcutaneous or intravenous). Interventions will have been administered for the alleviation of any potential pain and discomfort with femoral sheath removal.

Types of outcome measures

Primary outcomes

The primary outcome for this review is the reduction in pain score as measured by either a visual analogue scale (VAS), self reported global scale, verbal rating scale, numerical rating scale, categorical pain relief scale, self reported pain relief or use of rescue analgesia.

We used the effectiveness measures as reported during the sheath removal process.

Secondary outcomes

Secondary outcomes measures are:

- the incidence of vascular complications of haematoma, bleeding, pseudoaneurysm;
- the incidence of procedural complications of vasovagal reaction, nausea, vomiting.

Other outcomes to be recorded:

- patient satisfaction with the procedure;
- the cost-effectiveness (time involved with preparation, costs) associated with the preparation and administration of pain relief interventions.

Search methods for identification of studies

Electronic searches

Electronic databases we searched were the Cochrane Pain, Palliative and Supportive Care Group Trials Register (last searched August 2007, the Cochrane Heart Group Trials Register (15 December 2005), the Cochrane Controlled Trials Register (CENTRAL) in *The Cochrane Library* (Issue 3, 2007, subsequent search June 2011), MEDLINE (1977 to August 2006, subsequent search June 2011), EMBASE (1977 to August 2007, subsequent search June 2011), CINAHL (1982 to August 2007, subsequent search June 2011) and Australia's Australasian Medical Index (August 2007, subsequent search February 2011). We applied no language restrictions.

We developed detailed search strategies for each electronic database. We did not apply a controlled trials filter. The subject search used a combination of controlled vocabulary and free-text terms See [Appendix 1](#) for the MEDLINE search strategy, [Appendix 2](#) for the EMBASE search strategy, [Appendix 3](#) for the CENTRAL search strategy and [Appendix 4](#) for the CINAHL search strategy.

Searching other resources

Databases searched for unpublished data were the National Research Centre (May 2006), Web of Knowledge (May 2006, subsequent search February 2011), Digital Dissertations (May 2006, subsequent search February 2011), ClinicalTrials.gov (February 2011) and Current Controlled Trials (May 2006). We searched reference lists of all relevant trials and maintained contact with experts in the field since the first publication. We did not search TrialsCentral™ or review conference proceedings of international cardiac conferences.

Data collection and analysis

Selection of studies

Three review authors (CW, MM, SP) independently screened the titles and abstracts from electronic searches. No differences arose that required consultation with a fourth review author.

Data extraction and management

Two review authors (CW and MM or SP) independently extracted data using a specifically developed data extraction form. Data collected were study design, participants, interventions, co-

interventions, outcome measures including the methods of pain assessment, and results. We also extracted the role of the person pulling the sheath and the technique for achieving haemostasis because the review team speculated that these factors may impact on patients' pain scores. So that all outcome data were compatible for the meta-analysis, we converted pain scores measured using a zero to 100 VAS to a one to 10 scale, by dividing by 10, before data entry.

Assessment of risk of bias in included studies

We assessed the quality of the included studies using the following criteria.

Method of allocation concealment

We graded this depending on whether the assigned treatment was adequately concealed prior to allocation. We used four grading categories: A is adequate concealment, B is unclear, C is inadequate concealment and D, concealment has not been undertaken.

The three-point Oxford Quality Score Assessment Scale

This scale (Jadad 1996) covers three dimensions of study quality: randomisation, blinding and study withdrawals. The maximum possible score is five. The scale scoring system is as follows:

Randomisation

- Was the study described as randomised? (1 = yes; 0 = no).
- Was the method of randomisation well described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate.

Blinding

- Was the study described as double-blind? (1 = yes; 0 = no).
- Was the double-blinding well described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate.

Description of study withdrawals and dropouts

- Were withdrawals and dropouts described? (1 = yes; 0 = no).

Selective reporting

This update has also included an assessment of selective reporting. For each included study we sought any differences between either the research methods or protocol (as available) and the results published.

Measures of treatment effect

We used the Cochrane Review Manager Software, RevMan 5.1 (RevMan 2011) to compute the treatment effects for the comparisons involved in meta-analysis. The effect measure for these continuous data was the mean difference (MD) with 95% confidence intervals (CI). MD was an appropriate summary statistic as:

- the pain scales from all studies went in the same direction, that is higher numbers represented greater pain;
- the 11-point (zero to 10) Numeric Weighting Scale (NRS) and the 10 cm Visual Analogue Scale (VAS) have good correlation (Downie 1978);
- MD gives a pooled estimate in terms of millimetres on the VAS scale which is more easily understood compared to the standardised mean difference (SMD).

Both the VAS and NRS are reliable and valid tools for measuring pain intensity and were identified as appropriate methods of pain measurement in the research protocol.

Unit of analysis issues

Studies with multiple treatment groups

Where studies had two treatment arms analysed in the same comparison, we halved the number of participants in the control group. This avoided inflating the number of control participants in the meta-analysis.

Dealing with missing data

Vish 2001 lacked standard deviations for the data that had been adjusted for co-intervention use. The author's co-variate analysis of the effect of co-interventions on pain outcomes had shown no significant difference and the use of unadjusted data in meta-analysis was therefore judged as appropriate (Plummer 2006). However, standard deviations for the unadjusted 'no injection' and placebo group data were not available. These two groups had been combined to create one 'control group' in the published study. Attempts to obtain missing data from the author were unsuccessful and meta-analysis using the pooled control group data was unavoidable. There were inconsistencies in the published means for these data as the text reported mean pain scores of 2.9 for the saline group and 3.73 for control (Vish 2001, p49). The mean for these pooled groups should be 3.3 but was recorded as 3.667 in Table 8 (Vish 2001). The author has not been able to resolve this discrepancy. As standard deviation (SD) data were only available from the Table, we selected the mean of 3.667 (Vish 2001, Table 8) for use in Comparison 01.01. Clinically, the discrepancy between the two means is small.

Assessment of heterogeneity

We analysed statistical heterogeneity using the I^2 statistic and χ^2 test on N-1 degrees of freedom, for which we defined a P value of less than 0.1 as significant heterogeneity. Prior to the pooling of data, we considered potential clinical heterogeneity such as differences in dose of lignocaine, method of compression, use of retrospective pain measurement and use of placebo versus no intervention in the control arm.

Data synthesis

Meta-analysis used the fixed-effect model, which utilises the inverse variance approach to combine results of studies. It was not possible to determine the effect of pain relief on complication rate by meta-analysis as there was wide variation in the way complications were measured and reported. A narrative analysis of the key findings from primary studies was therefore provided.

RESULTS

Description of studies

Results of the search

The initial search yielded 85 studies from which we identified 10 possible studies. This update has identified no new studies. The ongoing study (Cook 2007) identified in the 2008 review is now completed but no study data are available (see the 'Characteristics of studies awaiting classification').

Included studies

Four studies were suitable for inclusion (see 'Characteristics of included studies' table).

Participants

In the four studies, there were a total of 971 participants, all of whom met the inclusion criteria having coronary artery disease, age of 18 years or over, and undergoing femoral sheath removal following Percutaneous Coronary Intervention (PCI). The median age was 64.8 years (Fulton 2000), mean age 63.6 years (Timlin 2005), mean age 50 to 62 years (Kiat Ang 2007) or over 50 years in 82% of patients (Vish 2001). Where reported, the majority of participants were male (Fulton 2000; Kiat Ang 2007; Vish 2001) with this difference being statistically significant in one study (Kiat Ang 2007). Femoral sheath removal was performed by medical (Fulton 2000) or nursing staff (Kiat Ang 2007; Timlin 2005; Vish 2001). In all participants sheaths were removed within four to six hours after the procedure. Sheath size was unreported in one study (Kiat Ang 2007) but was 6 or 8 French in 93% (291/310) of participants in the other three studies. Method of achieving haemostasis varied between manual pressure (Fulton 2000), C-Clamp (Vish 2001), assisted manual compression with FemoStop (Kiat Ang 2007) and manual pressure with or without FemoStop (Timlin 2005). Prior patient experience of sheath removal was recorded as 20% in one study (Vish 2001) and a non-significant difference between groups in another (Timlin 2005).

Interventions

The interventions used for relief of pain and discomfort were opioid, local anaesthetic and anxiolytic; see 'Characteristics of included studies' table. Timlin 2005 compared subcutaneous levobupivacaine with a matched placebo. Fulton 2000 compared intravenous morphine with intravenous fentanyl with lignocaine with intravenous saline placebo. Vish 2001 compared buffered lignocaine with lignocaine with intravenous saline placebo with no injection. Kiat Ang 2007 compared intravenous sedation (fentanyl and midazolam) with lignocaine with both intravenous sedation

and lignocaine with neither. In all studies involving lignocaine this was given subcutaneously immediately prior to sheath removal; levobupivacaine was administered immediately following PCI.

Outcomes

Pain scores were evaluated using a zero to 100 Visual Analogue Score (VAS) (Fulton 2000), a zero to 10 VAS scale (Kiat Ang 2007; Timlin 2005) and zero to 10 hospital chest pain scale which is equivalent to an 11-point Numerical Rating Score (NRS). In all pain scales, higher numbers represented greater pain.

Real time assessment of pain during sheath removal occurred in two studies as follows: one minute and 20 minutes postremoval (Fulton 2000); on C-Clamp application and 30 minutes postremoval (Vish 2001). The other studies collected data retrospectively. Pain data in the Kiat Ang 2007 study were recorded as the worst episode of pain during sheath removal, and were measured after FemoStop removal. In Timlin 2005, patients were interviewed the following morning when pain scores were recorded for three time points: sheath insertion; waiting for removal; and sheath removal. Patients were asked how painful the process of sheath removal was therefore pain score data would reflect pain experienced from both the withdrawal of the sheath and any subsequent pressure (Leslie 2006).

Excluded studies

We excluded five studies as two were non-randomised, two had an anaesthetic infusion sleeve as the intervention, and data were unavailable for an unpublished study; see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

Two review authors (CW and MM or SP) independently assessed each study. We agreed on a consensus score in consultation with BK. Details of the methodological quality for each included study are given in the 'Characteristics of included studies' table and presented in the 'Risk of bias' graph (Figure 1).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

The method of random sequence generation and allocation concealment was unclear in one study and attempts to contact the author for clarification were unsuccessful (Fulton 2000). In another study, the randomisation method was stated as "manual blocks of ten" although the exact method of sequence generation was not provided. Allocation concealment was also unclear; sealed envelopes were used but it could not be established whether these were sequentially numbered or allocated using a third party (Kiat Ang 2007). Inadequate allocation concealment can overestimate treatment effects by as much as 30% (Schultz 1995). Both of these studies were involved in the comparison of intravenous pain regimen with control and an overestimation of treatment effect cannot be ruled out.

Blinding

Intravenous regimens

The intravenous arms were appropriately blinded in Fulton 2000 but no blinding was used in Kiat Ang 2007. It is possible that lack of blinding could have contributed to the size of the treatment effect observed with the intravenous pain regimen in Kiat Ang 2007, although one would expect an over-estimation in the lignocaine intervention arm as well.

Subcutaneous lignocaine

In Fulton 2000, the subcutaneous lignocaine intervention was prepared and administered by the outcome assessor, and did not have a matched placebo. The Vish 2001 study had two blinded subcutaneous treatment arms and one matched placebo. However, there was the potential for un-blinding as the syringes were identified by a simple code that, if broken, could identify the active study intervention for future participants. No treatment assignments were blinded in Kiat Ang 2007. An overestimation of the effect in an unblinded lignocaine group is of limited relevance because there was no statistically significant difference in favour of lignocaine in the primary studies.

Levobupivacaine

In the Timlin 2005 study, a matched placebo was used but the blinding of participants and outcome assessors could potentially have been broken as stickers were placed in the chart and on the leg of the participants receiving levobupivacaine. A false-positive error cannot therefore be ruled out.

Incomplete outcome data

One study confirmed intention-to-treat (ITT) analysis and no withdrawals (Timlin 2005). However, we considered all included studies to have complete outcome data as no withdrawals or dropouts were identified in the results tables and the very short duration of follow-up made this unlikely.

Selective reporting

All pre-specified primary and secondary outcomes were reported in all included studies (Fulton 2000; Kiat Ang 2007; Timlin 2005; Vish 2001), however, Fulton 2000 did not provide secondary outcome data by treatment group meaning that meta-analysis was not possible. Meta-analysis of secondary outcome data was unlikely to change the overall conclusions of this review as the number of complications were small, opportunities for meta-analysis limited,

and non-significant findings by treatment group were reported in all four studies. Overall, we considered risk of bias from selective reporting low.

Other potential sources of bias

Administration of co-interventions

Co-interventions were present in all studies. Opioids and anxiolytics were administered to participants on an as-needed basis almost certainly before randomisation (Vish 2001), or after randomisation but before sheath removal (Timlin 2005) and as rescue analgesia on an as-needed basis for breakthrough pain experienced during the sheath removal procedure (Fulton 2000; Kiat Ang 2007; Timlin 2005).

Pre-randomisation administration

In Vish 2001 adjusted analysis was performed for co-intervention use but these data could not be used for meta-analysis as not all standard deviations were published (refer to the section on 'Dealing with missing data'). However, as co-variate analysis of the effects of the co-interventions by the author had shown no significant difference to the pain outcome we therefore judged the use of unadjusted data in meta-analysis as appropriate (Plummer 2006).

Administration during sheath removal

Opioids given on an as-needed basis for breakthrough pain during the sheath removal procedure, and therefore after the study treatment, may bias the estimate of effectiveness if given preferentially to a particular treatment arm. There were no significant differences between groups in the use of rescue analgesia for breakthrough pain in the Fulton 2000 and Kiat Ang 2007 studies. In Timlin 2005 opioids were given on an as-needed basis after randomisation but no statistical adjustment was made for potential differences in opioid use between the two study arms. More participants in the control group (11/30, 37%) received morphine than in the intervention group (2/30, 7%). However, a statistically significant reduction in pain scores was demonstrated in the group given levobupivacaine, despite increased morphine use by those in the control group.

Use of placebo

The placebo effect has been associated with a reduction in the self report of pain (Sauro 2005; Vickers 2000). The placebo arms may, therefore, have resulted in an underestimation of the effect of the active interventions used in the included studies. Conversely, no expectation of pain relief administration may result in an increased perception of pain in an unblinded control group. Certainly, higher than expected mean pain scores have been observed when pain relief has not been given before sheath removal in a research setting (Mlekusch 2006; Vish 2001). A meta-analysis of the treatment effect using a control only group as a comparison was not possible in this review.

Timing of pain score measurements

Determining the exact time of pain score measurement and whether participants were receiving compression at the time was problematic. This issue was compounded by the use of retrospective pain measurement. The timing of pain measurement is of particular relevance as pain and discomfort associated with femoral sheath removal is time-dependent (Chlan 2005; Fulton 2000). An increase in pain score is experienced at one minute from

baseline with return to baseline levels occurring at 10 minutes and to minimal levels 10 minutes after release of compression. The pain on C-Clamp application (Vish 2001) and at one minute (Fulton 2000) would represent the most painful part of the procedure. Pain data in the Kiat Ang 2007 study were stated as representing the worst episode of pain during sheath removal. Meta-analysis was considered appropriate for data from these time points as it was judged to reflect the most painful part of the procedure.

Both the Kiat Ang 2007 and Timlin 2005 studies used retrospective pain data measurements. There is some evidence that indicates that patients remember the worst part of the pain and the final part of the procedure (Redelmeier 1996) and that patient recall of acute painful procedures is accurate for at least one week (Singer 2001). However, it is noted that pain measured using patient recall may not accurately describe the pain experienced at the time of the procedure. The possible impact on the treatment effect from retrospective outcome measurements is unclear.

Two studies measured pain scores while the participants were receiving compression (Fulton 2000; Vish 2001) but this could not be clearly ascertained in the Timlin 2005 and Kiat Ang 2007 studies. These participants were asked to score their worst pain (Kiat Ang 2007), or pain experienced during sheath removal (Timlin 2005) and it was judged that the pain scores in these studies would be while the participant was receiving compression.

Lignocaine dose

Doses of lignocaine in the included studies ranged from 50 mg to 100 mg. These doses are within the recommended dose range (Sweetman 2005) and do not appear to be an explanation for the non-significant reduction in pain observed with lignocaine.

Skewed data

The data from the primary studies had a skewed distribution. This was evident from the standard deviations that were of similar magnitude to the means, although scales had a lower limit of zero. In all comparisons, however, the single mean score was based on about 30 observations. This was considered sufficient to ensure a near normal distribution for the differences between group means, so that consequences of skewness would be minimal (Plummer 2006a).

Effects of interventions

In the three comparisons we pooled the one-minute data (Fulton 2000), pain on C-Clamp data (Vish 2001) and pain score data 'during' sheath removal, describing the worst episode of pain during sheath removal (Kiat Ang 2007). It was assumed that these scores would consistently represent the highest level of pain for all three studies. All pain scores were reported using a one to 10 pain scale with higher pain scores representing more pain.

Subcutaneous lignocaine compared with control

Three studies (four treatment arms) involving 498 participants were involved in this analysis. Lignocaine doses ranged from 50 mg (Kiat Ang 2007) to 100 mg (Fulton 2000; Vish 2001) and included a buffered lignocaine group equating to 66.7 mg (Vish 2001). There was no statistically significant difference between pain scores of participants administered subcutaneous lignocaine when compared to those in the control group; mean difference (MD) 0.12 (95% confidence interval (CI) -0.46 to 0.69). For all groups the pain

intensity was relatively mild with mean pain scores ranging from 1.88 to 4.10 in the lignocaine groups and 2.67 to 3.67 in the control group. Heterogeneity was slight but not significant with $I^2 = 22.5\%$ and $P = 0.28$ (see Comparison 01.01: Analysis 1.1).

Intravenous pain regimen compared with control

Meta-analysis involved two studies (three treatment arms) with a total of 399 participants. Three-quarters (303/399) of these participants came from a single study using a fentanyl and midazolam combination (Kiat Ang 2007). The other two treatment arms consisted of morphine only and fentanyl only (29 and 37 participants respectively) (Fulton 2000). Meta-analysis showed a statistically significant reduction in pain scores for intravenous pain relief when compared with control; MD -0.90 (95% CI -1.54 to -0.27). We performed subgroup analysis to test and visualise the treatment effect obtained from combining midazolam with opioid in a pain regimen compared to the effect observed with opioid only (Comparison 02.01: Analysis 2.1).

Subcutaneous levobupivacaine compared with control

One study involving 60 participants showed that there was a statistically significant reduction of 1.10 in pain score for levobupivacaine when compared with control; mean difference of -1.10 (95% CI -1.26 to -0.94) (see Comparison 03.01: Analysis 3.1).

Use of rescue analgesia

Analgesia given as a co-intervention on an as-needed basis for breakthrough pain during sheath removal was measured in three studies. The definition of breakthrough pain, or the threshold for treatment, was not provided in any study. Pain scores that defined when this was given were not provided. Rescue analgesia was administered to 8.5% of participants (11/130) (Fulton 2000) and 6.8% (11/161) to 11.8% participants (18/153) (Kiat Ang 2007). There were no significant differences in fentanyl use between groups. In Timlin 2005, 6.7% (2/30) of participants had morphine either in the four to six hours prior to sheath removal or during the removal procedure itself, while 36.7% (11/30) received morphine in the control group over this time period.

Complications

Vascular and procedural complications were reported in all included studies. Meta-analysis was not possible due to the wide variation in the way complications were measured and reported. Primary analysis indicated that there was no significant statistical correlation between the pain regimens reviewed and the type or incidence of vascular or procedural complications.

Nausea and vomiting

The incidence of nausea and vomiting was measured in two studies (Fulton 2000; Timlin 2005). Fulton 2000 had an overall incidence of nausea and vomiting of 8% (10/130). Chi² tests and analysis of variance showed no significant differences among the four treatment groups. Timlin 2005 reported this outcome only for participants who had received morphine.

Vasovagal reaction

Vasovagal reaction was measured in three studies (Fulton 2000; Kiat Ang 2007; Vish 2001). Primary analysis showed no significant differences in the incidence of a vasovagal reaction across the treatment groups but the numbers were small. Kiat Ang 2007

reported a 5.7% incidence (35/ 611) with 60% (21/35) treated with atropine, 89% (31/35) receiving a bolus of intravenous fluids and 9% (5/35) receiving metoclopramide. There was a lower incidence of vasovagal reaction for participants receiving intravenous pain relief 4% (12/297), compared with those not receiving the intravenous intervention 7% (23/314) with $P = 0.08$. The incidence of a vasovagal reaction requiring atropine was 6% (8/130) in [Fulton 2000](#) and 1.6% (2/120) in [Vish 2001](#).

Vascular complications

Vascular complications were measured in all studies with no correlation found between their incidence and the pain regimen or pain score. [Fulton 2000](#) reported haematoma development in 28% (36/130) of participants. [Timlin 2005](#) reported no haematomas greater than 5 cm in size and one small pseudoaneurysm. [Vish 2001](#) rated vascular complications on a zero to four scale where zero = no complications and four = fistula. The means for each treatment group were small (buffered lignocaine 0.18, lignocaine 0.13 and control group 0.007). The [Kiat Ang 2007](#) study reported the incidence of vascular complications as: femoral pseudoaneurysms (14 participants); arteriovenous fistulas (six participants); and a non-occlusive femoral venous thrombosis (one participant).

Patient satisfaction

Only one study measured participant satisfaction outcomes ([Vish 2001](#)). Satisfaction with the procedure was measured on a scale of one to five where one is "strong disagreement to being satisfied and five is strong agreement that it has been a satisfying experience" ([Vish 2001](#), p15). A statistically significant difference in satisfaction with the clamp was seen with lignocaine (buffered lignocaine and lignocaine) compared to control (placebo and no injection). Co-variate analysis showed a positive effect of anxiolytic with this result.

DISCUSSION

Summary of main results

As no new studies have been found the findings from the last version of this review remain unchanged.

A statistically significant reduction in pain score was observed with the intravenous pain regimen when compared with control; mean difference (MD) -0.90 (95% confidence interval (CI) -1.54 to -0.27). A statistically significant reduction of 1.10 in pain score was also observed in the primary study comparing levobupivacaine with control; MD -1.10 (95% CI -1.26 to -0.94). Data from the meta-analysis were insufficient to assess the hypothesis that administration of pain relief reduces the incidence of vascular or other complications associated with femoral sheath removal because very few complications were recorded. It was not possible to determine whether the type of pain relief influenced the incidence of complications as either complication data were not available per intervention, or measurements were inconsistent between studies. Multivariate logistic regression analysis in one study identified a higher pain score (odds ratio (OR) 1.18, 95% CI 1.12 -1.24, $P = 0.001$), use of glyceryl trinitrate during sheath removal, a low body mass index, and the left anterior descending artery as the treated vessel as independent predictors of the occurrence of a vasovagal reaction ([Kiat Ang 2007](#)). There was no evidence of a relationship between infiltration of local anaesthetic and adverse events but the numbers of adverse events were small.

Overall completeness and applicability of evidence

The effectiveness of pain regimens is dependent on a number of independent variables that may impact on the experience of pain associated with femoral sheath removal. These may include the expertise of the clinician administering the lignocaine and the length of time waited for it to take effect, the effectiveness of general comfort measures, the level of participant preparation and the participant's expectation of pain, the expertise and confidence of the person pulling the sheath, prior experience of the participant and the environment in which the procedure is performed. Many of these variables were not reported in the primary studies.

The generally mild to moderate pain experienced by the participants make the impact of any intervention more difficult to evaluate ([Collins 1997](#)). In addition, interpretation of the clinical significance of the statistically significant reduction in pain score observed is difficult as the size of the reduction is small. Estimates of a clinically relevant pain reduction have been developed for participants experiencing pain of traumatic and non-traumatic aetiology. The Minimum Clinical Significant Difference (MCSD) ranges from a reduction of 0.9 (CI 0.6 to 1.3) on a zero to 10 Visual Analogue Scale (VAS) ([Kelly 1998](#)) to 1.39 (1.0 to 1.7) on a Numerical Rating Score (NRS)-11 ([Kendrick 2005](#)). Procedural pain tends to be short-lived and non-cumulative in nature ([Puntillo 2001](#)) and while the MCSD may be appreciably different it has not been calculated for pain of this aetiology. However, the estimation above may be useful in exploring the clinically relevant reduction in pain score for these participants. For example, it is estimated that the mean MCSD ranges from 0.9 (zero to 10 VAS) to 1.39 (NRS-11). As these estimates are of a comparable magnitude to estimates of mean pain reductions achieved with intravenous pain relief and levobupivacaine, it would be expected that some clinically relevant pain reduction can be experienced by at least some patients. The decision to administer pain relief therefore requires consideration of the clinical significance of any reduction in pain achieved. This should be balanced by awareness that pain responses can vary considerably between individuals and consideration of the benefits of pain relief when compared to the likelihood of side effects without it.

The meta-analysis of data for vascular and procedural complications was not possible. Analysis in the included studies indicated no correlation between pain relief administration and adverse events or complications, although a higher pain score was identified as one of several independent predictors of a vasovagal event during femoral sheath removal ([Kiat Ang 2007](#)). The association of a vasovagal event with major adverse clinical events (MACE) has traditionally been stated as the rationale for the routine use of pain relief. [Juergens 2008](#) explored this association by extending the follow-up of the 661 participants undergoing Percutaneous Coronary Intervention (PCI) in the [Kiat Ang 2007](#) study included in this review. No increase in MACE was observed at 30-day follow-up in the 35 (7.7%) participants who had experienced a vasovagal event at sheath removal. No other publications have explored this issue beyond case reports ([Barbiere 1994](#); [Ilia 1997](#)). Although the [Juergens 2008](#) study is limited by the small number of events, it indicates that routine use of pain relief for the purpose of preventing MACE is not well supported in the stent era.

Prior to the initial publication of this review a survey of practice from 54 sites in Australia and New Zealand identified considerable variation in analgesic regimens used for femoral sheath removal

after PCI (Sanders 2005). A 2009 survey of Australian and New Zealand cardiovascular nurses indicates that, in those countries at least, practice diversity continues (Rolley 2010). However, a preference for mild opioid analgesia (with or without sedation) emerged with 50.9% (56/110) of respondents selecting this option. Non-opioid pain relief was selected by 29.1% (32/110) suggesting a marked reduction from four years earlier when, if pain relief was to be administered, 46% (16/35) administered lignocaine (alone or in combination with opioids) prior to femoral sheath removal (Sanders 2005). There also appears to be a small shift away from protocol-driven analgesia in preference to an 'as-needed' prescription that enables nurses to administer pain relief based on clinical judgement (Delphi Consensus Discussion 2009). The absence of strong evidence of effectiveness may give nurses more confidence to use clinical judgement, informed by individualised patient assessment, when making the decision to administer pain relief. Such practice decisions are congruent with the recommendations, derived from both the evidence and clinical expert consensus, in a recently published nursing clinical practice guideline for the care of people undergoing percutaneous coronary interventions (Rolley 2011). With the increasing use of radial access the challenge is to maintain the skills that support clinical judgement.

Quality of the evidence

The main limitations of these findings are the small numbers of studies involved and the methodological weaknesses in the studies. In particular, successful blinding is very important in trials with subjective outcomes such as pain scores (Schulz 2002) and assessment of risk of bias placed particular emphasis on appropriate blinding. No trials reported appropriate blinding for all treatment arms involved. Unsuccessful blinding can exaggerate treatment effects by 17% (Juni 2001) and this may be sufficient to produce a type one or false-positive error. Even with a possible overestimation of treatment effect, the size of any statistically significant reduction in pain scores observed was small.

Potential biases in the review process

Although we used a comprehensive search strategy we cannot rule out the possibility that smaller unpublished studies such as PhD or Masters theses have been missed. However, two unpublished randomised controlled trials were identified and one of these, an unpublished thesis located from Digital Dissertations, was included in the review (Vish 2001). The other was a protocol listed in ClinicalTrials.gov (Cook 2007). This RCT is now completed but we have not been able to obtain any data, although it appears that it was a small study with recruitment stopping early after recruitment of 78 participants. Smaller studies do tend to have results that differ from larger studies (Sterne 2000) and this is true to some extent for the smaller studies involved in our review. These differences can simply be due to random effects of chance (Moore 1998). This may be the reason here as, with the possible exception of Timlin 2005, the over-exaggeration of effect from methodological limitations associated with smaller studies (Nuesch 2010; Sterne 2000) was not especially apparent. The results of the more precise and larger study (Kiat Ang 2007) currently dominate the conclusions reached for the main outcome, although this too has methodological limitations. While we cannot rule out that the addition of a number of small, methodologically sound studies would not change our conclusions, it seems unlikely that unpublished RCTs would be present in sufficient numbers for this to occur with any degree of

accuracy, or with treatment effects large enough to be clinically relevant.

A bias for publishing studies with statistically significant results does not necessarily apply to this review. As the predominant practice has been to administer analgesia for femoral sheath removal, studies that suggest that this intervention is not effective may have been considered to be of more interest, and therefore more likely to be published. Of the two smaller published studies one showed statistical significance for an innovative therapy (Timlin 2005) while the other (Fulton 2000) reported non-significant findings. We considered the number of studies involved in this review too few for meaningful analysis of publication bias by funnel plot asymmetry.

Agreements and disagreements with other studies or reviews

Intravenous pain regimens did not produce a consistent response across the two studies involved in meta-analysis (Comparison 02.01: Analysis 2.1). We performed subgroup analysis to test the effect of combining opioid-only with opioid and anxiolytic data. Visually the forest plot suggests that the addition of midazolam may be an important aspect of the effectiveness of the intravenous pain regimen. However, as there is no significant ($P = 0.67$) or appreciable ($I^2 = 0\%$) heterogeneity over the trials with and without midazolam there is no quantitative evidence to support this. The finding that morphine, as a co-intervention, had no impact on the estimate of treatment effect could also suggest that opioid alone may not produce a reduction in pain score. However, the small number of participants (13/60) who received morphine in the Timlin 2005 study meant that no firm conclusion can be drawn.

The non-significant reduction in pain intensity observed with subcutaneous lignocaine was consistent with the results from two non-randomised trials (Bowden 1995; Wadas 1998). Wadas 1998, in a non-randomised, non-blinded study involving 50 participants undergoing femoral sheath removal, compared the effectiveness of 4 mg intravenous morphine (25 participants with coronary stent) with 4 mg morphine plus 10 ml of 1% lignocaine (25 participants after angioplasty). There was no statistically significant difference between groups indicating that the addition of lignocaine to the pain regimen was not beneficial to participant comfort. The pain intensity score published for the entire sample was 2.0 ± 2.1 (zero to 10 VAS) immediately after the release of manual pressure. Bowden 1995 evaluated the comfort levels of 111 non-randomised participants undergoing sheath removal after PCI. Comfort levels were acceptable (able to lie still; regular calm respirations with oxygen saturations $> 90\%$; self report of pain at zero to three on a zero to 10 scale) in 95% (105/111) of participants without local infiltration of lignocaine.

AUTHORS' CONCLUSIONS

Implications for practice

The implications are unchanged from the original review.

Intravenous pain regimens and subcutaneous levobupivacaine appear to produce reductions in pain score not seen with subcutaneous lignocaine or control. However, interpretation of the clinical relevance of these findings is difficult as the size of the reduction is small and the size of a clinically important reduction in

procedural pain is not known. This review did not demonstrate any correlation between pain relief administration and either adverse events or complications.

In the absence of a definitive finding, clinical judgement and consideration of patient preference is required to identify those who may potentially benefit from pain relief. The mild level of pain generally experienced during this procedure should not influence the decision to consider pain relief as it is evident from the range of pain scores that some people experience moderate levels of pain.

Clinical judgement is informed by an assessment of factors that are thought to impact on the individual's pain experience. During sheath removal these factors may include the patient's past experiences of procedure-related pain, the level of anxiety, the effectiveness of basic comfort measures prior to the procedure, existing vascular complications such as haematoma, the extent of patient preparation, the patient-practitioner therapeutic relationship and the clinical setting. However, information on how these aspects may influence the participant's experience is lacking. Where analgesic requirement is anticipated, administration before the procedure rather than in reaction to breakthrough pain is considered good practice.

Implications for research

To determine the effectiveness of intravenous pain regimens further evaluation is warranted by means of an adequately powered randomised controlled trial with appropriate blinding. The success of blinding should be tested and reported. A clinically

relevant threshold for pain reduction is required to interpret the results. Given the higher pain intensity reported in trials using no intervention (that is no placebo) as a control, inclusion of a 'no intervention' arm may be of value. The extent to which the placebo effect contributes to the true treatment effect requires measurement against a control of no treatment. The accuracy of pain scores obtained by participant recall, compared to real time assessment, should be ascertained before choosing the method of pain score measurement. To enable meta-analysis of secondary outcomes, complication rates of femoral sheath removal should be reported by treatment group using standardised definitions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Fulton 2000

Methods	Randomised trial, parallel-group design with 4 comparisons
Participants	130 patients. Femoral sheath removed by medical staff 4 to 6 hours after elective or urgent PCI. Manual compression. Median age 64.8 years. 72% males. 20% had previous experience of sheath removal.
Interventions	IV morphine 0.05 mg/kg or IV fentanyl 0.5 µg/kg or SC lignocaine 2% 5 ml (100 mg) or IV saline placebo Rescue analgesia (fentanyl) was made available to all groups
Outcomes	Pain score using VAS during sheath removal (10 minutes prior, 1 minute and 20 minutes after) Secondary outcomes: use of rescue analgesia; incidence of haematoma and vascular complications, vasovagal reactions, nausea and vomiting Pain scores from patients given analgesia (SC lignocaine, IV morphine, IV fentanyl) were not significantly different from pain scores in placebo group
Notes	Quality score 2/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated, sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported. Efforts to obtain additional information from author were unsuccessful.
Blinding (performance bias and detection bias) Subcutaneous lignocaine	High risk	No subcutaneous placebo
Blinding (performance bias and detection bias) Intravenous pain regimens	Low risk	Appropriate blinding of participants, clinicians and assessors for intravenous arms (IV placebo, mixed in pharmacy and diluted to same volume)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting for primary outcomes. Data were not reported by treatment group for secondary outcomes. This meant that meta-analysis was not possible but this is unlikely to change the conclusions of the review.
Other bias	Low risk	Statistical adjustment performed for use of fentanyl as co-intervention

Fulton 2000a

Methods	Refer to Fulton 2000
Participants	Refer to Fulton 2000
Interventions	SC lignocaine 2% 5 ml (100 mg) or IV saline placebo

Fulton 2000a (Continued)

Rescue analgesia (fentanyl) was made available to all groups

Outcomes	Refer to Fulton 2000
Notes	Refer to Fulton 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated, sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported. Efforts to obtain additional information from author were unsuccessful.
Blinding (performance bias and detection bias) Subcutaneous lignocaine	High risk	No subcutaneous placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting for primary outcomes. Data were not reported by treatment group for secondary outcomes. This meant that meta-analysis was not possible but this is unlikely to change the conclusions of the review.
Other bias	Low risk	Statistical adjustment performed for use of fentanyl as co-intervention

Fulton 2000b

Methods	Refer to Fulton 2000
Participants	Refer to Fulton 2000
Interventions	IV morphine 0.05 mg/kg or IV saline placebo Rescue analgesia (fentanyl) was made available to all groups
Outcomes	Refer to Fulton 2000
Notes	Refer to Fulton 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated, sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported. Efforts to obtain additional information from author were unsuccessful.
Blinding (performance bias and detection bias)	Low risk	Appropriate blinding of participants, clinicians and assessors for intravenous arms (IV placebo, mixed in pharmacy and diluted to same volume)

Fulton 2000b (Continued)

Intravenous pain regimens

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting for primary outcomes. Data were not reported by treatment group for secondary outcomes. This meant that meta-analysis was not possible but this is unlikely to change the conclusions of the review.
Other bias	Low risk	Statistical adjustment performed for use of fentanyl as co-intervention

Fulton 2000c

Methods	Refer to Fulton 2000
Participants	Refer to Fulton 2000
Interventions	IV fentanyl 0.5 µg/kg or IV saline placebo Rescue analgesia (fentanyl) was made available to all groups
Outcomes	Refer to Fulton 2000
Notes	Refer to Fulton 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated, sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported. Efforts to obtain additional information from author were unsuccessful.
Blinding (performance bias and detection bias) Intravenous pain regimens	Low risk	Appropriate blinding of participants, clinicians and assessors for intravenous arms (IV placebo, mixed in pharmacy and diluted to same volume)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting for primary outcomes. Data were not reported by treatment group for secondary outcomes. This meant that meta-analysis was not possible but this is unlikely to change the conclusions of the review.
Other bias	Low risk	Statistical adjustment performed for use of fentanyl as co-intervention

Kiat Ang 2007

Methods	Randomised, parallel-group design with 4 comparisons
Participants	661 patients undergoing femoral sheath removal. Removal by experienced dedicated angioplasty research nurse 4 to 6 hours after PCI using assisted manual compression with FemoStop device. Mean age range 59 to 62 years. Males 66.5% to 86%
Interventions	IV sedation (fentanyl 25 mcg and midazolam 1 mg) or lignocaine 1% 5 ml infiltrated around the sheath site or both or neither. Additional doses of analgesia were available on request for any participant experiencing breakthrough pain after sheath removal (fentanyl 0.5 µg/kg to a maximum of 50 µg)
Outcomes	Patient comfort during sheath removal (VAS 0 to 10 scale), use of rescue analgesia; incidence of vasovagal reaction and vascular complications There was a significant difference in pain scores across the 4 groups. Mean pain score was highest in the local anaesthetic only arm (4.1 ± 3.4) and lowest in the IV sedation only arm (2.5 ± 3.3). There were no significant difference in the number of patients requesting additional analgesia, incidence of vasovagal reaction or vascular complications.
Notes	Quality score = 2/5 Additional information obtained from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Probably random: contact with author states randomised using manually generated blocks of 10 although actual method of sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	Allocation via blinded sealed envelopes but involvement of 3rd party not stated.
Blinding (performance bias and detection bias) Subcutaneous lignocaine	High risk	Neither participants or the angioplasty research nurse were blinded. Outcome assessors blinded for vascular complications only.
Blinding (performance bias and detection bias) Intravenous pain regimens	High risk	Neither participants or the angioplasty research nurse were blinded. Outcome assessors blinded for vascular complications only.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	Statistical adjustment performed for fentanyl co-intervention. Pain assessed at the end of FemoStop removal - patient asked to rate their worst episode of pain.

Timlin 2005

Methods	Randomised double-blind, parallel-group, placebo control
Participants	60 patients undergoing femoral sheath removal 4 to 6 hours after PCI. Manual compression with or without FemoStop. Mean age 63.6 years. Sheath size: 6 French. Number of previous femoral punctures mean (SD) 0.9 (0.2) in control group and 1.2 (0.2) in intervention group.
Interventions	Levobupivacaine 10 ml 0.5% SC immediately after PCI or matched saline placebo Both groups received usual care of IV morphine and metoclopramide on an as-needed basis during sheath removal
Outcomes	Pain score before and during sheath removal using 0 to 10 VAS; morphine use; vascular and procedural complications Pain scores were lower in the levobupivacaine group during sheath removal (2.2 ± 0.4) compared with placebo (1.1 ± 0.2) ($P = 0.02$) Co-interventions: morphine use at the time of sheath removal was greater in the placebo group 11/30, compared with levobupivacaine patients (2/30) (exact time not stated)
Notes	Quality score 3/5 Additional information obtained from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) Levobupivacaine	High risk	Clinicians not blinded, participants and outcome assessors blinded but possible that blinding could be broken as levobupivacaine group identified by a sticker on the participants leg and in the clinical record
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No statistical adjustment for morphine use for breakthrough pain during sheath removal, however data for co-intervention use published Retrospective pain scores measurement by interview the following morning

Vish 2001

Methods	Randomised trial, double-blind, parallel-group design with 4 comparisons (3 subcutaneous and a 'no injection' group)
Participants	N = 120. Adults undergoing femoral sheath removal by nursing staff 4 to 6 hours after elective PCI. Sheath size of 6 or 8 French in 84% of participants. Method of haemostasis used: C-Clamp. Age: 42% > 65 years 73% males.

Vish 2001 (Continued)

Interventions	SC buffered lignocaine (0.67% lignocaine and 1.3% soda bic) 10 ml or SC lignocaine 1% 10 ml or SC saline placebo 10 ml or no injection Opioid and anxiolytic administered on an as-needed basis prior to randomisation
Outcomes	Pain score at C-clamp application and at 30 minutes using 0 to 10 Hospital Chest Pain Score; site complications (oozing, haematoma, pseudoaneurysm, fistula); vasovagal reaction; patient satisfaction Mean pain score for pain on clamp application was buffered lignocaine 3.5 ± 3.29 ; lignocaine 4.06 ± 3.14 , saline 2.9 (no SD supplied)*, no injection 3.73 (no SD supplied)* No significant differences found between the 4 groups for pain score, site complications, vasovagal reaction and patient satisfaction
Notes	* as SDs were not available we used the pain scores for saline and no injection group combined (as published) in meta-analysis Efforts to obtain additional information from author were unsuccessful Quality score 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly numbered squares
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) Subcutaneous lignocaine	Unclear risk	Blinding of patient, clinicians and assessors but could be potentially broken as syringes were labelled in pharmacy using a code that identified the study arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	Adjusted analysis for co-interventions performed but standard deviations not published; pooled data for these 2 groups had to be used in the meta-analysis

Vish 2001a

Methods	Refer to Vish 2001
Participants	Refer to Vish 2001
Interventions	SC lignocaine 1% 10 ml or SC saline placebo 10 ml or no injection Opioid and anxiolytic administered on an as-needed basis prior to randomisation
Outcomes	Refer to Vish 2001
Notes	Refer to Vish 2001

Vish 2001a (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly numbered squares
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) Subcutaneous lignocaine	Unclear risk	Blinding of patient, clinicians and assessors but could be potentially broken as syringes were labelled in pharmacy using a code that identified the study arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	Adjusted analysis for co-interventions performed but standard deviations for 'placebo' and 'no injection' group pain outcomes were not published; pooled data for these 2 groups had to be used in the meta-analysis

Vish 2001b

Methods	Refer to Vish 2001
Participants	Refer to Vish 2001
Interventions	SC buffered lignocaine (0.67% lignocaine and 1.3% soda bic) 10 ml Opioid and anxiolytic administered on an as-needed basis prior to randomisation
Outcomes	Refer to Vish 2001
Notes	Refer to Vish 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly numbered squares
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) Subcutaneous lignocaine	Unclear risk	Blinding of patient, clinicians and assessors but could be potentially broken as syringes were labelled in pharmacy using a code that identified the study arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts

Vish 2001b (Continued)

Selective reporting (re-reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	Adjusted analysis for co-interventions performed but standard deviations for 'placebo' and 'no injection' group pain outcomes were not published; pooled data for these 2 groups had to be used in the meta-analysis

IV: intravenous

N/A: not applicable

PCI: Percutaneous Coronary Intervention

SC: subcutaneous

SD: standard deviation

VAS: Visual Analogue Scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bowden 1995	Non-randomised study
Deane 2002	Research completed on approximately 20 patients with IV diazepam as the intervention. Efforts to obtain data were unsuccessful
Lambert 1996	Anaesthesia infusion sleeve
Lambert 1997	Anaesthesia infusion sleeve
Wadas 1998	Case control study

Characteristics of studies awaiting assessment [ordered by study ID]

Cook 2007

Methods	Randomised controlled trial
Participants	Aimed for 200 participants undergoing removal of femoral arterial sheath after percutaneous coronary intervention (PCI)
Interventions	Subcutaneous local anaesthetic (lidocaine 2% without epinephrine) or no local prior to removal of femoral arterial sheath
Outcomes	Incidence of vasovagal reaction during femoral sheath removal Pain intensity during femoral sheath removal
Notes	Study located via ClinicalTrials.gov. Study NCT00465439. It is catalogued as Completed; "No study results posted". Efforts to obtain data from author contact have been unsuccessful. This study appears to have enrolled 78 participants before closure

DATA AND ANALYSES

Comparison 1. Effect of subcutaneous lignocaine (buffered, unbuffered) compared with control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score on a 0 to 10 scale after sheath removal	4	498	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.46, 0.69]

Analysis 1.1. Comparison 1 Effect of subcutaneous lignocaine (buffered, unbuffered) compared with control, Outcome 1 Pain score on a 0 to 10 scale after sheath removal.

Comparison 2. Effect of intravenous pain regimen compared with control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score on a 0 to 10 scale during sheath removal	3	399	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.54, -0.27]
1.1 Opioid only	2	96	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-1.61, 0.67]
1.2 Opioid and anxiolytic	1	303	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.87, -0.33]

Analysis 2.1. Comparison 2 Effect of intravenous pain regimen compared with control, Outcome 1 Pain score on a 0 to 10 scale during sheath removal.

Comparison 3. Effect of levobupivacaine compared with control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score on a 0 to 10 pain scale	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.26, -0.94]
1.1 Levobupivacaine	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.26, -0.94]

Analysis 3.1. Comparison 3 Effect of levobupivacaine compared with control, Outcome 1 Pain score on a 0 to 10 pain scale.

APPENDICES

Appendix 1. MEDLINE search strategy

Search strategy for searching MEDLINE via OVID

1. Pain/
2. Pain Measurement/
3. pain\$.mp.
4. discomfort.mp.
5. 1 or 2 or 3 or 4
6. Femoral Artery/
7. femoral.mp.
8. 6 or 7
9. (sheath and remov\$).mp.
10. 8 and 9
11. 5 and 10

Appendix 2. EMBASE search strategy

Search strategy for searching EMBASE

1. 'pain'/de
2. 'pain assessment'/de
3. pain*
4. discomfort
5. 1 or 2 or 3 or 4
6. 'femoral artery'/de
7. femoral
8. 6 or 7
9. sheath and remov*
10. 8 and 9
11. 5 and 10

Appendix 3. CENTRAL search strategy

Search strategy for searching CENTRAL

1. MESH descriptor Pain/
2. MESH descriptor Pain Measurement/
3. pain* (search all text)
4. discomfort (search all text)
5. 1 or 2 or 3 or 4
6. Femoral Artery/
7. femoral (search all text)
8. 6 or 7
9. (sheath and remov*) (search all text)
10. 8 and 9
11. 5 and 10

Appendix 4. CINAHL search strategy via EBSCO

Search strategy for searching CINAHL

1. Pain [MH]
2. Pain Measurement [MH]
3. pain*
4. discomfort
5. 1 or 2 or 3 or 4
6. Femoral Artery [MH]
7. femoral
8. 6 or 7
9. (sheath and remov*)
10. 8 and 9
11. 5 and 10

WHAT'S NEW

Date	Event	Description
15 July 2019	Amended	Contact details updated.
31 January 2019	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2008

Date	Event	Description
24 July 2013	Review declared as stable	This review will be assessed for further updating in 2018 due to a current lack of new evidence.
24 June 2011	New search has been performed	<p>A new search was performed in February 2011 and brought up to date prior to publication in June 2011. No new studies were found and the conclusions remain unchanged. The previous review identified an ongoing study that has now been completed (Cook 2007). It is now 'awaiting classification' as efforts to obtain data from author contact have been unsuccessful to date.</p> <p>The review was converted to new RevMan 5 format and the 'Risk of bias' tables were completed.</p> <p>The Discussion section has been revised to include the results of a 2009 survey of clinical practice (Rolley 2010) and a recently published nursing clinical practice guideline for people undergoing percutaneous coronary interventions (Rolley 2011). Discussion of the risk of a vasovagal event has been updated and includes a new reference (Juergens 2008).</p> <p>Errors noted in the 'Characteristics of included studies' table have been corrected as follows:</p> <ul style="list-style-type: none"> Characteristics of included studies for Fulton 2000a, Fulton 2000b, Fulton 2000c - all had stated "adequate allocation concealment" instead of "unclear allocation concealment" as per Fulton 2000 table entry (which is the same study). Vish 2001b was incorrectly identified as Vish 2000b. All forest plots automatically amended to show the correct study ID. This has not resulted in any changes in the meta-analysis <p>The title was changed (original title 'Pain relief for the removal of femoral sheath in interventional cardiology adult patients') to improve retrieval using keyword searching.</p>
9 November 2009	Amended	Contact details updated.
31 March 2009	Amended	Software bug corrected.

CONTRIBUTIONS OF AUTHORS

CW: literature search and identification of trials for inclusion; evaluation of methodological quality of included trials; data extraction; analysis and interpretation of data; writing up the original view and its updates.

BK: design of the review; methodological support throughout; evaluation of methodological quality of included trials; interpretation of data; appraising the review write-up; general advice and support.

SP: screening the search results; assessment of methodological quality; data extraction; expert nursing knowledge and perspective; reviewing the review write-up.

MM: screening the search results; evaluation of methodological quality of included trials; data extraction; expert nursing knowledge and perspective; reviewing the review write-up.

JS: expert medical advice and support, interpretation of data; appraisal of the review write-up.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Source of support, Other.

External sources

- No sources of support supplied

NOTES

A search in July 2018 did not identify any potentially relevant studies 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 three years. 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 necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthetics, Local; Angioplasty, Balloon, Coronary [*instrumentation]; Bupivacaine [analogs & derivatives]; Device Removal [*adverse effects]; Femoral Artery; Levobupivacaine; Pain [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Stents

MeSH check words

Humans