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Drug therapy for preventing post-dural puncture headache (Review)

Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X

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Drug therapy for preventing post-dural puncture headache.
Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD001792.
DOI: 10.1002/14651858.CD001792.pub3.

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[Intervention Review]

Drug therapy for preventing post-dural puncture headache

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2016.

Citation: Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for preventing post-dural puncture headache. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD001792. DOI: 10.1002/14651858.CD001792.pub3.

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ABSTRACT

Background

Post-dural (post-lumbar or post-spinal) puncture headache (PDPH) is one of the most common complications of diagnostic, therapeutic or inadvertent lumbar punctures. Many drug options have been used to prevent headache in clinical practice and have also been tested in some clinical studies, but there are still some uncertainties about their clinical effectiveness.

Objectives

To assess the effectiveness and safety of drugs for preventing PDPH in adults and children.

Search methods

The search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2012, Issue 5), MEDLINE (from 1950 to May 2012), EMBASE (from 1980 to May 2012) and CINAHL (from 1982 to June 2012). There was no language restriction.

Selection criteria

We considered randomised controlled trials (RCTs) that assessed the effectiveness of any drug used for preventing PDPH.

Data collection and analysis

Review authors independently selected studies, assessed risks of bias and extracted data. We estimated risk ratios (RR) for dichotomous data and mean differences (MD) for continuous outcomes. We calculated a 95% confidence interval (CI) for each RR and MD. We did not undertake meta-analysis because participants' characteristics or assessed doses of drugs were too different in the included studies. We performed an intention-to-treat (ITT) analysis.

Main results

We included 10 RCTs (1611 participants) in this review with a majority of women (72%), mostly parturients (women in labour) (913), after a lumbar puncture for regional anaesthesia. Drugs assessed were epidural and spinal morphine, spinal fentanyl, oral caffeine, rectal indomethacin, intravenous cosyntropin, intravenous aminophylline and intravenous dexamethasone.

All the included RCTs reported data on the primary outcome, i.e. the number of participants affected by PDPH of any severity after a lumbar puncture. Epidural morphine and intravenous cosyntropin reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to placebo. Also, intravenous aminophylline reduced the number of participants affected by PDPH of

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any severity after a lumbar puncture when compared to no intervention, while intravenous dexamethasone increased it. Spinal morphine increased the number of participants affected by pruritus when compared to placebo, and epidural morphine increased the number of participants affected by nausea and vomiting when compared to placebo. Oral caffeine increased the number of participants affected by insomnia when compared to placebo.

The remainder of the interventions analysed did not show any relevant effect for any of the outcomes.

None of the included RCTs reported the number of days that patients stayed in hospital.

Authors' conclusions

Morphine and cosyntropin have shown effectiveness for reducing the number of participants affected by PDPH of any severity after a lumbar puncture, when compared to placebo, especially in patients with high risk of PDPH, such as obstetric patients who have had an inadvertent dural puncture. Aminophylline also reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention in patients undergoing elective caesarean section. Dexamethasone increased the risk of PDPH, after spinal anaesthesia for caesarean section, when compared to placebo. Morphine also increased the number of participants affected by adverse events (pruritus and nausea and vomiting)

There is a lack of conclusive evidence for the other drugs assessed (fentanyl, caffeine, indomethacin and dexamethasone).

These conclusions should be interpreted with caution, owing to the lack of information, to allow correct appraisal of risk of bias and the small sample sizes of studies.

PLAIN LANGUAGE SUMMARY

Drugs for preventing headache after a lumbar puncture

Lumbar puncture is an invasive procedure that medical personnel use to get a sample of cerebrospinal fluid for diagnostic purposes (e.g. to diagnose meningitis or subarachnoid haemorrhage) by inserting a needle into the lower spinal region. It can also be used to inject medications such as anaesthetics and analgesics (to perform regional anaesthesia), chemotherapy or radiological contrast agents.

Post-dural puncture headache (PDPH) is the most common complication of a lumbar puncture. The symptoms are a constant headache that worsens in the upright position and improves when lying down and resolves spontaneously within five to seven days. Several interventions have been used before, during or immediately after lumbar puncture to prevent PDPH, but there are still uncertainties about their clinical effectiveness, especially regarding drug treatments. Therefore, the aim of this review was to determine the effectiveness of these medications to prevent PDPH in children and adults.

We included 10 randomised clinical trials (RCTs), with a total of 1611 participants, that assessed seven medications (epidural and spinal morphine, spinal fentanyl, oral caffeine, rectal indomethacin, intravenous cosyntropin, intravenous aminophylline and intravenous dexamethasone). Epidural morphine and intravenous cosyntropin proved to be effective at reducing the number of participants affected by PDPH of any severity after lumbar puncture compared to placebo. Aminophylline also reduced the number of participants affected by PDPH of any severity after a lumbar puncture compared to no intervention. Dexamethasone increased the risk of PDPH when compared to placebo after spinal anaesthesia for caesarean section.

Morphine also increased the number of participants affected by adverse events such as itching, nausea and vomiting. The other interventions (fentanyl, caffeine, indomethacin and dexamethasone) did not show conclusive evidence of effectiveness.

Combining data was possible only for subgroups of one study comparing different dosages of caffeine to placebo, because the other RCTs appraised diverse drugs, outcomes or populations.

A meta-analysis (combining of data) was not possible because all the included RCTs assessed different drugs, different doses, different outcomes or different baseline participants' characteristics.

These conclusions should be interpreted carefully, given the lack of information to evaluate the risk of bias properly, and the small number of participants in the included studies.

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BACKGROUND

Description of the condition

Post-dural (post-lumbar or post-spinal) puncture headache (PDPH) is one of the most common complications of diagnostic, therapeutic or inadvertent lumbar puncture (Bezov 2010; Davignon 2002). PDPH is defined as any headache after a lumbar puncture that worsens within 15 minutes of sitting or standing and is relieved within 15 minutes of lying down (International Headache Society 2004). Ninety per cent of PDPHs occur within three days of the procedure and 66% start in the first 48 hours (Turnbull 2003).

The pathophysiology of PDPH has not been fully described. It is well known that the puncture in the dura allows cerebrospinal fluid (CSF) to leak from the subarachnoid space, resulting in a decrease of CSF volume and pressure (Grande 2005). This CSF volume loss may cause a downwards pull on pain-sensitive structures resulting in a headache (Ahmed 2006; Baumgarten 1987; Davignon 2002; Denny 1987; Harrington 2004). Alternatively, the loss of CSF may cause an increase in blood flow, resulting in arterial and venous vasodilation and PDPH. A third explanation involves the role of substance P and the regulation of neurokinin-1 receptors (NK1R) (Clark 1996).

Occurrence of PDPH varies from 1% to 40%, according to the needle gauge, needle orientation, operator skill level and presence of risk factors such as age group or history of PDPH (Turnbull 2003). This frequency is related to the type of lumbar puncture. During anaesthetic procedures, such as epidural anaesthesia, PDPH is most commonly caused by an unintentional dural puncture (Thew 2008; Turnbull 2003). In contrast, in diagnostic or therapeutic lumbar puncture, the need for adequate CSF flow requires an intentional lesion that may generate the PDPH phenomenon (Kuczkowski 2006). Estimated frequencies vary from less than 10% following spinal anaesthesia (Hafer 1997; Vallejo 2000) to 36% for diagnostic lumbar puncture (Lavi 2006; Vallejo 2000) and up to 81% (Banks 2001) in obstetric patients with inadvertent dural puncture during active labour. Reported risk of inadvertent dural puncture placement during epidural anaesthesia in an obstetric population ranges from 0.04% to 6% (Berger 1998; Choi 2003). Therefore, obstetric analgesia is probably the main source of PDPH patients.

The features of PDPH are often variable. PDPH may be accompanied by neck stiffness, tinnitus, hearing loss, photophobia or nausea; other features, such as the location and duration, are also unpredictable (Lybecker 1995). Although PDPH is not a life-threatening condition, physical activity is often restricted. Likewise patients are usually required to stay in bed the whole day, and length of stay and medical care increases (Angle 2005).

The variability of symptoms makes PDPH a diagnosis of exclusion. Other alternative diagnoses should be ruled out (e.g. viral meningitis, sinus headache or intracranial haemorrhage) (Turnbull 2003). Once PDPH is diagnosed, the initial treatment involves conservative measures such as bed rest and analgesics. If PDPH continues for more than 72 hours, a more specific treatment is indicated (Ahmed 2006). Severe PDPH may respond to some therapeutic drugs and administration of an epidural blood patch (EBP) (Lavi 2006).

How the intervention might work

Owing to the fact that no clear pathophysiology has been asserted for PDPH, many drugs options are used to prevent headache in clinical practice and in clinical trials: for example EBP mechanically blocking the leakage of CSF, postures such as a prone position, reducing pressure in the subarachnoid space and allowing a seal to form over the dura, hydration increasing CSF production (Ahmed 2006), methylxanthines, sumatriptan and caffeine increasing vasoconstriction of cerebral blood vessels or adrenocorticotropic hormone (ACTH) (Kuczkowski 2006), or epidural saline infusion (Morewood 1993) increasing intravascular volume.

Preventive drugs should help to decrease the frequency of patients with PDPH, reduce the headache severity as much as possible, avoid the need for any therapeutic option, improve daily activity, reduce the length of hospital stay and decrease the occurrence of adverse events overall.

Why it is important to do this review

Two Cochrane systematic reviews about treatment and management of PDPH have been published using EBP (Boonmak 2010) and drugs (Basurto 2011). One Cochrane systematic review about prevention of PDPH with epidural catheter replacement and intrathecal catheter techniques is also in production (Newman 2010), alongside two published reviews using EBP (Boonmak 2010), and posture and fluids (Arevalo-Rodriguez 2011).

Numerous preventive drugs have been proposed for treating this condition based on limited randomised controlled trials (RCTs) and case series, including: caffeine, morphine, paracetamol, fentanyl, vasopressin (Turnbull 2003) and epidural saline infusion (Morewood 1993). Therefore, there is weak evidence to support the preventive treatment of PDPH with drugs and the existing uncertainties require a systematic review to clarify their potential benefits. In addition, this review would like to inspire future guidelines as well as future good-quality studies regarding this topic.

OBJECTIVES

To assess the effectiveness and safety of drugs for preventing PDPH in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs (parallel or cross-over) conducted in any setting. We excluded studies using alternation, date of birth, hospital record number or other quasi-randomised methods of allocation of treatment.

Types of participants

Participants undergoing lumbar puncture for any of the reasons outlined: CSF sampling or pressure measurement, or both; spinal anaesthesia; myelography; intrathecal drug administration or accidental puncture of the dura during epidural anaesthesia. We included individuals of all ages and any gender.

The use of a standardised diagnostic criteria for PDPH was not required, but it should at least have been described as an orthostatic headache that worsened on standing and improved by

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lying down. We described the specific diagnostic criteria used in each included study.

Types of interventions

We considered any drug used for preventing PDPH. We considered interventions at any dose, formulation or route of administration given before, during or immediately after lumbar puncture.

Acceptable control groups included: placebo, no intervention, any other drug treatments, behavioural and physical therapies.

Types of outcome measures

Primary outcomes

Number of participants affected by PDPH of any severity after a lumbar puncture.

Secondary outcomes

1. Number of participants with severe PDPH (based on the author's definition of severity).
2. Number of participants with any headache, not only those explicitly described as PDPH.
3. Number of days that patients stayed in hospital.
4. Any possible adverse events of drugs taken to prevent PDPH.
5. Missing data (withdrawals, drop-outs and participants lost to follow-up).

Search methods for identification of studies

We designed the search in the context of an extensive review about prevention and treatment drugs used for PDPH. The Cochrane Central Register of Controlled Trials (CENTRAL) was our primary source for identifying studies. Our search terms were a combination of thesaurus-based and free-text terms covering both the procedure of interest (dural puncture performed for diagnosis, anaesthesia or myelography) and headache. For MEDLINE, EMBASE and CINAHL we used a modified version of the strategy used to search CENTRAL. We considered articles written in any language.

In addition, we searched the reference lists of all studies and review articles identified by electronic searching. We requested information about any potentially relevant studies when we contacted trialists from every included study.

Electronic searches

We searched:

- CENTRAL (*The Cochrane Library* 2012, Issue 5);
- MEDLINE (from 1950 to May 2012);
- EMBASE (from 1980 to May 2012);
- CINAHL (from 1982 to June 2012).

We include the complete search strategies designed for CENTRAL, MEDLINE, EMBASE and CINAHL in Appendix 1, Appendix 2, Appendix 3 and Appendix 4 respectively.

Data collection and analysis

Selection of studies

Two independent review authors (XB, SU) screened titles and abstracts of studies identified by the literature search for eligibility. We resolved disagreements through discussion. We retrieved eligible studies in full to confirm whether or not they fulfilled the inclusion criteria. Review authors were not blinded to the authors' names and institutions, journal of publication or study results at this or any stage of the review.

Data extraction and management

For included studies, we used specially designed, pre-tested data forms to extract information from the original studies on participants, methods of randomisation and blinding, the comparison(s) of interest, the number of participants originally randomised in each arm of the study, any losses to follow-up and the occurrence in each arm of the outcomes of interest. If information on any of these was incomplete, we attempted to obtain it by writing to the study author concerned. One review author (XB) extracted the data from studies and a second review author (SU) checked data for accuracy, resolving any disagreement by discussion. We entered data into Review Manager 5.1 (RevMan 2011).

When efficacy outcomes were reported in dichotomous form (e.g. number of people with severe PDPH, number of people with any headache, any possible adverse events of drug and missing data), we recorded the number of participants assigned to each treatment arm and the number with each outcome. For outcomes reported on a continuous scale (e.g. number of days participants stayed in hospital), we recorded data on the variance associated with their means.

If reported we recorded the frequency and type of adverse events for each treatment arm.

Assessment of risk of bias in included studies

We used The Cochrane Collaboration's tool for assessing risk of bias in the studies included in this review, which addresses six specific domains (Higgins 2011) summarised in a specific table. For this review we assessed five of the domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting). Each domain has a description of what was reported. One review author (XB) completed the 'Risk of bias' judgements for each study and a second review author (SU) checked them for accuracy. Any disagreement was resolved by discussion.

Assessment of heterogeneity

This review did not include a meta-analysis.
We would have assessed heterogeneity of effect sizes by means of the Q (Chi^2 statistic) using the methods of Peto and Mantel-Haenszel. If statistical evidence had existed for homogeneity of effect sizes, the analysis would have used a fixed-effect model.
If significant heterogeneity had been present (Chi^2 test with P value < 0.1 or I^2 statistic value > 50%), we would have made an attempt to explain the differences based on the clinical characteristics of the included studies. We would not have combined studies that were dissimilar in terms of interventions and participants. However, if a group of studies with heterogeneous results had appeared to be similar, we would have combined the study estimates using a random-effects model (Higgins 2002; Higgins 2003).

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Data synthesis

The differences between the studies included in this review, in terms of participants' characteristics, interventions assessed and outcomes measured, only permitted a combined analysis in one of the comparisons (caffeine plus paracetamol versus placebo). For the other comparisons we presented a narrative summary.

We analysed the results for different drugs separately, except for caffeine plus paracetamol versus placebo, using Review Manager 5.1 (RevMan 2011). We performed analysis on an intention-to-treat (ITT) basis (i.e. all participants remained in their original trial arm, whether or not they actually received the intervention allocated).

We used dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI). In future updates of this review, we hope to be able to calculate the numbers needed to treat for an additional beneficial outcome (NNTB) with 95% CI, as the reciprocal of the risk difference (RD) (McQuay 1998). We will use data on the proportion of participants reporting adverse events to calculate RD and numbers needed to treat for an additional harmful outcome (NNTH) with 95% CI for significant differences.

For continuous outcomes reported using the same scale, we calculated mean differences (MD) with 95% CI. In future updates of this review, we hope to be able to calculate standardised mean differences (SMD) for pooling results of continuous outcomes measured with different scales.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, if sufficient data are available, we plan to carry out the following subgroup analyses:

Follow-up time subgroup analyses

When possible, we will assess the impact of the assessed interventions at short-term (< 24 hours), medium-term (24 to 48 hours) or long-term time periods (> 48 hours) for the preventive drugs.

Population subgroup analyses

Where data allow in the future, we plan to conduct separate outcome analyses to test the following null hypotheses:

1. there is no difference between obstetric participants and all other participants;
2. there is no difference between men and non-obstetric women participants;
3. there is no difference between young participants (18 to 35 years old) and all other adult participants.

Sensitivity analysis

In future updates of this review, and depending on study availability, we will conduct a sensitivity analyses formulated a priori:

- We will examine the effect on the primary outcome of excluding any study judged to be at a high risk of bias by two of the domains, sequence generation and allocation concealment.
- If applicable we will also perform a sensitivity analysis excluding those trials with a cross-over design.

RESULTS

Description of studies

See the 'Characteristics of included studies', 'Characteristics of excluded studies' and 'Characteristics of ongoing studies' tables.

Results of the search

We identified 1894 references in primary electronic databases up to May 2012 from our extended search strategy for prevention and treatment with drugs for PDPH. We excluded 1768 references after a detailed reading of the title and abstract. We obtained the full-text reports for the remainder of the studies (137 papers) to check if they strictly fulfilled all the inclusion criteria. We finally excluded 127 studies after a complete full-text review and we contacted the study authors by email in some cases when more information was needed to decide eligibility. Ten studies completely fulfilled the inclusion criteria for this review (Abboud 1992; Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Hakim 2010; Sadeghi 2012; Strelec 1994; Yousefshahi 2012).

See Figure 1.

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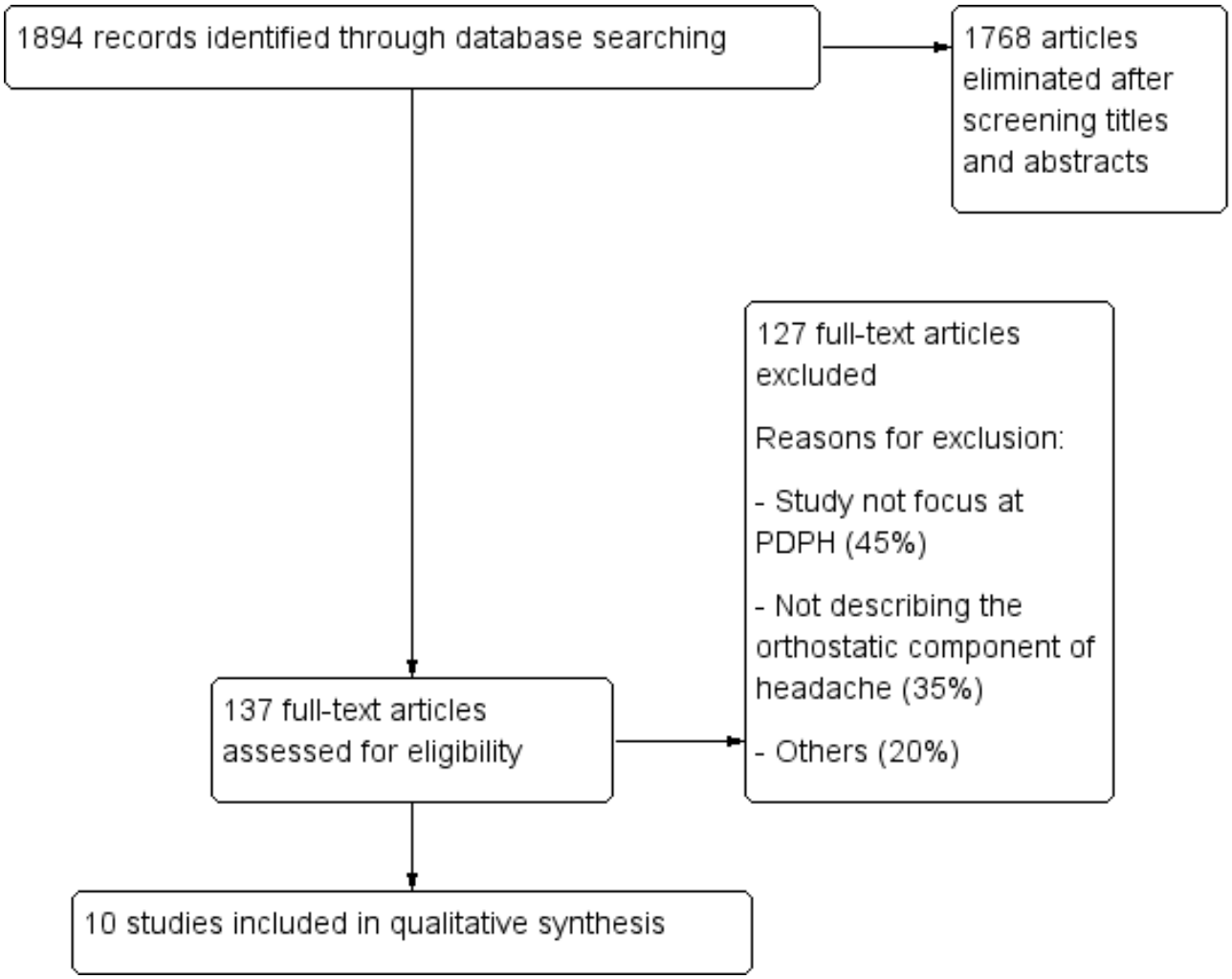
Figure 1. Study flow diagram.



Included studies

Included studies are described in detail in the 'Characteristics of included studies' table.

Study design

All 10 included studies (involving a total of 1611 participants) were RCTs with a parallel design. Most of them were placebo-controlled, except Devcic 1993 and Sadeghi 2012, which used a control group without an intervention.

Setting

All included studies were single-centre studies. Three studies were conducted in the US (Abboud 1992; Devcic 1993; Strelec 1994), three studies in Iran (Doroudian 2011; Sadeghi 2012; Yousefshahi 2012) and the remainder in Norway (Flaatten 1987), Turkey (Esmaoglu 2005), Egypt (Hakim 2010) and Saudi Arabia (Al-metwalli 2008).

All the studies recruited the participants from hospital settings and the intervention took place while they were admitted.

Sample size

The studies included a total of 1611 participants. The smallest study had 50 participants (Al-metwalli 2008) and the largest had 372 (Yousefshahi 2012).

Participants

The majority of participants were women (1160/1611; 72%), mostly parturients (woman in labour) (913) that required a lumbar puncture for regional anaesthesia (Abboud 1992; Al-metwalli 2008; Devcic 1993; Hakim 2010; Sadeghi 2012; Yousefshahi 2012). There were four studies that included men (451); three with surgical patients after a spinal anaesthesia (Doroudian 2011; Esmaoglu 2005; Flaatten 1987) and one with lumbar puncture for myelography (Strelec 1994).

The median age among participants from all studies ranged from 26.1 to 48.5 years old.

Intervention

Three included studies assessed two different opioid drugs to prevent PDPH; morphine (administered into the subarachnoid space (Abboud 1992) or into the epidural space (Al-metwalli 2008))

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and fentanyl (administered into the subarachnoid space (Devcic 1993)) .

Two studies used caffeine as an intervention to prevent PDPH. Strelec 1994 compared oral caffeine 300 mg to placebo. Esmaoglu 2005 assessed oral caffeine 75 mg and 125 mg, combined with paracetamol, compared to placebo.

Two studies used intravenous dexamethasone compared to placebo to prevent PDPH (Doroudian 2011; Yousefshahi 2012).

One study compared rectal indomethacin, a non-steroidal anti-inflammatory drug, to placebo (Flaatten 1987). Intravenous cosyntropin, a synthetic derivative of ACTH, was compared to placebo in one study (Hakim 2010) and intravenous aminophylline, a xanthine derivative, was compared to no intervention in another study (Sadeghi 2012).

Follow-up was short in general terms and differed between the included trials at 48 hours (Sadeghi 2012), three days (Abboud 1992; Flaatten 1987; Yousefshahi 2012) and three weeks (Devcic 1993).

Outcomes of interest

The number of participants affected by PDPH of any severity after a lumbar puncture (primary outcome) was reported in all included studies. Missing data were reported in six studies (Devcic 1993; Doroudian 2011; Flaatten 1987; Hakim 2010; Strelec 1994; Yousefshahi 2012). Adverse events related to study drugs were reported in five studies (Abboud 1992; Al-metwalli 2008; Esmaoglu 2005; Hakim 2010; Strelec 1994).

The number of participants with severe PDPH was reported in five studies (Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Yousefshahi 2012).

The number of participants with any headache was detailed in two studies (Esmaoglu 2005; Yousefshahi 2012).

The number of days that participants stayed in hospital was the only outcome not reported in the included studies.

Conflict of interest

Only three studies reported any conflict of interest. Flaatten 1987 stated that Dumex-Norway supplied the intervention drugs and placebo, Hakim 2010 stated that support was provided solely from institutional or departmental (or both) sources and Yousefshahi 2012 stated no conflict of interest.

Excluded studies

A total of 127 studies did not fulfil the inclusion criteria and were excluded.

The most frequent reasons for exclusion were that the study did not focus on PDPH (45% of studies) or describe the orthostatic component of headache (35% studies). Other less frequent reasons(20% of the excluded studies) were: was not a RCT, intervention did not aim to prevent PDPH, allocation was not randomised or did not assess an individual drug.

For a summary of the reasons for exclusion see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

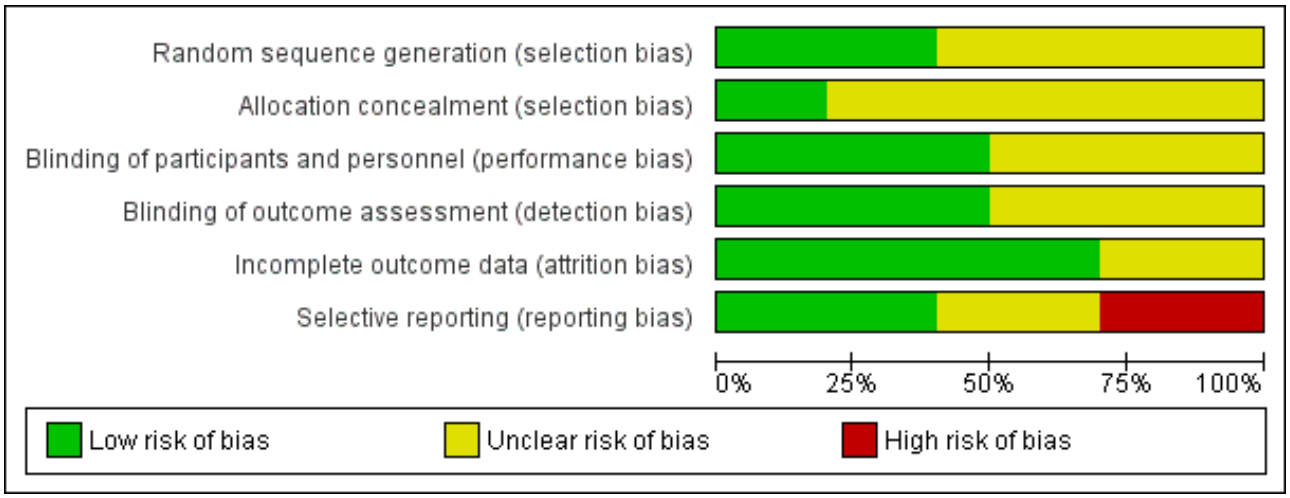

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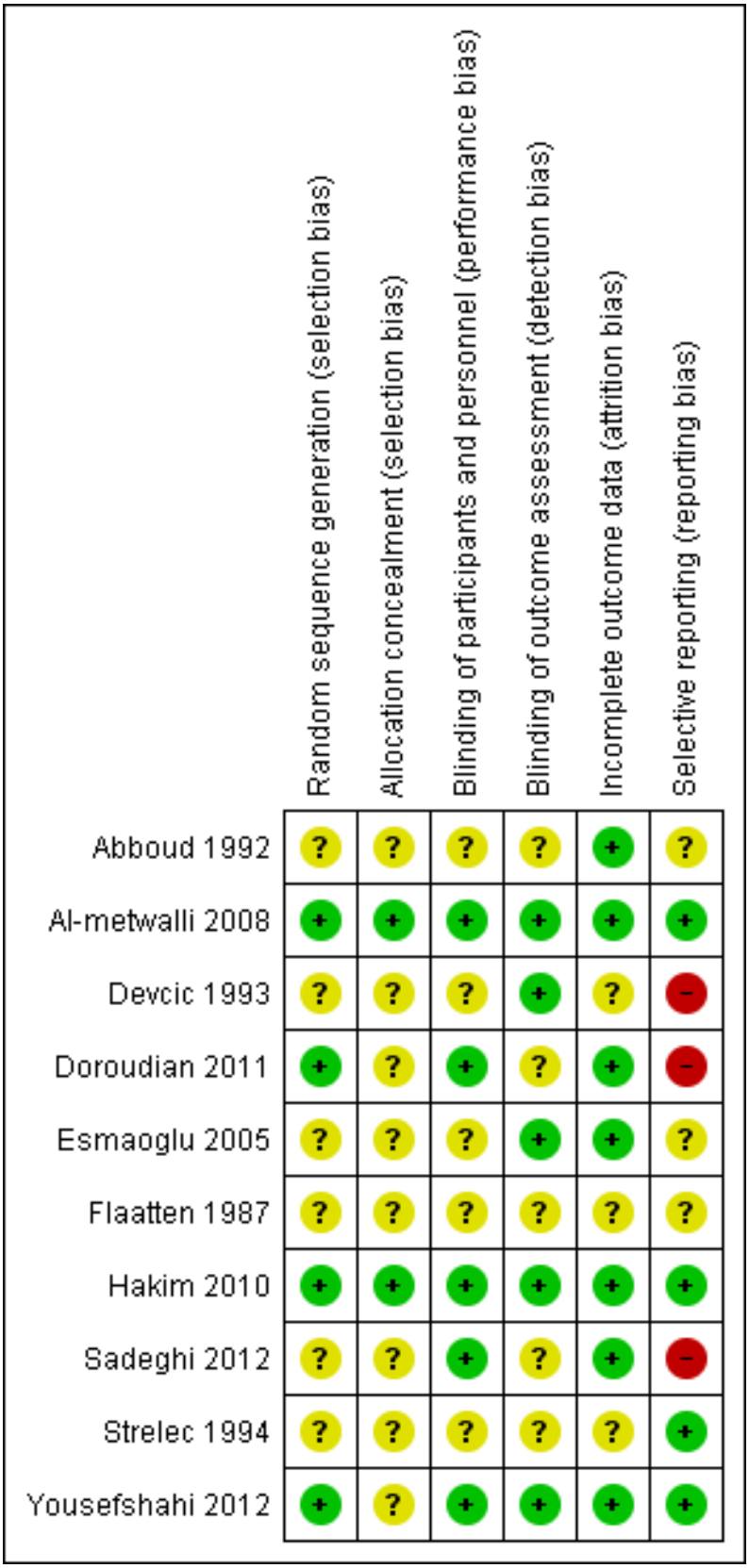
Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



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Allocation

Sequence generation

Allocation sequence was adequately generated in three studies (Al-metwalli 2008; Hakim 2010; Yousefshahi 2012) that reported a computer-generated random number sequence explicitly.

The other seven included studies were described as randomised but no information was provided, so we judged them as having an unclear risk of selection bias (Abboud 1992; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994).

Allocation concealment

Two studies reported the method used to conceal the randomisation sequences (Al-metwalli 2008; Hakim 2010) and we judged them as having a low risk of selection bias.

The other eight studies did not provide information regarding allocation concealment (Abboud 1992; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994; Yousefshahi 2012) and we judged them as having an unclear risk of selection bias.

Blinding

Blinding of participants and personnel (performance bias)

The blinding method was adequate in five of the studies (Al-metwalli 2008; Doroudian 2011; Hakim 2010; Sadeghi 2012; Yousefshahi 2012). The rest of the studies (Abboud 1992; Devcic 1993; Esmaoglu 2005; Flaatten 1987; Strelec 1994) did not report detailed data to allow assessment of performance bias.

Blinding of outcome assessment (detection bias)

Blinding of outcome assessment was adequate in four of the included studies (Al-metwalli 2008; Devcic 1993; Hakim 2010; Yousefshahi 2012). The six remaining studies (Abboud 1992; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994) did not report information to allow assessment of detection bias.

Incomplete outcome data

Seven studies presented results for all randomised patients or reported the number of participants lost in follow-up with reasons explicitly stated and we judged them as having a low risk of attrition bias (Abboud 1992; Al-metwalli 2008; Doroudian 2011; Esmaoglu 2005; Hakim 2010; Sadeghi 2012; Yousefshahi 2012).

The remainder of the studies stated explicitly the number of participants lost to follow-up without detailed data to allow assessment of attrition bias; Devcic 1993 with six participants lost out of 194, Flaatten 1987 with three out of 250 and Strelec 1994 with two out of 60. Gender of participants lost to follow-up in Flaatten 1987 and Strelec 1994 was not reported.

Selective reporting

Four studies presented outcomes according to objectives stated in the methods section and we judged them as having a low risk of reporting bias (Al-metwalli 2008; Hakim 2010; Strelec 1994; Yousefshahi 2012). We judged three studies as having an unclear risk of bias because no information was provided (Abboud 1992; Esmaoglu 2005; Flaatten 1987). We judged Devcic 1993, Doroudian 2011 and Sadeghi 2012 as having a high risk as they did not report outcomes about adverse effects.

Effects of interventions

We present in this section a narrative synthesis of the results for the different outcomes of interest.

Number of participants affected by post-dural puncture headache (PDPH) of any severity

Opioids

Opioids were assessed in three studies for this primary outcome. Epidural morphine (Al-metwalli 2008) showed a significant risk reduction of the number of participants affected by PDPH of any severity compared to placebo (15 events in 50 participants; risk ratio (RR) 0.25; 95% confidence interval (CI) 0.08 to 0.78; Analysis 2.1).

In contrast, spinal morphine and spinal fentanyl showed no differences compared to placebo in Abboud 1992 (17 events in 82 participants; RR 1.18; 95% CI 0.51 to 2.76; Analysis 1.1) or no intervention in Devcic 1993 (11 events in 194 participants; RR 1.79; 95% CI 0.54 to 5.91; Analysis 3.1) respectively, in the number of participants affected by PDPH of any severity.

We did not undertake meta-analysis of these three studies (Abboud 1992; Al-metwalli 2008; Devcic 1993). The Al-metwalli 2008 results were not combined with other studies because baseline incidence of PDPH was much higher in obstetric patients with inadvertent dural puncture during active labour than following spinal anaesthesia for caesarean section. We did not combine the results from Abboud 1992 and Devcic 1993 because opioid interventions were not dose equivalent; Devcic 1993 assessed 20 µg of fentanyl, which is dose equivalent of morphine 2 mg, which is 10 times higher than the morphine 0.2 mg used in Abboud 1992.

Intravenous cosyntropin

Intravenous cosyntropin (Hakim 2010) showed a significant risk reduction of the number of participants affected by PDPH of any severity (46 events in 95 participants; RR 0.49; 95% CI 0.31 to 0.79; Analysis 8.1) compared to placebo.

Oral caffeine

Oral caffeine plus paracetamol was assessed by Esmaoglu 2005 with two different doses of caffeine, 75 mg and 125 mg, and compared to placebo. The combined analysis from these two doses of caffeine, compared to placebo, showed no significant risk reduction (42 events in 280 participants; RR 0.91; 95% CI 0.52 to 1.59; Analysis 11.1). Neither comparison showed a significant result: caffeine 75 mg versus placebo (21 events in 140 participants; RR 0.91; 95% CI 0.41 to 2.00; Analysis 4.1), caffeine 125 mg versus placebo (21 events in 140 participants; RR 0.91; 95% CI 0.41 to 2.00; Analysis 5.1) or 75 mg caffeine versus caffeine 125 mg (20 events in 140 participants; RR 1.00; 95% CI 0.44 to 2.25; Analysis 6.1). Strelec 1994 also showed no significant risk reduction (18 events in 60 participants; RR 2.00; 95% CI 0.86 to 4.63; Analysis 9.1) when comparing oral caffeine 300 mg to placebo.

We did not undertake meta-analysis of these two studies (Esmaoglu 2005; Strelec 1994) because the caffeine doses used were too different (75 mg/125 mg and 300 mg, respectively) and also

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because the intervention was different; caffeine plus paracetamol in Esmaoglu 2005 while Strelec 1994 used caffeine alone.

Rectal indomethacin

Rectal indomethacin (Flaatten 1987) showed no significant risk reduction when compared to placebo (51 events in 250 participants; RR 0.70; 95% CI 0.42 to 1.15; Analysis 7.1).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in two studies for this primary outcome. Doroudian 2011 showed no significant risk reduction when compared to placebo (34 events in 178 participants; RR 0.79; 95% CI 0.43 to 1.45; Analysis 10.1). Yousefshahi 2012 showed a significant risk of increasing the number of participants affected by PDPH of any severity compared to placebo (39 events in 372 participants; RR 2.55; 95% CI 1.31 to 4.96; Analysis 10.1).

We did not undertake a meta-analysis of these two studies (Doroudian 2011; Yousefshahi 2012) because participants' characteristics were too different in terms of age, gender, length of gestation and spinal needle size used, and also because of statistical evidence of significant heterogeneity of effect sizes (Chi^2 test with P value = 0.01 and I^2 statistic value = 85%).

Intravenous aminophylline

Intravenous aminophylline (Sadeghi 2012) showed a significant risk reduction of the number of participants affected by PDPH of any severity at 24 and 48 hours after umbilical cord clamping compared to no intervention (at 24 hours: 22 events in 120 participants; RR 0.16; 95% CI 0.05 to 0.51; Analysis 12.1; at 48 hours: 17 events in 120 participants; RR 0.21; 95% CI 0.06 to 0.71; Analysis 12.1).

Number of participants with severe PDPH (based on the author's definition of severity)

Opioids

Opioids were assessed in two studies for this outcome. Epidural morphine (Al-metwalli 2008) showed no significant risk reduction compared to placebo (six events in 50 participants; RR 0.08; 95% CI 0.00 to 1.30; Analysis 2.2). Spinal fentanyl (Devcic 1993) also showed no significant risk reduction when compared to no intervention (four events in 194 participants; RR 3.06; 95% CI 0.32 to 28.93; Analysis 3.2).

We did not undertake meta-analysis of these two studies (Al-metwalli 2008; Devcic 1993) because of the difference between participants' characteristics.

Oral caffeine

Data for oral caffeine doses plus paracetamol assessed in Esmaoglu 2005 were analysed in combination, caffeine 75 mg and 125 mg, showing no significant risk reduction compared to placebo (15 events in 280 participants; RR 0.88; 95% CI 0.33 to 2.35; Analysis 11.2). Individual comparisons showed no significant risk reduction in any of the reported comparisons: caffeine 75 mg compared to placebo (10 events in 140 participants; RR 1.50; 95% CI 0.44 to 5.09; Analysis 4.2), caffeine 125 mg compared to placebo (five events in 140 participants; RR 0.25; 95% CI 0.03 to 2.18; Analysis 5.2) or caffeine 75 mg compared to caffeine 125 mg (seven events in 140 participants; RR 6.00; 95% CI 0.74 to 48.55; Analysis 6.2).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in two studies. Doroudian 2011 showed no significant risk reduction compared to placebo (10 events in 178 participants; RR 0.25; 95% CI 0.05 to 1.14; Analysis 10.2). Yousefshahi 2012 could not estimate this outcome because none of the participants experienced a severe PDPH. For this reason and because of clinical differences these two studies could not be combined.

Number of participants with any headache, not only those explicitly described as PDPH

Oral caffeine

A combined analysis of caffeine 75 mg with 125 mg in Esmaoglu 2005 showed no significant risk reduction compared to placebo (61 events in 280 participants; RR 0.79; 95% CI 0.51 to 1.24; Analysis 11.3). All other comparisons showed no significant risk reduction: 75 mg caffeine compared to placebo (10 events in 140 participants; RR 0.67; 95% CI 0.20 to 2.26; Analysis 4.3), 125 mg caffeine compared to placebo (nine events in 140 participants; RR 0.50; 95% CI 0.13 to 1.92; Analysis 5.3) or caffeine 75 mg compared to caffeine 125 mg (seven events in 140 participants; RR 1.33; 95% CI 0.31 to 5.74; Analysis 6.3).

Dexamethasone

Dexamethasone was assessed in Yousefshahi 2012 and showed no significant risk reduction compared to placebo (16 events in 372 participants; RR 2.20; 95% CI 0.78 to 6.21; Analysis 10.3).

Number of days that patients stayed in hospital

None of the included studies reported this outcome.

Any possible adverse events of drugs taken to prevent PDPH

Opioids

Opioids were assessed in two studies for this outcome. Spinal morphine (Abboud 1992) showed a significant risk for increasing the number of participants affected by pruritus (28 events in 82 participants; RR 8.75; 95% CI 2.86 to 26.72; Analysis 1.2) compared to placebo, but a non-significant result for the number of participants affected by nausea and vomiting (41 events in 82 participants; RR 0.82; 95% CI 0.53 to 1.27; Analysis 1.2).

Epidural morphine (Al-metwalli 2008) significantly increased the number of participants affected by nausea and vomiting (15 events in 50 participants; RR 2.75; 95% CI 1.01 to 7.48; Analysis 2.3) compared to placebo. This study (Al-metwalli 2008) showed three participants affected by pruritus, all of them in the morphine group, with a non-significant result (three events in 50 participants; RR 7.00; 95% CI 0.38 to 128.87; Analysis 2.3).

We did not undertake meta-analysis of these two studies (Abboud 1992; Al-metwalli 2008) for this outcome because of the difference between participants' characteristics.

Caffeine

Oral caffeine 300 mg (Strelec 1994) showed a significant risk for increasing the number of participants affected by insomnia (11 events in 60 participants; RR 4.50; 95% CI 1.06 to 19.11; Analysis 9.2) compared to placebo. Esmaoglu 2005 reported no adverse events in either the caffeine 75 mg plus paracetamol group or in

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caffeine 125 mg plus paracetamol group. The study did not report this outcome in the placebo group.

Intravenous cosyntropin

Intravenous cosyntropin compared to placebo (Hakim 2010) showed two participants affected by mild hypersensitivity reaction (urticaria) in the cosyntropin group, with a non-significant result (two events in 95 participants; RR 5.10; 95% CI 0.25 to 103.57; Analysis 8.2).

Missing data (withdrawals, drop-outs and participants lost to follow-up)

Opioids

Spinal fentanyl (Devcic 1993) showed no significant risk of losing participants to follow-up (six events in 194 participants; RR 2.04; 95% CI 0.38 to 10.89; Analysis 3.3) when compared to no intervention.

Rectal indomethacin

Rectal indomethacin (Flaatten 1987) showed no significant risk of losing participants to follow-up (three events in 250 participants; RR 0.14; 95% CI 0.01 to 2.74; Analysis 7.2) when compared to placebo.

Intravenous cosyntropin

Intravenous cosyntropin (Hakim 2010) show no significant risk of losing participants to follow-up (five events in 95 participants; RR 0.68; 95% CI 0.12 to 3.89; Analysis 8.3) when compared to placebo.

Oral caffeine

Oral caffeine (Strelec 1994) showed no significant risk of losing participants to follow-up when comparing 300 mg oral caffeine to placebo (two events in 60 participants; RR 0.20; 95% CI 0.01 to 4.00; Analysis 9.3).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in Yousefshahi 2012 and showed no significant risk of losing participants to follow-up (12 events in 372 participants; RR 0.50; 95% CI 0.15 to 1.63; Analysis 10.4) compared to placebo. Doroudian 2011 could not estimate this outcome because none of the participants were lost to follow-up.

We did not undertake meta-analysis of the six RCTs included in this outcome because of the different intervention drugs assessed.

DISCUSSION

Summary of main results

This systematic review identified three randomised controlled trials (RCTs) assessing opioids for preventing post-dural puncture headache (PDPH): epidural morphine (Al-metwalli 2008), spinal morphine (Abboud 1992) and spinal fentanyl (Devcic 1993). Two studies assessed oral caffeine (Esmaoglu 2005; Strelec 1994) and two studies assessed intravenous dexamethasone (Doroudian 2011; Yousefshahi 2012). Three other studies assessing different drugs for preventing PDPH were identified: rectal indomethacin (Flaatten 1987), intravenous cosyntropin (Hakim 2010) and intravenous aminophylline (Sadeghi 2012).

All the included studies reported data on the primary outcome, the number of participants affected by PDPH of any severity after a lumbar puncture. For this outcome, epidural morphine (Al-metwalli 2008) and intravenous cosyntropin (Hakim 2010) reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to placebo. In both RCTs participants were obstetric patients who had an inadvertent dural puncture. Also intravenous aminophylline (Sadeghi 2012) reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention in patients undergoing elective caesarean section. Intravenous dexamethasone after caesarean section increased the risk of PDPH in Yousefshahi 2012 and showed no significant effect in adults with lower extremity surgery (Doroudian 2011). The rest of the interventions assessed for this outcome, spinal morphine (Abboud 1992) and spinal fentanyl (Devcic 1993), oral caffeine (Esmaoglu 2005; Strelec 1994) and rectal indomethacin (Flaatten 1987), did not show any relevant effect.

When assessing any possible adverse events of drugs taken to prevent PDPH, spinal morphine (Abboud 1992) increased the number of participants affected by pruritus when compared to placebo and epidural morphine (Al-metwalli 2008) increased the number of participants affected by nausea and vomiting when compared to placebo. Also three participants in the epidural morphine group experienced pruritus. Two participants in the cosyntropin group and none in the placebo group (Hakim 2010) were affected by a mild self limiting hypersensitivity reaction (urticaria) that required no treatment. Oral caffeine 300 mg every eight hours for three days increased the number of participants affected by insomnia (Strelec 1994); however, Esmaoglu 2005 found no relevant adverse effect.

The drugs assessed in the included studies did not show any relevant effect for the rest of the outcomes of interest for this review. The number of participants with severe PDPH was similar between the interventions and their controls in five studies (Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Yousefshahi 2012). The number of participants with any headache, not just that explicitly described as PDPH, was reported in two studies (Esmaoglu 2005; Yousefshahi 2012) without relevant effect. Missing data (withdrawals, drop-outs and participants lost to follow-up) were reported in five studies (Devcic 1993; Flaatten 1987; Hakim 2010; Strelec 1994; Yousefshahi 2012), which showed no significant differences between the interventions and their controls. None of the included studies reported data showing the number of days participants stayed in hospital.

Three studies (Abboud 1992; Al-metwalli 2008; Devcic 1993) compared opioids versus placebo but we did not undertake meta-analysis because of the difference between participants' characteristics or because the opioid doses were not equivalent. The baseline incidence of PDPH was much higher in obstetric patients with inadvertent dural puncture during active labour than following spinal anaesthesia for caesarean section in the Al-metwalli 2008 study. Data from Abboud 1992 and Devcic 1993 could not be combined because the opioids used were not dose equivalents. In Devcic 1993, fentanyl 20 µg was the dose equivalent of morphine 2 mg and this was different from the 0.2 mg dose of morphine that was used in Abboud 1992.

Two studies (Esmaoglu 2005; Strelec 1994) compared caffeine to placebo but we chose not to combine results because the range

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of caffeine doses used was too wide (75 mg, 125 mg and 300 mg) and also the intervention was different; caffeine plus paracetamol was used in Esmaoglu 2005 while Strelec 1994 used caffeine alone. The two intervention groups in Esmaoglu 2005 were analysed in combination (i.e. caffeine 75 mg and caffeine 125 mg) compared to placebo, showing no relevant effect.

Two studies (Doroudian 2011; Yousefshahi 2012) compared dexamethasone to placebo but could not be combined because participants' characteristics were too varied in terms of age, gender, length of gestation and spinal needle size used, and also because of statistical evidence of significant heterogeneity of effect sizes.

In future updates of this review, if sufficient data are available, we plan to carry out the subgroup and sensitivity analyses formulated a priori.

Overall completeness and applicability of evidence

All participants included in this review were recruited from acute care hospitals and their characteristics seemed to be similar to patients seen in usual clinical practice.
The lumbar punctures were performed during hospital stay, which is the most common setting for this technique. Most of the participants in the included studies underwent lumbar puncture to administer regional anaesthesia (spinal and epidural anaesthesia), which is the most common reason for lumbar puncture. No lumbar puncture in the included studies was done for diagnostic purposes.

The opioids (morphine and fentanyl), indomethacin, aminophylline and dexamethasone, used in the included studies, are widely marketed and frequently used. Caffeine and cosyntropin are also commercialised but for more specific indications and therefore they are less widely available.

Outcomes reported from the included studies were patient-relevant. In fact, all included studies reported on the primary effectiveness outcome, that is the number of participants affected by PDPH of any severity after a lumbar puncture. The second most reported outcome was a safety issue, that is any possible adverse events of drugs taken to prevent PDPH.

Quality of the evidence

The outlined results should be interpreted with caution owing to the diversity of drugs and doses assessed, and outcomes measured, the small sample sizes of the studies included, and the bias presented. There was a lack of data reported to allow a complete appraisal of the risk of bias; review authors' judgements about each 'Risk of bias' item were unclear in around 50% across all included studies (Figure 2). We judged three included studies (Abboud 1992; Flaatten 1987; Strelec 1994) as having an unclear risk of bias in at least five out of the six items evaluated. We judged three other included studies (Al-metwalli 2008; Hakim 2010; Yousefshahi 2012) as having a low risk of bias in at least five out of the six items evaluated (Figure 3). We judged three studies (Devcic 1993; Doroudian 2011; Sadeghi 2012) as having a high risk of bias in only one item each.

Potential biases in the review process

This review was conducted in accordance with the previously published protocol. We are unaware of any biases in the review process. To minimise bias, the selection, assessment for inclusion eligibility, risk of bias and data extraction were done independently by more than one review author. We also contacted study authors for clarification of study data. None of the review authors have been involved in any of the included studies and none have any commercial or other conflict of interest.

Agreements and disagreements with other studies or reviews

We have found no other systematic review specifically assessing the efficacy of drugs for preventing PDPH. In one systematic review (Apfel 2010) analysing any treatment options to prevent PDPH after accidental dural puncture (e.g. prophylactic EBP, epidural morphine, intrathecal catheters, and epidural or intrathecal saline) no strong evidence was found to make a clinical recommendation but, as in this review, epidural morphine was the only drug with proven efficacy, based on a study also included in this review (Al-metwalli 2008). One narrative review (Bezov 2010) about PDPH concluded, as we do, that caffeine was not helpful in preventing PDPH based on a study that we also included (Esmaoglu 2005).

Other Cochrane reviews (Arevalo-Rodriguez 2011; Boonmak 2010) have investigated measures other than drugs to prevent PDPH (e.g. posture, fluids and EBP), without reaching strong recommendations. One published guideline (Verma 2011) only considers the use of smaller gauge (≥ 25 G) and pencil-point needles for regional anaesthesia in day-surgery patients.

AUTHORS' CONCLUSIONS

Implications for practice

Available studies show that morphine, cosyntropin and aminophylline could be a first-line drug therapy when trying to prevent post-dural puncture headache (PDPH) after a lumbar puncture.

Epidural morphine and intravenous cosyntropin decreased the number of patients affected by PDPH of any severity after a lumbar puncture compared to placebo, especially in those patients with a high risk of PDPH, such as woman giving birth who have had an inadvertent dural puncture during administration of regional anaesthesia. Pruritus, nausea and vomiting due to morphine and urticaria due to cosyntropin are the adverse events reported but these are less frequent than the benefits, are not severe or life-threatening and, if necessary, efficacious and safe drugs exist to treat them.

Aminophylline also provides the same benefit, reducing the number of participants affected by PDPH of any severity, but in this case when compared to no intervention and in patients undergoing spinal anaesthesia for elective caesarean section.

Dexamethasone increased the risk of PDPH, after spinal anaesthesia for caesarean section, when compared to placebo.

These conclusions should be interpreted with caution, owing to the lack of information to allow a complete appraisal of risk of bias and the small sample sizes of studies.

There is a lack of conclusive results for the other drugs assessed (fentanyl, caffeine, indomethacin and dexamethasone).

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Implications for research

Future research in this field should focus on the design of trials with larger samples (including the reporting of how sample size was determined) in order to provide more sound and accurate information on the effectiveness of drugs in this setting and situation.

The reporting of trials could also be improved by endorsing the CONSORT statement (Schulz 2010), which would allow a better appraisal of them for their potential inclusion into systematic reviews.

ACKNOWLEDGEMENTS

Xavier Basurto is a PhD student at the Pediatrics, Obstetrics and Gynecology, and Preventive Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain.
We are grateful to Caroline Struthers (former Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Review Group) and Jane Hayes for undertaking the searches; to Marta Roqué (Iberoamerican Cochrane Center) for her help in the statistical analysis; to Richard Vanderkleyn for his help in editing the review; and to Cathie Sudlow and Charles Warlow for writing the first draft of the protocol.

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CHARACTERISTICS OF STUDIES

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

Abboud 1992

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: US (Los Angeles) Setting: hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: double-blind Follow-up period: 3 days
Participants	Randomised: 82 (intervention group: 40; control group: 42) Excluded (post-randomisation): not described Gender (women): 82 (100%) Age (years): mean (SD): intervention group: 30.3 (6.3); control group: 29.6 (5.8) Inclusion criteria: healthy pregnant women at term, ASA I or II with no medical complications, who underwent caesarean delivery with spinal anaesthesia Exclusion criteria: not described
Interventions	Intervention group: intraspinal administration of morphine 0.2 mg in 0.2 mL solution Control group: intraspinal administration of 0.2 mL of normal saline Co-interventions: spinal anaesthesia with 0.75% bupivacaine in 8.25% dextrose plus 0.2 mL of 1:1000 epinephrine. Hydration with 1500 mL lactated Ringer's solution
Outcomes	• Number of participants affected by PDPH of any severity • Number of any possible adverse effects from the drug taken to prevent PDPH
Notes	PDPH defined as: quote: "PDPH if it occurred after the patient became ambulatory, was aggravated by sitting or standing position, was relieved by lying supine, and was mostly occipital or frontal" (Page 34) Sample size calculation: quote: "Consultation with a statistician determined the sample size of the study. The statistical approach was analysed to ensure that the power of these data was adequate to decrease below the level of statistical probability that a Type II error could have been made" (Page 35)

Risk of bias

Bias	Authors' judgement	Support for judgement

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Abboud 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information provided. Quote: "Patients were randomly assigned to receive, in a double-blind fashion, either 0.2 mg of morphine (Group 1, n = 40) or saline (Group 2, n = 42)..."
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 82 randomised patients
Selective reporting (reporting bias)	Unclear risk	No information available

Al-metwalli 2008

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Saudi Arabia (Al-Khobar) Setting: hospital Study design: parallel Randomisation: computer-generated random number table Allocation concealment: opaque envelope labelled with the study subject number Blinding: double-blind Follow-up period: minimum 5 days in those without PDPH and 3 days after resolution of the headache in those with PDPH
Participants	Randomised: 50 (intervention group: 25, control group: 25) Excluded (post-randomisation): not described Gender (women): 50 (100%) Age (years): mean (SD): intervention group 28.4 (6.0); control group 29.6 (5.4) Inclusion criteria: postpartum woman with inadvertent dural puncture during epidural analgesia in labour Exclusion criteria: temperature > 37.8 °C, coagulopathy and delivering by caesarean section
Interventions	Intervention group: epidural morphine 3 mg in 10 mL saline and repeated the same treatment after 24 h

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Al-metwalli 2008 *(Continued)*

	Control group: epidural 10 mL saline and repeated the same treatment after 24 h Co-interventions: 3 mL of lidocaine 2% with fentanyl 15 µg administered to all patients before delivery to test correct epidural placement. Next, 10 mL bupivacaine 0.25% with 50 µg of fentanyl was injected followed by a continuous infusion of bupivacaine 0.125% with 1 µg/mL of fentanyl at 10 mL/h
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of any possible adverse effects from the drug taken to prevent PDPH
Notes	PDPH defined as: quote "PDPH was defined as the presence of a headache or neck ache that improved significantly or completely when the subject assumed the supine position" Sample size calculation: 24 participants calculated estimating an incidence decrease of PDPH from 75% to 35%. Significance level of 0.05 and power of 80% VRSP: 0 = no pain and 10 = worst possible pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised (via a computer-generated random number table) to treatment (morphine) group or control (saline) group" (Page 848)
Allocation concealment (selection bias)	Low risk	Quote: "Group assignment was determined by opening an opaque envelope labelled with the study subject number" (Page 848)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "An anaesthetist, who was blind to the study drug, injected 10 ml saline (control group) or 3 mg of morphine in 10 ml saline (morphine group)" (Page 848)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An anaesthetist unaware of the treatment group evaluated the subjects postpartum to ascertain the presence of PDPH" (Page 848)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 50 randomised patients
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Devcic 1993

Methods	Randomised, blinded, controlled trial Study type: single-centre study Location: US (Milwaukee) Setting: hospital Study design: parallel Randomisation: not described

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Devcic 1993 *(Continued)*

	Allocation concealment: not described Blinding: blinding of patients and outcome assessors Follow-up period: 3 weeks
Participants	Randomised: 194 (Sprotte needle with fentanyl: 47; Sprotte needle without fentanyl: 49; Quincke needle with fentanyl: 49; Quincke needle without fentanyl: 49) Excluded (post-randomisation): not described Gender (women): 194 (100%) Age (years): mean (SD): Sprotte needle with fentanyl: 28.2 (5.8); Sprotte needle without fentanyl: 29.5 (4.4); Quincke needle with fentanyl: 28.3 (5.6), Quincke needle without fentanyl: 28.7 (5.5) Inclusion criteria: healthy obstetric patients requiring caesarean delivery who consented to spinal anaesthesia Exclusion criteria: previously attempted or performed labour epidural analgesia or spinal anaesthesia attempted with other kind of needles
Interventions	Intervention group: subarachnoid fentanyl 20 µg through a 24-gauge Sprotte needle or through a 25-gauge Quincke needle Control group: subarachnoid anaesthesia without fentanyl through a 24-gauge Sprotte needle or through a 25-gauge Quincke needle Co-interventions: all patients received 1000 to 1500 mL of 0.9% normal saline or Ringer's lactate solution before spinal anaesthesia and continued for 48 h Spinal anaesthesia with hyperbaric bupivacaine 0.75% to all patients. The total dose was decided by the anaesthesiologist performing the spinal anaesthesia Opioids via patient–controlled pump during the first 24 h postoperative and followed the next day by oral analgesics as needed
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "If the headache occurring on mobilization was aggravated by an erect position and was relieved by lying flat, it was considered to be a PDPH" (Page 223) Sample size calculation: not described PDPH severity: mild (annoying, but tolerable on ambulation, requiring oral analgesics); moderate (very annoying, very uncomfortable on ambulation, requiring bed rest, scheduled analgesia with intravenous fluids); severe (bedridden requiring EBP) Email contact

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

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Devcic 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients were evaluated daily during the first 4 postoperative days by the designated nurse, who was blinded to the type of needle and medication used... Investigators conducting telephone follow-up were blinded to the type of needle and anaesthetic solution used" (Page 223)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 lost to follow-up described (4 in fentanyl group, 2 in control group), but is unlikely that this loss may influence the outcomes
Selective reporting (reporting bias)	High risk	Adverse events not reported

Doroudian 2011

Methods	Randomised, blinded, controlled trial Study type: single-centre study Location: Iran (Kerman) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random allocation Allocation concealment: not described Blinding: blinding of patients and the spinal anaesthesia staff Follow-up period: 7 days
Participants	Randomised: 178 (intervention group: 89; control group: 89) Excluded (post-randomisation): none Gender (women): 61 (34.3%) Age (years): mean (range): intervention group 41.7 (31 to 53); control group 40 (30 to 50) Inclusion criteria: all adults admitted to hospital for lower-extremity surgery Exclusion criteria: hypo/hypertension, diabetes, dexamethasone intolerance or past hypersensitivity reaction, intake of any analgesic or anti-inflammatory agent during the week prior to admission, past history of chronic headache, recent-onset acute headache, contraindication for LP, a surgical procedure estimated to last longer than 90 minutes, current pregnancy, past/active peptic ulcer disease, active systemic fungal infection, any kind of addiction, more than 2 attempts at spinal anaesthesia, any history of cardiopulmonary disorder, long-term admission, severe post-spinal haemodynamic changes and strong dependency to tea or caffeine
Interventions	Intervention group: intravenous dexamethasone 8 mg (2 mL) of before spinal anaesthesia Control group: 2 mL of intravenous normal saline before spinal anaesthesia

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Doroudian 2011 *(Continued)*

	Co-interventions: all patients received 500 mL of normal saline intravenously before intervention and spinal anaesthesia
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: an exclusion criteria was: quote: "long term admission which does not permit patient to resume the upright position within the first 7 days" (Page 144) and Class I intensity headache was: quote: "Patient suffers from a mild headache while sitting or walking" (Page 144) Sample size calculation: not described PDPH severity: Class I: "Patient suffers from a mild headache while sitting or walking", Class II: "Patient suffers from a moderate to severe headache while sitting or walking" and Class III: "Patient suffers from a moderate to severe headache even in supine position which impedes his/her daily activities"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization process was performed using Random Allocation Software®" (Page 143)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For all injections, the anesthetic staff was blind with respect to the group allocation whereas patients were also unaware regarding the content of the study injectate" (Page 144)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 178 randomised patients
Selective reporting (reporting bias)	High risk	Adverse events not reported

Esmaoglu 2005

Methods	Randomised, blinded, controlled trial Study type: single-centre study Location: Turkey (Kayseri) Setting: admitted to hospital Study design: parallel Randomisation: not described

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Esmaoglu 2005 *(Continued)*

	Allocation concealment: not described Blinding: outcome assessors and probably patients Follow-up period: 7 days
Participants	Randomised: 210 (caffeine 75 group: 70; caffeine 125 group: 70; control group: 70) Excluded (post-randomisation): not described Gender (women): 83 (39.5%) Age (years): mean (SD): caffeine 75 group: 38 (12); caffeine 125 group: 38 (11); control group: 37 (14) Inclusion criteria: patients scheduled for elective lower extremity surgery, ASA I-II Exclusion criteria: hypertension, diabetes mellitus, caffeine consumption > 250 mg/day, intolerance to caffeine, chronic headache, contraindication to spinal anaesthesia
Interventions	Caffeine 75 group: paracetamol 500 mg + caffeine 75 mg orally Caffeine 125 group: paracetamol 500 mg + caffeine 125 mg orally Control group: placebo orally All 3 groups received intervention 1 h before the spinal anaesthesia and the same doses repeated every 6 hours for 3 days. Spinal anaesthesia with 3 mL of hyperbaric bupivacaine 0.5% Co-interventions: all patients hydrated with at least 0.5 L of intravenous crystalloid solution before the procedure
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of participants with any headache • Number of any possible adverse effects from the drug taken to prevent PDPH
Notes	PDPH defined as: quote: "headache was categorized as a PDPH if it was worse on sitting or standing and relieved or reduced by lying flat" (Page 59) PDPH severity: quote: "class I, mild headache when sitting or ambulating; class II, moderate to severe headache when sitting or ambulating; and class III, moderate to severe headache when supine" (Page 60) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The interviewer was blinded as to study group assignment" (Page 59)

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Esmaoglu 2005 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No explicit information but it seems that no patients were lost
Selective reporting (reporting bias)	Unclear risk	No information available

Flaatten 1987

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Norway (Bergen) Setting: admitted to hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: double-blind Follow-up period: 3 days
Participants	Randomised: 250 (intervention group: 125; control group: 125) Excluded (post-randomisation): not described Gender (women): 85 (34%) Age (years): mean: intervention group 34.2; control group 33.0 Inclusion criteria: young (< 55 years old) hospitalised patients of either sex of ASA groups I and II, receiving spinal anaesthesia Exclusion criteria: not described
Interventions	Intervention group: indomethacin 100 mg per rectum 4 hours post operation Control group: placebo per rectum 4 hours post operation Co-interventions: all spinal anaesthesia were performed using a 25-G spinal needle
Outcomes	• Number of participants affected by PDPH of any severity • Number of missing data (participants lost to follow-up)
Notes	PDPH defined as: quote "occurred after mobilisation, aggravated by the erect or sitting position, relieved by lying flat, mostly occipital or frontal, accompanied by dizziness, vomiting, rigidity of the neck and visual disturbances" (Page 202) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement

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Flaatten 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information provided. Quote: "following this they were randomly allocated in a double-blind manner to receive either indomethacin 100mg or a placebo per rectum 4 hours postoperatively" (Page 202)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Three patients were lost to follow-up and their results are not included in the study." (Page 202). All 3 patients from placebo group, and not reasons stated. Unlikely to produce bias, but incomplete information available
Selective reporting (reporting bias)	Unclear risk	No information available

Hakim 2010

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Egypt (Cairo) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random number list Allocation concealment: yes Blinding: blinding of patients, hospital health personnel and outcome assessors Follow-up period: 14 days
Participants	Randomised: 95 (intervention group: 47; control group: 48) Excluded (post randomisation): 5 (intervention group: 2; control group: 3) Gender (women): 95 (100%) Age (years): mean (SD): intervention group: 31.3 (4.8); control group: 29.7 (4.9) Inclusion criteria: parturients who had epidural analgesia for normal vaginal delivery and who suffered an inadvertent dural tap Exclusion criteria: contraindication to steroid or ACTH therapy (e.g. hypertension or diabetes mellitus), pre-eclampsia, or contraindication to EBP (e.g. fever or leukocytosis)
Interventions	Intervention group: cosyntropin 1 mg (Cortrosy®, Amphastar Pharmaceuticals Inc) in 1 mL solution, intravenously over 5 min Control group: 1 mL of normal saline intravenously

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Hakim 2010 *(Continued)*

	Co-interventions: epidural analgesia: test with 3 mL of 2% lidocaine with 1:200,000 epinephrine. Loading dose of 8 to 15 mL of bupivacaine 0.125% plus fentanyl 50 µg. Continuous infusion of bupivacaine 0.125% with fentanyl 2 µg/mL at 8 to 15 mL/h. Patients with accidental dural puncture were encouraged to ambulate and to drink plenty of fluids, with prescription of stool softeners
Outcomes	• Number of participants affected by PDPH of any severity • Number of any possible adverse effects from the drug taken to prevent PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "PDPH if they developed headache within 5 days after dural puncture, which worsened within 15 min of sitting or standing, and improved within 15 min after lying, with at least one of the following criteria: neck stiffness, tinnitus, hypacusia, photophobia, or nausea" (Page 414) Sample size calculation: estimated 44 patients in each group for detecting at least a 30% difference between the groups the incidence of PDPH, a beta error of 0.2, 2-tailed alfa-error of 0.05 and degree of freedom of 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to one of two groups using a computer-generated random number list. The list was created using the GraphPad StatMate version 1.01i software" (Page 414)
Allocation concealment (selection bias)	Low risk	Quote: "The list... was accessible to anaesthesiologist attending to patients in labor through the computer database" (Page 414)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Injections were prepared by assistants not participating in the study, and both the patients and those involved in the study were blinded as to the patients' group" (Page 414)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Nurses and anaesthesiologists involved in headache assessment were blinded as to the patients' group" (Page 414)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Flowchart showing incidence of accidental dural puncture, patient recruitment and randomisation, incidence of PDPH and need for EBP and repeat EBP" (Page 415)
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Sadeghi 2012

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Iran (Shiraz) Setting: admitted to hospital Study design: parallel Randomisation: not described

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Sadeghi 2012 *(Continued)*

	Allocation concealment: not described Blinding: double-blind (patient and researcher) Follow-up period: 48 hours after elective caesarean section
Participants	Randomised: 120 (intervention group: 60; control group: 60) Excluded (post-randomisation): not described Gender (women): 120 (100%) Age (years): mean (SD): intervention group 26.11 (4.4); control group 26.35 (5.3) Inclusion criteria: patients undergoing elective caesarean section Exclusion criteria: headache, psychiatric problems, back pain, pre-eclampsia, coagulation disorders, convulsion background, spinal anaesthesia history and those who used any kinds of opiates
Interventions	Intervention group: after the child birth and umbilical cord clamping, aminophylline 1 mg/kg intravenously Control group: no intervention Co-interventions: 2 mL lidocaine 1% used for skin anaesthesia. A combination of 55 mg lidocaine 5% (dose and concentration as cited in the publication) and meperidine 5 mg were used for spinal anaesthesia. Needle nº 23 used for the spinal anaesthesia. In case of hypotension in both groups, ephedrine 5 mg intravenously. In both groups, the patients rested 24 h after the operation and then started walking
Outcomes	• Number of participants affected by PDPH of any severity
Notes	PDPH defined as: quote "Post dural puncture headache (PDPH) is a kind of headache that worsens by standing up and dwindles with recumbency" (Page 13) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly divided into two groups with an accidental allocation" (Page 14)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomised study (patient and researcher)" (Page 14) Quote: "data collection performed by a trained nurse that did not know anything about the intervention, the other stages of the study were performed by the doctors who knew the whole project and it may cause bias in the study" (Page 15)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "data collection performed by a trained nurse that did not know anything about the intervention, the other stages of the study were performed by the doctors who knew the whole project and it may cause bias in the study" (Page 15)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No explicit information but it seems that no patients were lost

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Sadeghi 2012 *(Continued)*

Selective reporting (reporting bias)	High risk	Adverse events not reported

Strelec 1994

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: US (Pittsburgh) Setting: hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: described as double-blind Follow-up period: 4 days
Participants	Randomised: 60 (intervention group: 30; control group: 30) Excluded (post randomisation): 2 (intervention group: 0; control group: 2) Gender (women): 18 (31%) Age (years): mean (SD): intervention group: 40.2 (13.3); control group: 48.5 (13) Inclusion criteria: participants who have had a lumbar myelography Exclusion criteria: not described
Interventions	Intervention group: oral anhydrous caffeine capsules, 300 mg every 8 hours for 3 days Control group: placebo capsules every 8 hours for 3 days Co-interventions: all other caffeinated substances were forbidden
Outcomes	• Number of participants affected by PDPH of any severity • Number of any possible adverse effects from the drug taken to prevent PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "PDPH criteria included postural headache, associated N/V, photophobia and neck stiffness" (Page 79) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

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Strelec 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 lost. No information provided about the reasons or the moment, but unlikely this is a cause of bias
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Yousefshahi 2012

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Iran (Tehran) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random number list Allocation concealment: not described Blinding: described as double-blind Follow-up period: 3 days
Participants	Randomised: 372 (intervention group: 186; control group: 186) Excluded (post randomisation): 12 (intervention group: 4; control group: 8) Gender (women): 372 (100%) Age (years): mean: intervention group: 28.5; control group: 28.9 Inclusion criteria: parturient after spinal anaesthesia for caesarean section Exclusion criteria: patients ASA class higher than II, sensitive to local anaesthetics, anticoagulant therapy, pre-eclampsia or skin infection at the site of needle insertion
Interventions	Intervention group: intravenous dexamethasone 8 mg (2 mL) after clamping the umbilical cord Control group: 2 mL of intravenous normal saline after clamping the umbilical cord Co-interventions: all patients received 500 mL of normal saline or Ringer's solution intravenously before spinal anaesthesia. Ondansetron, metoclopramide and H2-blockers as needed
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of participants with any headache

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Yousefshahi 2012 *(Continued)*

- Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Notes	PDPH defined as: quote: "PDPH was defined as a headache located in the occipital and/or frontal areas which was worsened by standing or sitting, and alleviates by lying down" (Page 2) Sample size calculation: quote: "The study was designed to achieve 80 % power to detect a 15 % difference in the population, in which the prevalence of the condition was 8.9 % based on previous studies. The level of statistical significance was reported to be 5 %" (Page 3) Email contact with Fardin Yousefshahi MD on April 2012 for clarification about missing data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were divided into two groups based on a computer random number generator" (Page 2)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each patient received a specific row number for grouping into the dexamethasone or placebo group, corresponding to a computerized randomization system; grouping was not reflected in the patient's data sheet" (Page 2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trained nurses, who were unaware of the objectives of the study, asked the patients about any occurrence of headache every 24 h for 72 h. The patients complaining of possible PDPH were then visited by an anesthesiologist, similarly unaware of the study objectives, to rule out other causes of headache" (Page 2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twelve patients were excluded from the study due to missing data" (Page 2). 4 patients from the intervention group and 8 from the control group
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

ACTH: adrenocorticotropic hormone; ASA: American Society of Anesthesiologists; EBP: epidural blood patch; LP: lumbar puncture; PDPH: post-dural puncture headache; SD: standard deviation; VRSP: Verbal Rating Score for Pain.

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

Study	Reason for exclusion
Ackerman 2004	No individual drug assessed
Altunkaya 2005	The study did not focus on PDPH
Aziz 1968	The orthostatic component of headache not described
Balestrieri 2003	The study was not a RCT (letter)
Beilin 2003	The orthostatic component of headache not described

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Study	Reason for exclusion
Breebaart 2003	The study did not focus on PDPH
Caldwell 1994	The orthostatic component of headache not described
Camann 1992	The orthostatic component of headache not described
Camann 1993	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Campbell 1995	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Cesur 2009	The study was not a RCT (retrospective observational study)
Chalmers 1988	The study did not focus on PDPH Intervention was not aimed at preventing PDPH
Chilvers 1997	Intervention was not aimed at preventing PDPH
Cho 2008	The study did not focus on PDPH
Clarke 2009	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Colonna-Romano 1989	No individual drug assessed
Cowan 1980	The orthostatic component of headache not described
D'Angelo 1994	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Danelli 2004	The study did not focus on PDPH
Dayioglu 2009	The orthostatic component of headache not described
De Pietri 2006	The orthostatic component of headache not described
Delfino 2001	The orthostatic component of headache not described
Dijkstra 2008	The orthostatic component of headache not described Intervention was not aimed to prevent PDPH
Dilli 2008	The study did not focus on PDPH
Dominguez-Hervella 1993	The orthostatic component of headache not described
Edström 1986	The orthostatic component of headache not described
Elkhodair 2010	The study was not a RCT (Critically Appraised Topics)
Fogarty 1993	The study did not focus on PDPH

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Study	Reason for exclusion
Fogarty 1995	The study did not focus on PDPH
Frey 1998	The orthostatic component of headache not described
Frizelle 1997	The orthostatic component of headache not described
Fu 2008	The study did not focus on PDPH
Fujii 1998	The study did not focus on PDPH
Förster 2006	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Gangopadhyay 2010	The orthostatic component of headache not described
Ganzi 1995	No individual drug assessed
Garg 2010	The study did not focus on PDPH
Gielen 1986	The study did not focus on PDPH
Ginsberg 1996	The study did not focus on PDPH
Girgin 2008	The study did not focus on PDPH
Gogarten 2004	The study did not focus on PDPH
Gurbet 2008	The study did not focus on PDPH
Hansen 1979	The orthostatic component of headache not described
Hansen 1980	The study was not a RCT (letter)
Harsten 1997	The orthostatic component of headache not described
Hein 2010	The orthostatic component of headache not described
Hendriks 2009	The orthostatic component of headache not described
Ilioff 1990	The orthostatic component of headache not described
Imbelloni 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Imbelloni 2009	Intervention was not aimed at preventing PDPH
Imbelloni 2010	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Jacobsohn 2005	The orthostatic component of headache not described
Kallio 2004	The study did not focus on PDPH

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Study	Reason for exclusion
Kallio 2005	The study did not focus on PDPH
Kaukinen 1981	Allocation was not randomised
Kouri 2004	The study did not focus on PDPH
Lanz 1982	The study did not focus on PDPH
Lauretti 1999	The study did not focus on PDPH
Lauretti 1999b	The study did not focus on PDPH
Lauretti 2000	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Lauretti 2000b	The study did not focus on PDPH
Lee 2005	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Lewis 1992	The study did not focus on PDPH
Lierz 2004	The study did not focus on PDPH
Luck 2008	The study did not focus on PDPH
López-Soriano 2002	The orthostatic component of headache not described
Manaa 2005	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Martlew 2009	The study was not a RCT (letter)
Massou 2008	The study was not a RCT (letter)
Meininger 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Michalek-Sauberer 2008	The orthostatic component of headache not described
Morrison 1994	The study did not focus on PDPH
Mosavy 1975	Allocation was not randomised
Murto 1999	The orthostatic component of headache not described
Møller 1984	The orthostatic component of headache not described
Neilson 2008	The study did not focus on PDPH
Ogun 2003	The study did not focus on PDPH

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Study	Reason for exclusion
Paech 1993	The orthostatic component of headache not described
Palahniuk 1979	Allocation was not randomised No individual drug assessed
Pan 2001	The study did not focus on PDPH
Patra 2005	The study did not focus on PDPH
Phero 1987	The orthostatic component of headache not described
Plaja 2000	The study did not focus on PDPH
Prusinski 1974	Allocation was not randomised
Radpay 2003	The study did not focus on PDPH
Reinhart 1985	The study did not focus on PDPH
Rivera-Ordonez 2005	The study did not focus on PDPH
Roux 1983	The orthostatic component of headache not described
Rucci 1985	The study did not focus on PDPH
Ryan 1983	The study did not focus on PDPH
Sakaguchi 2000	The study did not focus on PDPH
Sangarlangkarn 1987	The orthostatic component of headache not described
Sanli 2005	Intervention was not aimed at preventing PDPH
Santos 1986	The study was not a RCT (no control group) The orthostatic component of headache not described
Sawhney 2004	The study did not focus on PDPH
Sengupta 1989	No individual drug assessed
Seyhan 2005	The study was not a RCT (no control group)
Shah 2003	The study did not focus on PDPH
Singh 2006	The study did not focus on PDPH
Smith 2004	The study did not focus on PDPH
Soni 2001	The study did not focus on PDPH
Sudarshan 1995	The study did not focus on PDPH
Tekin 2007	The orthostatic component of headache not described

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Study	Reason for exclusion
	Intervention was not aimed at preventing PDPH
Thomas 2006	The study did not focus on PDPH
Trivedi 1993	Epidural saline infusion was not used as a pharmacological agent
Tsen 2001	The orthostatic component of headache not described
Tucker 2004	The study did not focus on PDPH
Tuncer 2005	The study did not focus on PDPH
Turan 2006	The study did not focus on PDPH
Turker 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Unlugenc 2006	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Unlugenc 2009	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Usubiaga 1967	Allocation was not randomised No individual drug assessed
Vaghadia 1997	Intervention was not aimed at preventing PDPH
Vale 1995	The study did not focus on PDPH
Vichitvejpaisal 1992	Intervention was not aimed at preventing PDPH
Viscusi 2005	The study did not focus on PDPH
Waxler 2004	The study did not focus on PDPH
Wells 2004	The study did not focus on PDPH
Whiteside 2003	Intervention was not aimed at preventing PDPH
Widerlöv 1979	The orthostatic component of headache not described
Wilder-Smith 1998	The study did not focus on PDPH
Wood 1993	The study did not focus on PDPH
Yanagidate 2004	The study did not focus on PDPH
Yeh 2000	The study did not focus on PDPH
Yücel 1999	The orthostatic component of headache not described
Zackova 2000	The study did not focus on PDPH

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PDPH: post-dural puncture headache; RCT: randomised controlled trial

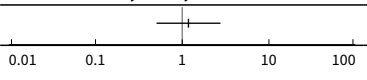
DATA AND ANALYSES

Comparison 1. Spinal morphine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.1 Pruritus	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Nausea and vomiting	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

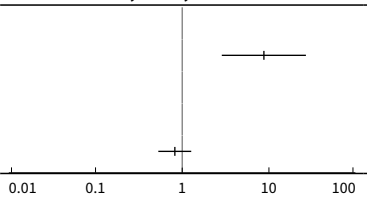
Analysis 1.1. Comparison 1 Spinal morphine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Spinal morphine n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Abboud 1992	9/40	8/42		1.18[0.51,2.76]



Analysis 1.2. Comparison 1 Spinal morphine versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Study or subgroup	Favours spinal morphine n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
1.2.1 Pruritus				
Abboud 1992	25/40	3/42		8.75[2.86,26.72]
1.2.2 Nausea and vomiting				
Abboud 1992	18/40	23/42		0.82[0.53,1.27]



Comparison 2. Epidural morphine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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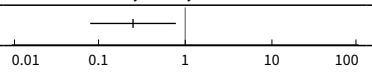
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.1 Pruritus	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Nausea and vomiting	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

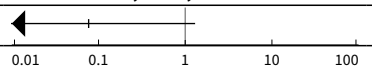
Analysis 2.1. Comparison 2 Epidural morphine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Epidural morphine n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Al-metwalli 2008	3/25	12/25		0.25[0.08,0.78]



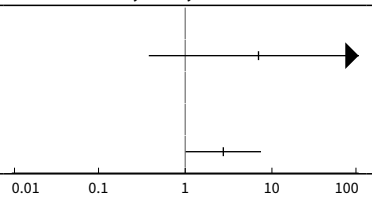
Analysis 2.2. Comparison 2 Epidural morphine versus placebo, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Epidural morphine n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Al-metwalli 2008	0/25	6/25		0.08[0,1.3]



Analysis 2.3. Comparison 2 Epidural morphine versus placebo, Outcome 3 Number of any possible adverse effects from the drug taken to prevent PDPH.

Study or subgroup	epidural morphine n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
2.3.1 Pruritus				
Al-metwalli 2008	3/25	0/25		7[0.38,128.87]
2.3.2 Nausea and vomiting				
Al-metwalli 2008	11/25	4/25		2.75[1.01,7.48]



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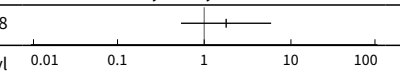
Comparison 3. Spinal fentanyl versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Spinal fentanyl versus no intervention, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Spinal fentanyl n/N	No intervention n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Devcic 1993	7/96	4/98		1.79[0.54,5.91]



Analysis 3.2. Comparison 3 Spinal fentanyl versus no intervention, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Spinal fentanyl n/N	No comparison n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Devcic 1993	3/96	1/98		3.06[0.32,28.93]

Analysis 3.3. Comparison 3 Spinal fentanyl versus no intervention, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Study or subgroup	Spinal fentanyl n/N	No intervention n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Devcic 1993	4/96	2/98		2.04[0.38,10.89]

Comparison 4. Caffeine 75 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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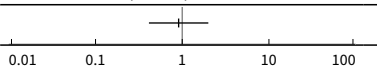
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

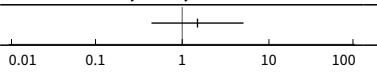
Analysis 4.1. Comparison 4 Caffeine 75 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	10/70	11/70		0.91[0.41,2]



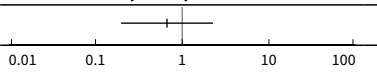
Analysis 4.2. Comparison 4 Caffeine 75 mg versus placebo, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	6/70	4/70		1.5[0.44,5.09]



Analysis 4.3. Comparison 4 Caffeine 75 mg versus placebo, Outcome 3 Number of participants with any headache.

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	4/70	6/70		0.67[0.2,2.26]



Comparison 5. Caffeine 125 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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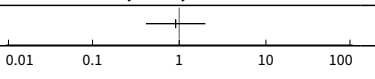
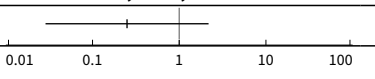
Analysis 5.1. Comparison 5 Caffeine 125 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	10/70	11/70		0.91[0.41,2]



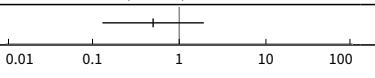
Analysis 5.2. Comparison 5 Caffeine 125 mg versus placebo, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	1/70	4/70		0.25[0.03,2.18]



Analysis 5.3. Comparison 5 Caffeine 125 mg versus placebo, Outcome 3 Number of participants with any headache.

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	3/70	6/70		0.5[0.13,1.92]



Comparison 6. Caffeine 75 mg versus caffeine 125 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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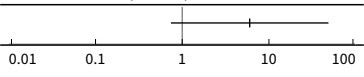
Analysis 6.1. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	10/70	10/70		1[0.44,2.25]

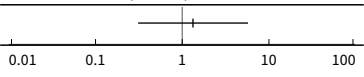
Analysis 6.2. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	6/70	1/70		6[0.74,48.55]



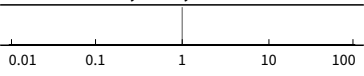
Analysis 6.3. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 3 Number of participants with any headache.

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	4/70	3/70		1.33[0.31,5.74]



Analysis 6.4. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 4 Number of any possible adverse effects from the drug taken to prevent PDPH.

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Esmaoglu 2005	0/70	0/70		Not estimable



Comparison 7. Indomethacin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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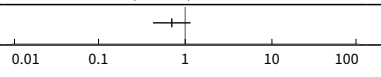
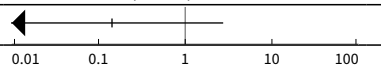
Analysis 7.1. Comparison 7 Indomethacin versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Indomethacin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Flaatten 1987	21/125	30/125		0.7[0.42,1.15]



Analysis 7.2. Comparison 7 Indomethacin versus placebo, Outcome 2 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Study or subgroup	Indometacin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Flaatten 1987	0/125	3/125		0.14[0.01,2.74]

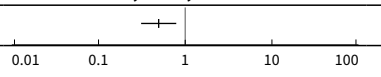


Comparison 8. Cosyntropin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

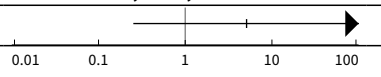
Analysis 8.1. Comparison 8 Cosyntropin versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Cosyntropin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Hakim 2010	15/47	31/48		0.49[0.31,0.79]



Analysis 8.2. Comparison 8 Cosyntropin versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Study or subgroup	Cosyntropin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Hakim 2010	2/47	0/48		5.1[0.25,103.57]



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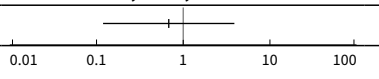
Analysis 8.3. Comparison 8 Cosyntropin versus placebo, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Study or subgroup	Cosyntropin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Hakim 2010	2/47	3/48		0.68[0.12,3.89]

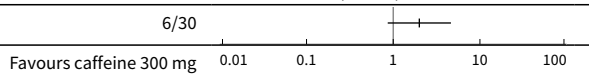


Comparison 9. Caffeine 300 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

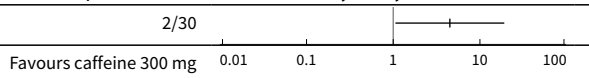
Analysis 9.1. Comparison 9 Caffeine 300 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Caffeine 300 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Strelec 1994	12/30	6/30		2[0.86,4.63]



Analysis 9.2. Comparison 9 Caffeine 300 mg versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Study or subgroup	Caffeine 300 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Strelec 1994	9/30	2/30		4.5[1.06,19.11]



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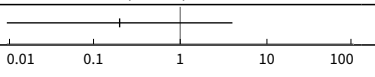
Analysis 9.3. Comparison 9 Caffeine 300 mg versus placebo, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Study or subgroup	Caffeine 300 mg n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Strelec 1994	0/30	2/30		0.2[0.01,4]

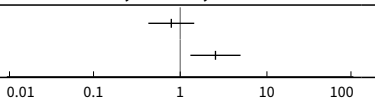


Comparison 10. Dexamethasone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

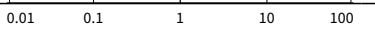
Analysis 10.1. Comparison 10 Dexamethasone versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Doroudian 2011	15/89	19/89		0.79[0.43,1.45]
Yousefshahi 2012	28/186	11/186		2.55[1.31,4.96]



Analysis 10.2. Comparison 10 Dexamethasone versus placebo, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Doroudian 2011	2/89	8/89		0.25[0.05,1.14]
Yousefshahi 2012	0/186	0/186		Not estimable



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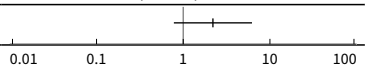
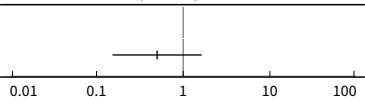
Analysis 10.3. Comparison 10 Dexamethasone versus placebo, Outcome 3 Number of participants with any headache.

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Yousefshahi 2012	11/186	5/186		2.2[0.78,6.21]



Analysis 10.4. Comparison 10 Dexamethasone versus placebo, Outcome 4 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Doroudian 2011	0/89	0/89		Not estimable
Yousefshahi 2012	4/186	8/186		0.5[0.15,1.63]

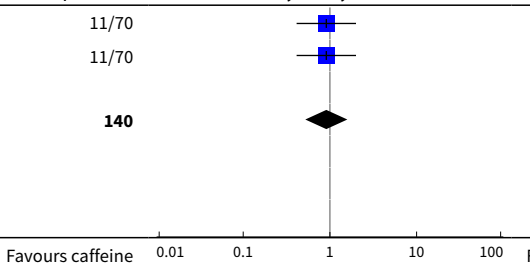


Comparison 11. Caffeine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.59]
2 Number of participants with severe PDPH	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.33, 2.35]
3 Number of participants with any headache	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.24]

Analysis 11.1. Comparison 11 Caffeine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Esmaoglu 2005	10/70	11/70		50%	0.91[0.41,2]
Esmaoglu 2005	10/70	11/70		50%	0.91[0.41,2]
Total (95% CI)	**140**	**140**		**100%**	**0.91[0.52,1.59]**
Total events: 20 (Caffeine), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					



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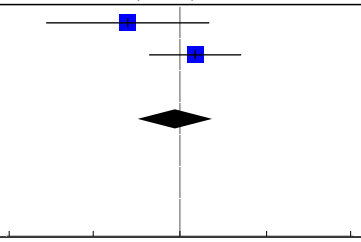
Analysis 11.2. Comparison 11 Caffeine versus placebo, Outcome 2 Number of participants with severe PDPH.

Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Esmaoglu 2005	1/70	4/70		50%	0.25[0.03,2.18]
Esmaoglu 2005	6/70	4/70		50%	1.5[0.44,5.09]
Total (95% CI)	**140**	**140**		**100%**	**0.88[0.33,2.35]**
Total events: 7 (Caffeine), 8 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.03, df=1(P=0.15); I²=50.82%					
Test for overall effect: Z=0.27(P=0.79)					



Analysis 11.3. Comparison 11 Caffeine versus placebo, Outcome 3 Number of participants with any headache.

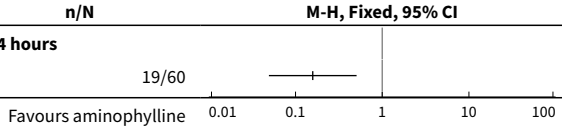
Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Esmaoglu 2005	14/70	17/70		50%	0.82[0.44,1.54]
Esmaoglu 2005	13/70	17/70		50%	0.76[0.4,1.45]
Total (95% CI)	**140**	**140**		**100%**	**0.79[0.51,1.24]**
Total events: 27 (Caffeine), 34 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%					
Test for overall effect: Z=1.01(P=0.31)					

Comparison 12. Aminophylline versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Number of participants affected by PDPH of any severity at 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Number of participants affected by PDPH of any severity at 48 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Aminophylline versus no intervention, Outcome 1 Number of participants affected by PDPH of any severity.

Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Number of participants affected by PDPH of any severity at 24 hours				
Sadeghi 2012	3/60	19/60		0.16[0.05,0.51]



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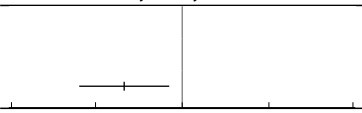
Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.1.2 Number of participants affected by PDPH of any severity at 48 hours				
Sadeghi 2012	3/60	14/60		0.21[0.06,0.71]



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 explode 'Anesthesia, Epidural' / all subheadings

#2 explode 'Anesthesia, Spinal' / all subheadings

#3 explode 'Injections, Spinal' / all subheadings

#4 explode 'Myelography' / all subheadings

#5 explode 'Spinal Puncture' / all subheadings

#6 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) near/10 (puncture* or inject* or anesth* or anaesth* or needle*)

#7 myelogra*

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 explode 'Headache disorders' / all subheadings

#10 headach* or cephalgia or (head near/2 pain) or (cranial adj2 pain)

#11 #9 or #10

#12 #8 and #11

Appendix 2. MEDLINE search strategy

#1 explode 'Anesthesia, Epidural' / all subheadings

#2 explode 'Anesthesia, Spinal' / all subheadings

#3 explode 'Injections, Spinal' / all subheadings

#4 explode 'Myelography' / all subheadings

#5 explode 'Spinal Puncture' / all subheadings

#6 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)

#7 myelogra*

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 explode 'Headache disorders' / all subheadings

#10 headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)

#11 #9 or #10

#12 #8 and #11

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The MEDLINE search strategy above was combined with the following highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format.

Cochrane Highly Sensitive Search Strategy for identifying randomised trials

1. randomised controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. humans.sh.

11. 9 and 10

Appendix 3. EMBASE search strategy

#1 explode 'Spinal Anesthesia' / all subheadings

#2 explode 'Lumbar Puncture' / all subheadings

#3 explode 'Myelography' / all subheadings

#4 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)

#5 myelogra*

#6 #1 or #2 or #3 or #4 or #5

#7 explode 'Headache and facial pain' / all subheadings

#8 headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)

#9 #7 or #8

The above EMBASE search strategy was combined with the following filter developed for EMBASE to identify randomised trials.

Search filter for EMBASE (Ovid format) 2008

1. random*.ti,ab.

2. factorial*.ti,ab. (5987)

3. (crossover* or cross over* or cross-over*).ti,ab.

4. placebo*.ti,ab.

5. (doubl* adj blind*).ti,ab.

6. (singl* adj blind*).ti,ab.

7. assign*.ti,ab.

8. allocat*.ti,ab.

9. volunteer*.ti,ab.

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10. CROSSOVER PROCEDURE.sh.

11. DOUBLE-BLIND PROCEDURE.sh.

12. RANDOMIZED CONTROLLED TRIAL.sh.

13. SINGLE BLIND PROCEDURE.sh.

14. or/1-13

15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/

16. HUMAN/

17. 15 and 16

18. 15 not 17

19. 14 not 18

Appendix 4. CINAHL search strategy

1 anaesthesia, epidural/ or analgesia, epidural/ or "epidural analgesia administration (iowa nic)"/ or exp injections, epidural/

2 exp injections, intraspinal/

3 myelography/

4 spinal puncture/ or anaesthesia, spinal/

5 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) and (puncture* or inject* or anesthe* or anaesthe* or needle*)).ti,ab

6 myelogra*.ti,ab

7 1 or 2 or 3 or 4 or 5 or 6

8 *headache/

9 (headach* or cephalgi* or cephalalgi*).ti,ab

10 8 or 9

11 7 and 10

12 exp clinical trials/

13 (clinical and trial*).ti

14 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti

15 (randomi?ed and control* and trial*).ti

16 random assignment/

17 (random* and allocat*).ti

18 placebo*.ti

19 placebos/

20 quantitative studies/

21 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22 11 and 21

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WHAT'S NEW

Date	Event	Description
25 July 2016	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 2, 2013

Date	Event	Description
25 February 2013	Amended	Added link to Appendix 4.

CONTRIBUTIONS OF AUTHORS

Conceiving the review (guarantor): Xavier Basurto (XB).

Screening search results: XB, Sonia Uriona (SU).

Screening retrieved papers against inclusion criteria: XB, SU, Laura Martínez (LM), Ivan Solà (IS), Xavier Bonfill Cosp (XBC).

Appraising quality of papers: XB, LM, SU.

Extracting data from papers: XB, LM, SU.

Data management for the review: XB, LM.

Entering data into Review Manager (RevMan 5.1): XB, LM.

Interpretation of data: XB, LM, IS, XBC.

Statistical analysis: XB, LM, IS.

Writing the review: XB, LM, SU, IS.

Comment and editing of review drafts: XB, LM, SU, IS, XBC.

Responsible for reading and checking review before submission: XB, LM, IS, XBC.

Responsible for initiating and running the update of this review: XB.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.
- CIBER de Epidemiología y Salud Pública (CIBERESP), Spain.

External sources

- Agencia de Calidad del Sistema Nacional de Salud, Ministerio de Salud y Consumo, Spain.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of participants: "The use of a standardized diagnostic criteria for PDPH was not required, but it should at least be described as orthostatic headache which worsens on standing and improved by lying down." The "it should at least be" has been added to emphasise the need to include only those studies that have used an orthostatic headache criteria to include participants.
- PaPaS Review Group Specialised Register electronic search eliminated.
- CINAHL search strategy included.
- Background has been adapted with a previous published Cochrane review on treatment drugs for PDPH (Basurto 2011).

NOTES

This protocol was originally published in Issue 1, 2000 by Cathie Sudlow. The review has now been taken over by Xavier Basurto Ona and the title split into one on prevention (this present review) and another on treatment, which is being written alongside this review.

Note added July 2016:

A search in July 2015 did not identify any relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review 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)

Aminophylline [administration & dosage]; Analgesics [*administration & dosage]; Caffeine [administration & dosage]; Cosyntropin [administration & dosage]; Dexamethasone [administration & dosage] [adverse effects]; Drug Administration Routes; Fentanyl [administration & dosage]; Indomethacin [administration & dosage]; Morphine [administration & dosage] [adverse effects]; Post-Dural Puncture Headache [*prevention & control]; Randomized Controlled Trials as Topic; Spinal Puncture [adverse effects]

MeSH check words

Adult; Child; Female; Humans; Male

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