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Drug therapy for treating post-dural puncture headache

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ABSTRACT

Background
Post-dural puncture headache (PDPH) is the most common complication of lumbar puncture, an invasive procedure frequently performed in the emergency room. Numerous pharmaceutical drugs have been proposed to treat PDPH but there are still some uncertainties about their clinical effectiveness.

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

Search strategy
The search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2011, Issue 2), MEDLINE (from 1950 to June 2011), EMBASE (from 1980 to June 2011) and CINAHL (from 1982 to June 2011). There was no language restriction.

Selection criteria
We considered randomised controlled trials (RCTs) assessing the effectiveness of any pharmacological drug used for treating 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 the included studies assessed different sorts of drugs or different outcomes. We performed an intention-to-treat (ITT) analysis.

Main results
We included seven RCTs (200 participants) in this review (between 88% and 90.5% were women; mostly parturients (84% to 87%) after a lumbar puncture for a regional anaesthesia). Pharmacological drugs assessed were oral and intravenous caffeine, subcutaneous sumatriptan, oral gabapentin, oral theophylline, intravenous hydrocortisone and intramuscular adrenocorticotropic hormone (ACTH).

One RCT reported data about PDPH persistence of any severity at follow up (primary outcome); caffeine reduced the number of participants with PDPH at one to two hours when compared to placebo. Treatment with caffeine also decreased the need for a
conservative supplementary therapeutic option. Treatment with gabapentin versus placebo reported better visual analogue scale (VAS) scores after one, two, three and four days; treatment with hydrocortisone plus conventional treatment showed better VAS scores than conventional treatment alone at six, 24 and 48 hours and treatment with theophylline showed a lower mean “sum of pain” when compared with placebo. Sumatriptan and ACTH did not show any relevant effect for this outcome.

There were no clinically significant drug adverse events.

The rest of the outcomes were not reported by the RCTs or did not show any relevant effect.

**Authors’ conclusions**

Caffeine has shown effectiveness for treating PDPH, decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions, when compared with placebo. Gabapentin, theophylline and hydrocortisone have also shown a decrease in pain severity scores when compared with placebo or conventional care.

There is a lack of conclusive evidence for the other drugs assessed (sumatriptan and ACTH).

These conclusions should be interpreted with caution, due to the lack of information to allow correct appraisal of risk of bias, the small sample sizes of studies and also the limited generalisability, as most participants were post-partum women in their 30s.

**PLAIN LANGUAGE SUMMARY**

**Drugs for treating headache after a lumbar puncture**

Lumbar puncture is an invasive procedure by which medical personnel try to get a sample of cerebrospinal fluid though a needle inserted into the lower lumbar area for diagnostic purposes (i.e. meningitis or subarachnoid haemorrhage). It is also used to inject medications such as anaesthetics and analgesics to perform a regional anaesthesia or chemotherapy. 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. Numerous medications are used in clinical practice to treat PDPH, so the aim of this review was to assess the effectiveness of these drugs.

We included seven randomised clinical trials (RCTs), with a total of 200 participants, that assessed six medications (caffeine, sumatriptan, gabapentin, hydrocortisone, theophylline and adrenocorticotropic hormone). Caffeine proved to be effective in decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions. Gabapentin, theophylline and hydrocortisone also proved to be effective, decreasing pain severity scores better than placebo or conventional treatment alone, respectively. A meta-analysis (combining of data) was not possible because all the included RCTs assessed different drugs or different outcomes. Lack of information to allow correct appraisal of the risk of bias and the small sample sizes (number of patients) of the RCTs may limit the conclusions of this review.

**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 punctures (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 percent 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 downward pull on pain-sensitive structures resulting in a headache (Ahmed 2006; Baumgarten 1987; Davignon 2002;
Drug therapy for treating post-dural puncture headache (Review)

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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 to the aforementioned, in diagnostic or therapeutic lumbar punctures, 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 punctures (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 (Grande 2005). 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 as well as medical attendance 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 epidural blood patch (Lavi 2006).

How the intervention might work

Due to the fact that no clear pathophysiology has been asserted for PDPH, many therapeutic options are used to relieve headache in clinical practice and also essayed in clinical trials: epidural blood patch (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) increasing intravascular volume (Kuczkowski 2006).

Treatment drugs should help to decrease the duration of headache, reduce the headache severity as much as possible, avoid the need for any other therapeutic option (e.g. EBP), 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

Three Cochrane systematic reviews about prevention of PDPH are in process (Arévalo-Rodríguez 2011; Basurto 2009; Newman 2010) alongside with one published review (Boonmak 2010). Treatment and management of PDPH is also focused on in Boonmak 2010.

Numerous therapeutic drugs have been proposed, based on limited randomised controlled trials (RCTs) and case series, including: analgesics, caffeine, theophylline, sumatriptan, epidural route administration of adrenocorticotropic hormones, morphine, 0.9% sodium chloride or dextran (Choi 1996; Turnbull 2003). Most of these trials’ sample sizes are small and there is inconsistency among them, therefore there is weak evidence to support the drug treatment of PDPH.

Current uncertainties about the clinical effectiveness of treatment drugs require a systematic review to clarify their potential benefits and inspire future guidelines on the topic.

OBJECTIVES

The objectives of this review were to assess the effectiveness and safety of drugs (in the form of any chemical substance) for treating PDPH in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies
We included randomised controlled trials (RCTs) (parallel, crossover or factorial) in any setting. We excluded studies using alternation, date of birth, hospital record number or other quasi-random methods of allocation of treatment.

Types of participants
Participants undergoing lumbar punctures 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 either sex. The use of a standardised diagnostic criteria for PDPH will not be required, but it should at least be described as orthostatic headache which worsens on standing and is improved by lying down. We described the specific diagnostic criteria used in each included study.

Types of interventions
We considered any pharmacological drug used for treating PDPH. Acceptable control groups included: placebo, no intervention, any other drug treatments, behavioural and physical therapies. We considered interventions at any dose, formulation or route of administration given after lumbar puncture.

Types of outcome measures

Primary outcomes
PDPH persistence of any severity at follow up. We considered the rate of persistent PDPH at short (< 12 hours), medium (< 24 hours) or long-term (≥ 24 hours) follow up.

Secondary outcomes
1. Daily activity limited by headache.
2. Conservative supplementary therapeutic option offered when trial drug intervention fails to relieve headache and following trial protocol (e.g. bed rest, fluid consumption, analgesics).
3. Epidural blood patch performed, administered when intervention drug and conservative option fail to relieve headache and following trial protocol.
4. Change in pain severity scores as defined by the trialist.
5. Improvements in pain severity scores as defined by the trialist.
6. Number of days participants stay in hospital.
7. Any possible adverse events of pharmacological drugs taken to treat PDPH.
8. 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 the 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, 2011, Issue 2);
- MEDLINE (from 1950 to June 2011);
- EMBASE (from 1980 to June 2011); and
- CINAHL (from 1982 to June 2011).

The search strategies for CENTRAL, MEDLINE and EMBASE can be found in Appendix 1, Appendix 2 and Appendix 3, respectively.

Data collection and analysis

Selection of studies
Two independent review authors (XB, IS) 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 (LM) checked data for accuracy, resolving any disagreement by discussion. We entered data into Review Manager 5.1.

When efficacy outcomes were reported in dichotomous form (primary outcome and all secondary outcomes except change in pain severity scores as defined by the trialist).
severity (outcome number 4) and number of days participants stay in hospital (outcome number 6), we recorded the number of participants assigned to each treatment arm and the number with each event.

For outcomes reported on a continuous scale (change in pain severity (outcome number 4) and number of days participants stay in hospital (outcome number 6)), we recorded data on the variance associated with their means.

In future updates of this review, when a study reports pre and post-treatment group means, without reporting data on the variance associated with these means, we will attempt to calculate or estimate variances based on primary data or test statistics, if these are reported. When a study uses pre and post-treatment scores to calculate a change score for each participant, and then uses these within-patient change scores to calculate a group mean change score, we will record and analyse these group mean change scores. When only post-treatment data are available, we will use these, relying on allocation to achieve between-group balance. If these calculations are needed, we will perform a sensitivity analyses excluding the studies involved, to assess the impact of the calculations.

We recorded the proportion of participants reporting adverse events for each treatment arm wherever possible. We recorded the identity and rates of specific adverse events.

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 2009) 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 (LM) checked these for accuracy, resolving any disagreement by discussion.

Assessment of heterogeneity

This review did not include a meta-analysis. In future updates of this review, if needed, we will assess heterogeneity of effect sizes by means of the Q (Chi^2 statistic) using the methods of Peto and Mantel-Haenszel. If statistical evidence exists for homogeneity of effect sizes, the planned analysis will use a fixed-effect model.

When significant heterogeneity is present (Chi^2 test with P value < 0.1 or I^2 statistic value greater than 50%), we will make an attempt to explain the differences based on the clinical characteristics of the included studies. We will not statistically combine studies that are dissimilar in terms of interventions and participants. However, when a group of studies with heterogeneous results appears to be similar, we will combine the study estimates using a random-effects model (Higgins 2002; Higgins 2003).

Data synthesis

The differences between the studies included in this review, in terms of interventions assessed and outcomes measured, only permitted a narrative summary.

We analysed the results for different drugs separately using Review Manager 5.1. 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 calculate the numbers needed to treat for an additional beneficial outcome (NNT) 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 (NNH) 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 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, when 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 (< 12 hours), medium (12 to 24 hours) or long-term time periods (≥ 24 hours) for the treatment drugs.

Population subgroup analyses

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

- there is no difference between obstetric participants and all other participants;
- there is no difference between men and non-obstetric women participants;
- 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, we will conduct a sensitivity analyses formulated \textit{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 studies with a cross-over design.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

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

**Results of the search**

We identified 1615 references in primary electronic databases on June 2011 from our extended search strategy for prevention and treatment drugs for PDPH. We excluded 1588 references after a detailed reading of the title and abstract. We obtained the full text report for the rest of the studies (27 papers) to check if they strictly fulfilled all the inclusion criteria. We finally excluded 18 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. Seven studies in nine articles published completely fulfilled the inclusion criteria for this review (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978).

**Included studies**

Included studies are detailed in the 'Characteristics of included studies' table.

**Study design**

All seven included studies (involving a total of 200 participants) were RCTs with a parallel design. Most of them were placebo-controlled except Noyan 2007 who used a control group.

**Setting**

Only Rucklidge 2004 was a multicentric study with five hospitals involved.

Three studies were conducted in the USA (Camann 1990; Connelly 2000; Sechzer 1978), one in the UK (Rucklidge 2004), one in Germany (Feuerstein 1986), one in Turkey (Dogan 2006) and one in Iran (Noyan 2007).

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 200 participants suffering from PDPH. The smallest study had 10 participants (Connelly 2000) and the largest one 60 (Noyan 2007). Rucklidge 2004 was the only RCT that described how the sample size was calculated.

**Participants**

The majority of participants were women (at least 140/159), mostly parturient after a lumbar puncture for a regional anaesthesia (at least 118/140). There were three RCTs that included men (at least 19/159) (Connelly 2000; Dogan 2006; Feuerstein 1986). Sechzer 1978 did not report statistics about gender. The median age among participants ranged from 24 to 46.6 years old.

**Intervention**

Six of the seven studies compared placebo with different drugs: oral theophylline (Feuerstein 1986), oral (Camann 1990) or intravenous (Sechzer 1978) caffeine, subcutaneous sumatriptan (Connelly 2000), oral gabapentin (Dogan 2006) or intramuscular adrenocorticotropic hormone (ACTH) (Rucklidge 2004). Intravenous hydrocortisone was compared with conventional care (bed rest, hydration, acetaminophen and pethidine) in Noyan 2007. Caffeine was assessed in two RCTs by different routes of administration but at equipotent doses; Camann 1990 with 300 mg anhydrous caffeine orally and Sechzer 1978 with 500 mg of caffeine sodium benzoate intravenously.

Four included studies (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004) used an epidural blood patch (EBP) as a supplementary analgesic in case the intervention drug failed to resolve the headache. Follow up differed between studies but the most common length of follow up was 48 hours in three studies (Connelly 2000; Noyan 2007; Rucklidge 2004). The shortest one was Camann 1990 with 24 hours and the longest was Dogan 2006 with four days. Two studies (Feuerstein 1986; Sechzer 1978) did not report length of follow up.

**Outcomes of interest**

Sechzer 1978 reported data on the primary outcome and proportion of participants with PDPH persistence of any level of severity at follow up. The most reported secondary outcome, described by six included RCTs (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004), was a change in the pain severity scores. The outcome was reported directly or could be...
calculated with the results on pain severity scores documented during the follow up.

Four RCTs reported data regarding proportion of participants with EBP performed (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004) and five studies reported the number of any possible adverse events of pharmacological drug (Camann 1990; Connelly 2000; Feuerstein 1986; Noyan 2007; Rucklidge 2004). The proportion of participants showing improvements in pain severity scores were detailed in two RCTs (Camann 1990; Connelly 2000).

The proportion of participants with a conservative supplementary therapeutic option offered when the trial drug intervention failed was reported in two RCTs (Feuerstein 1986; Sechter 1978). Only Feuerstein 1986 reported the number of missing data (dropout participants) but without specifying to which intervention group they belonged.

There were two secondary outcomes not reported in the included RCTs: proportion of participants with daily activity limited by existence of headache and the number of days participants stayed in hospital.

Only one study stated that it had been funded with a grant from Glaxo (Connelly 2000).

Excluded studies

Eighteen studies did not fulfil the inclusion criteria and were excluded. The two most frequent reasons for exclusion were not being a RCT in five studies (Aguilera 1988; De las Heras 1997; Eldor 1990; Hakim 2005; Hodgson 1997) and not assessing an individual pharmacological drug intervention in five studies (Bart 1978; Naja 2009; Oedit 2005; Sandesc 2005; van Kooten 2008). In four studies (Basso 1985; Flaatten 1987; Widerlöv 1979; Zenglein 1978) the reason for exclusion was because the intervention was not aiming to treat PDPH. In three RCTs (Lang 1993; Schwalbe 1991; Torres 1986) the reason was not describing the orthostatic component of headache. Finally, in one case the reason was that the study used quasi-randomisation (Ergün 2008). For a summary of the reasons for exclusion please see the 'Characteristics of excluded studies' table.

Conflict of interest

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 1 and Figure 2.

Figure 1. "Risk of bias" graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

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<th>Allocation concealment (selection bias)</th>
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**Allocation**

**Sequence generation**

Allocation sequence was adequately generated in three RCTs (Connelly 2000; Rucklidge 2004; Sechzer 1978). Connelly 2000 did not report the method used to generate the sequence but after contacting the study author, a computer random series was confirmed. Rucklidge 2004 explicitly reported a computer-generated random numbers sequence and Sechzer 1978 used a table of random numbers.

The other three studies did not report the method used for sequence generation (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007).

**Allocation concealment**

Three studies had adequately concealed randomisation sequences: Connelly 2000 by sealed containers (confirmed by e-mail), Rucklidge 2004 via an independent office (confirmed by e-mail) and Sechzer 1978 by pharmacy-controlled randomisation.

The other four included studies did not provide information regarding allocation concealment (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007).

**Blinding**

The blinding method was adequate in all of the included studies (Camann 1990; Connelly 2000; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978) except in Dogan 2006 that did not report detailed data to allow assessment of this issue.

**Incomplete outcome data**

All RCTs included in this review, except one (Feuerstein 1986), had a low risk of attrition bias. The studies detailed data for all the participants that were randomised at the beginning of the trials. Feuerstein 1986 was judged as at high risk of attrition bias.

**Selective reporting**

All included RCTs (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978) did not report results for key outcomes (PDPH persistence of any severity at follow up and number of any possible adverse events) that would be expected to have been reported for such a study.

**Effects of interventions**

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

**Post-dural puncture headache (PDPH) persistence of any severity at follow up**

One study included data for the primary outcome of the review. Sechzer 1978 showed a statistically significant risk ratio when comparing intravenous caffeine sodium benzoate with placebo (23 events in 41 participants; risk ratio (RR) 0.29, 95% confidence interval (CI) 0.13 to 0.64; see Analysis 7.1).

**Conservative supplementary therapeutic option offered when trial drug intervention fails to relieve headache**

Two studies reported this outcome. Sechzer 1978 showed a statistically significant risk ratio for conservative supplementary therapeutic option when comparing intravenous caffeine sodium benzoate with placebo (23 events in 41 participants; RR 0.29, 95% CI 0.13 to 0.64; see Analysis 7.2). Feuerstein 1986 also reported this outcome, showing a non-significant risk ratio when comparing theophylline with placebo (six events in 11 participants; RR 0.42, 95% CI 0.12 to 1.40; see Analysis 4.1).

**Epidural blood patch (EBP) performed**

The studies that reported this outcome did not show significant differences (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004).

Camann 1990 showed that the risk ratio for EBP performed was statistically non-significant when comparing caffeine with placebo (18 events in 40 participants; RR 0.64, 95% CI 0.31 to 1.30; see Analysis 1.1).

Connelly 2000 showed a non-significant risk ratio when comparing sumatriptan with placebo (nine events in 10 participants; RR 0.82, 95% CI 0.49 to 1.38; see Analysis 2.1).

Noyan 2007 showed a non-significant risk ratio when comparing hydrocortisone with control group (one event in 60 participants; RR 0.33, 95% CI 0.01 to 7.87; see Analysis 5.1).

Finally, Rucklidge 2004 showed a non-significant risk ratio when comparing adrenocorticotropic hormone (ACTH) with placebo (13 events in 18 participants; RR 0.86, 95% CI 0.48 to 1.53; see Analysis 6.1).
**Change in pain severity scores as defined by the trialist**

Six studies included in the review measured pain severity by means of visual analogue scale (VAS) scores (Camann 1990; Connelly 2000; Dogan 2006; Noyan 2007; Rucklidge 2004) or by mean sum of pain (Feuerstein 1986).

**Camann 1990** reported statistically similar baseline VAS scores for the caffeine group and for the placebo group (40 participants; mean difference (MD) 9.00, 95% CI -0.80 to 18.80; see Analysis 1.2). At four hours, pain scores decreased in both groups, but did not show a significant difference (40 participants; MD -16.00, 95% CI -34.07 to 2.07; see Analysis 1.2). This result was also shown at 24 hours post-treatment (40 participants; MD 7.00, 95% CI -18.10 to 32.10; see Analysis 1.2).

**Connelly 2000** showed statistically similar VAS scores at baseline (10 participants; MD -26.00, 95% CI -55.14 to 3.14; see Analysis 2.2), and when comparing sumatriptan with placebo after one hour (10 participants; MD -18, 95% CI -55.73 to 19.73; see Analysis 2.2).

**Dogan 2006** also reported a statistically similar baseline VAS score (20 participants; MD 0.20, 95% CI -0.17 to 0.57; see Analysis 3.1). Gabapentin showed a significant decrease in VAS scores when compared with placebo. The study showed a progressive reduction in VAS scores for participants receiving gabapentin after one, two and three days of follow up (20 participants; one day: gabapentin 4.1 (SD 0.31), placebo 5.7 (SD 0.42), MD -1.60, 95% CI -1.92 to -1.28; two days: gabapentin 1.8 (SD 0.29), placebo 4.4 (SD 0.33), MD -2.60, 95% CI -2.87 to -2.33; three days: gabapentin 0.3 (SD 0.15), placebo 3.2 (SD 0.29), MD -2.90, 95% CI -3.10 to -2.70; see Analysis 3.1). The effect was reduced after four days of follow up (20 participants; gabapentin 0.1 (SD 0.1), placebo 1.7 (SD 0.21), MD -1.60, 95% CI -1.74 to -1.46; see Analysis 3.1).

**Noyan 2007** reported a statistically similar baseline VAS score (60 participants; MD 0.13, 95% CI -0.22 to 0.48; see Analysis 5.2). Hydrocortisone showed a significant decrease in VAS scores when compared with conventional care. The studies showed a progressive reduction in pain scores for the participant receiving hydrocortisone at six hours and 24 hours of follow up (60 participants; six hours: hydrocortisone 2.77 (SD 1.07), conventional treatment 6.63 (SD 1.35), MD -3.86, 95% CI -4.48 to -3.24; 24 hours: hydrocortisone 0.73 (SD 0.74), conventional treatment 3.87 (SD 1.63), MD -3.14, 95% CI -3.78 to -2.50; see Analysis 5.2). The effect was reduced at 48 hours of follow up (60 participants; hydrocortisone 0.63 (SD 0.61), conventional treatment 1.87 (SD 0.93), MD -1.24, 95% CI -1.64 to -0.84; see Analysis 5.2).

**Rucklidge 2004** (18 participants) reported no significant differences for this outcome, but all the results were reported in a figure. In **Feuerstein 1986** a mean sum of pain among the participants during the treatment period was used to compare both groups. Treatment with theophylline showed a significant lower mean sum of pain when compared with placebo (11 participants; theophylline 16 (SD 3.91), placebo 28 (SD 4.73), MD -12.00, 95% CI -17.19 to -6.81; see Analysis 4.2).

**Improvements in pain severity scores**

**Camann 1990** showed a marginal significant difference in the rate of participants with an improvement when receiving caffeine compared to placebo (30 events in 40 participants; RR 1.50, 95% CI 1.02 to 2.21; see Analysis 1.3).

**Connelly 2000** reported an improvement for two participants, one in each group (two events in 10 participants; RR 1.00, 95% CI 0.08 to 11.93; see Analysis 2.3). While the effect of sumatriptan was maintained until the end of follow up (48 hours), the participant in the placebo group worsened after 13 hours from the injection.

**Any possible adverse events of pharmacological drug taken to treat PDPH**

**Camann 1990** reported one participant in each group with transient flushing and anxiety. **Feuerstein 1986** reported one participant in each group with gastric pain. **Dogan 2006**, **Noyan 2007** and **Rucklidge 2004** reported no adverse events.

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

**Feuerstein 1986** did not report sufficient information about participants randomised who dropped out (5/16).

**DISCUSSION**

This systematic review identified two randomised controlled trials (RCTs) assessing caffeine for treating post-dural puncture headache (PDPH) (Camann 1990; Sechzer 1978) and five RCTs assessing other different drugs for treating PDPH: theophylline (Feuerstein 1986), sumatriptan (Connelly 2000), gabapentin (Dogan 2006) and adrenocorticotropic hormone (ACTH) (Rucklidge 2004). Some data were available for PDPH persistence of any severity at follow up (only in Sechzer 1978) and for changes in pain severity scores derived from visual analogue scale (VAS) measures.

For PDPH persistence (primary outcome), intravenous caffeine sodium benzoate showed a significant decrease in the proportion of participants with PDPH persistence when compared with placebo in Sechzer 1978.

For the changes in pain severity scores outcome, gabapentin showed a significant decrease in pain scores when compared to placebo in Dogan 2006, with differences at one, two and three
days and decreased after four days of the intervention. Hydrocortisone showed a significant decrease in pain scores when compared with conventional care in Noyan 2007, with differences that were sustained at six and 24 hours and decreased after 48 hours of the intervention. Theophylline showed a significant lower mean sum of pain when compared with placebo in Feuerstein 1986.

The minimum clinically significant difference in acute pain VAS score has been poorly investigated, although some published studies (Gallagher 2002; Kelly 1998; Kelly 2001; Mark 2009; Todd 1996) have estimated it to be around 9 to 17 on a 0 to 100 VAS score. RCTs included in this review with statistically significant mean differences in VAS scores reported numbers around 2 to 4 on a 0 to 10 VAS score, giving to these values a clinically significant difference.

For the conservative supplementary therapeutic option, intravenous caffeine sodium benzoate showed a significant decrease in the proportion of participants needing supplementary interventions when compared with placebo in Sechzer 1978.

The drugs assessed in the included studies did not show any relevant effect for the rest of outcomes of interest for this review. The proportion of participants that required an epidural blood patch (EBP) was similar between the interventions and their controls in four studies (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004), and only two studies showed a marginal effect favouring caffeine (Camann 1990) and sumatriptan (Connelly 2000) over placebo in the proportion of participants that reported an improvement in pain scores.

The studies did not report any clinically significant adverse event derived from any of the assessed drugs (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004).

Two RCTs (Camann 1990; Sechzer 1978) used equipotent doses of caffeine but we did not undertake meta-analysis because they reported different outcomes.

The outlined results should be interpreted with caution due to the limited number of studies identified, the diversity of drugs assessed and outcomes measured, the small sample sizes of the studies included and the bias presented. The reporting bias risk was judged high in all the included RCTs and there is also an important lack of data reported to allow correct appraisal of the risk of other sources of bias. Most of the studies included labouring women (between 84% and 87% of the total sample derived from the included studies) experiencing PDPH after having received regional anaesthesia. The short duration of the included studies does not allow us to know the effect of the drugs that showed some effects at a mid-term. This lack of applicability of the results is similar to that observed in another Cochrane Review assessing EBP for treating PDPH (Boonmak 2010).

Larger studies (reporting how sample size was determined) with an extended duration, similar to the follow up in the study involving gabapentin (at least four days) (Dogan 2006), and the use of more pragmatic outcomes such as the persistence of pain at follow up and possible adverse events of pharmacological drugs, should provide more information on the impact of the assessed drugs in this setting and situation.

AUTHORS’ CONCLUSIONS

Implications for practice

From the studies available caffeine shows a significant decrease in the proportion of participants with post-dural puncture headache persistence and in those needing supplementary interventions, when compared with placebo. Gabapentin, theophylline and hydrocortisone have shown a decrease in pain severity scores when compared with placebo or conventional care.

However, this conclusion should be interpreted with caution because this result comes from studies with limited sample sizes (seven studies involving a total of 200 participants).

The other drugs assessed (sumatriptan and adrenocorticotropic hormone) have not shown a significant effect.

Implications for research

Future research in this field should focus on the design of trials with larger samples (reporting how sample size was determined), extended follow-up periods (at least four days) and the measurement of relevant outcomes for decision-making, such as the persistence of pain at follow up and possible adverse events of pharmacological drugs. The reporting of these trials should also be improved (i.e. using the CONSORT statement (Schulz 2010)) to allow medical literature users to appraise the results of these studies accurately.

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 (previously the Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Review Group) for undertaking the searches; to Marta Roqué (Iberoamerican Cochrane Center) for her help in the statistical analysis; to Sera Tort for her help in editing the review; and to Cathie Sudlow and Charles Warlow for writing the first draft of the protocol.
References to studies included in this review

Camann 1990 [published data only]

Connelly 2000 [published and unpublished data]

Dogan 2006 [published data only]

Feuerstein 1986 [published data only]

Noyan 2007 [published data only]

Rucklidge 2004 [published and unpublished data]

Sechzer 1978 [published data only]

Sechzer 1985 [published data only]

References to studies excluded from this review

Aguilera 1988 [published data only]

Bart 1978 [published data only]

Basso 1985 [published data only]

De las Heras 1997 [published data only]

Eldor 1990 [published data only]

Ergün 2008 [published and unpublished data]

Flaatten 1987 [published data only]

Hakim 2005 [published data only]

Hodgson 1997 [published data only]

Lang 1993 [published data only]
Lang SA, Yip RW, Comfort VK. Intravenous caffeine as a treatment for postdural puncture headaches: will it replace the epidural blood patch?. Anaesthesia and Analgesia 1993;76(S1):S207.

Naja 2009 [published data only]

Oedit 2005 [published data only]

Sandesc 2005 [published data only]
management of postdural puncture headache increases

2006; P. Expectant


1978 {published data only}

Widerlöv 1979 {published data only}


Zenglein 1978 {published data only}


Additional references

Ahmed 2006


Ańgle 2005


Arévalo-Rodríguez 2011


Banks 2001


Basurto 2009


Baumgarten 1987


Berger 1998


Bezov 2010


Boonmak 2010


Choi 1996


Choi 2003


Clark 1996


Davignon 2002


Denny 1987


Gallagher 2002


Grande 2005


Hafer 1997


Harrington 2004


Higgins 2002

Higgins 2003

Higgins 2009

International Headache Society 2004

Kelly 1998
Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Academic Emergency Medicine 1998;5:1086-90.

Kelly 2001
Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal 2001;18(3):205-7.

Kuczkowski 2006

Lavi 2006

Mark 2009

McQuay 1998

Newman 2010

Review Manager 5.1

Schulz 2010

Thew 2008

Todd 1996

Turnbull 2003

Vallejo 2000

* Indicates the major publication for the study
# Characteristics of included studies [ordered by study ID]

## Camann 1990

| Methods | Randomised, double-blind, placebo-controlled trial  
|         | Study type: single-centre study  
|         | Location: USA (Massachusetts)  
|         | Study design: parallel  
|         | Randomisation: not described  
|         | Allocation concealment: not described  
|         | Blinding: blinding of participants and key study personnel. Investigational pharmacist was not blinded  
|         | Follow-up period: 24 hours  

| Participants | Randomised: 40 (intervention group: 20; control group: 20)  
|             | Excluded (post-randomisation): not described  
|             | Gender (women): 40 (100%)  
|             | Age (years); mean (standard deviation - SD): intervention group 29.8 (6.26), control group 30.6 (5.36)  
|             | Baseline VAS score; mean (SD): intervention group 69 (13.42), control group 60 (17.89)  
|             | **Inclusion criteria:**  
|             | Post-partum woman  
|             | **Exclusion criteria:**  
|             | Hypertension, pre-eclampsia, seizure disorder, intolerance to caffeine or consumed beverages containing caffeine within the previous 4 hours  

| Interventions | **Intervention group:** once oral capsule with 300 mg of caffeine  
|              | **Control group:** once oral placebo capsule with lactose  
|              | **Co-interventions:**  
|              | • Fail to resolve headache within 4 h: rest, increase fluid consumption and analgesics  
|              | • If previous fail to relieve headache: EBP  

| Outcomes | 1. Number of participants with EBP performed  
|         | 2. Change in pain severity VAS score after 4 and 24 hours  
|         | 3. Number of participants showing improvements in pain severity VAS score at 4 hours  
|         | 4. Number of any possible adverse events  

| Notes | Post-dural puncture headache (PDPH): Quote “Frontal and/or occipital discomfort worsened by upright posture and relieved by lying supine” (page 181)  
|       | Visual analogue scale (VAS): 0 = no headache and 100 = worst headache imaginable  
|       | Sample size calculation: not described  

## Risk of bias

| Bias | Authors’ judgement | Support for judgement |
Camann 1990  (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk</th>
<th>Details</th>
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<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>No information provided. Reported as randomised.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding</td>
<td>Low risk</td>
<td>Quote: &quot;Capsules, prepared by our investigational pharmacy, contained either anhydrous caffeine powder (USP 300 mg, Spectrum Chemical Mfg. Corp., Gardena, Calif.) or placebo (lactose powder) and appeared identical.&quot; (Pages 181 to 182)</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>No missing outcome data</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>The study report fails to include results for a key outcome (PDPH persistence of any severity at follow-up) that would be expected to have been reported for such a study</td>
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Connelly 2000

<table>
<thead>
<tr>
<th>Study Details</th>
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</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Study type: single-centre study</td>
<td>Study design: parallel</td>
</tr>
<tr>
<td>Location: USA (Massachusetts)</td>
<td>Randomisation: computer random numbers series</td>
</tr>
<tr>
<td>Study design: parallel</td>
<td>Allocation concealment: sealed container with a random code</td>
</tr>
<tr>
<td>Follow-up period: 48 hours</td>
<td>Blinding: blinding of participants and key study personnel</td>
</tr>
</tbody>
</table>

| Participants                      | Randomised: 10 (intervention group: 5; control group: 5) |
|-----------------------------------| Excluded (post-randomisation): not described |
| Gender (women): 8 (80%); intervention group 3 (60%); control group 5 (100%) |
| Age (years); mean (SD): intervention group 43 (12); control group 24 (8) |
| Baseline VAS score; mean (SD): intervention group 61 (24), control group 87 (23) |
| Inclusion criteria:               | Patients with severe PDPH |
| Exclusion criteria:               | History of migraine, a contraindication to an EBP, or contraindication to sumatriptan (ischaemic heart disease, hypertension, pregnancy, pre-eclampsia or being treated with ergot medications or MAO inhibitors) |

| Interventions                     | Intervention group: once subcutaneous sumatriptan, 6 mg (0.5 ml) |
|-----------------------------------| Control group: once subcutaneous saline (0.5 ml) |
| Co-interventions:                 | • Conservative treatment (fluid hydration, bed rest and caffeine beverages) for at
Connelly 2000  (Continued)

| least 12 hours prior to study participation  
| • EBP if headache remained severe after 1 hour |

| Outcomes | 1. Number of participants with EBP performed  
| 2. Change in pain severity VAS score after 1 hour  
| 3. Number of participants showing improvements in pain severity |

Notes

Post-dural puncture headache (PDPH): Quote “Headache which is characterized by relieved with recumbency”. (Page 316)
Visual analogue scale (VAS): 0 = no headache and 100 = worst headache imaginable
Sample size calculation: not described
Email contact with MD Neil Roy Connelly on January 2010 for clarification about randomisation, allocation concealment, blinding and statistical questions

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The investigator reported the use of a computer random number generator</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>The investigator reported the use of a sealed container with a random code</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “Patients received, in a randomised fashion, either subcutaneous sumatriptan, 6 mg (0.5 mL), or saline (0.5 mL) using the Glaxo injector”. (Page 317) The investigator report blinding the VAS recorder</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No missing outcome data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study report fails to include results for a key outcomes (PDPH persistence of any severity at follow-up and number of any possible adverse events) that would be expected to have been reported for such a study</td>
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### Dogan 2006

**Methods**

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<th>Randomised, placebo-controlled trial</th>
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<tr>
<td>Study type: single-centre study</td>
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<td>Location: Turkey (Afyon)</td>
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<tr>
<td>Study design: parallel</td>
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<tr>
<td>Randomisation: not described</td>
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<tr>
<td>Allocation concealment: not described</td>
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<tr>
<td>Blinding: not described</td>
</tr>
<tr>
<td>Follow-up period: 4 days</td>
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</tbody>
</table>

**Participants**

| Randomised: 20 (intervention group: 10; control group: 10) |
| Excluded (post-randomisation): not described |
| **Gender** (women): 8 (40%); intervention group 4 (40%); control group 4 (40%) |
| **Age** (years); mean (SD): intervention group 36.30 (9.54); control group 46.60 (17.10) |
| **Baseline VAS score**; mean (SD): intervention group 7.5 (0.428); control group 7.3 (0.423) |
| **Inclusion criteria:** |
| • ASA I and II |
| • PDPH after spinal anaesthesia |
| **Exclusion criteria:** |
| Known allergy or contraindications (pancreatitis, galactosaemia) to gabapentin, migraine, asthma and hepatic or renal insufficiency |

**Interventions**

| **Intervention group:** gabapentin 900 mg/day orally (300 mg every 8 hours) during 4 days |
| **Control group:** placebo |
| **Co-interventions:** |
| • All patients were treated with bed rest and fluid hydration |

**Outcomes**

1. Change in pain severity VAS score after 1, 2, 3 and 4 days
2. Number of any possible adverse events

**Notes**

Post-dural puncture headache (PDPH): Quote “PDPH was diagnosed by the postural component of the pain”. (Page 170)

Visual analogue scale (VAS): 0 = no pain and 10 = worst pain imaginable

Sample size calculation: not described

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided. Described as randomised.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
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<tr>
<td>All outcomes</td>
<td>Unclear risk</td>
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### Incomplete outcome data (attrition bias)

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<tr>
<th>All outcomes</th>
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### Selective reporting (reporting bias)

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The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study.

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### Feuerstein 1986

#### Methods

- Randomised, double-blind, placebo-controlled trial
- Study type: single-centre study
- Location: Germany (Freiburg)
- Study design: parallel
- Randomisation: not described
- Allocation concealment: not described
- Blinding: blinding of participants and evaluation personnel
- Follow-up period: until healing of the headache

#### Participants

- Randomised: 16 (not described the number of participants initially allocated to each group)
- Excluded (post-randomisation): 5 (not described how many from each group). Analysed: 11 (intervention group: 6; control group: 5)

  - **Gender** (women): 6 (54%)
  - **Age** (years); n (%): 4 (36.4%) 10 to 30 years old (intervention group 3; control group 1); 4 (36.4%) 31 to 50 years old (intervention group 1; control group 3); 3 (27.3%) > 50 years old (intervention group 2; control group 1)

  - **Baseline VAS score**: not evaluated

  - **Inclusion criteria**: patients with a diagnostic lumbar puncture performed, with no headache during the last week before the lumbar puncture and a severe headache

  - **Exclusion criteria**: not described

#### Interventions

- **Intervention group**: orally theophylline 281.7 mg tablets (verum Euphyllin retard tablets) 3 times a day
- **Control group**: orally placebo tablets 3 times a day

  - **Co-interventions**: analgesics and hypotonic saline solution as needed

#### Outcomes

1. Number of participants with a conservative supplementary therapeutic option offered
2. Change in pain severity ("sum of pain") during the treatment period
3. Number of any possible adverse events
4. Missing data (withdrawals, drop-outs and participants lost to follow up)

#### Notes

Post-dural puncture headache (PDPH): Quote "Subjective severe headache occurring only after arising and ceasing within a few minutes after lying down.". (Page 217)

Sum of pain: 1 = slight headache; 2 = intermediate headache and 3 = severe headache. Three values per day.
Sample size calculation: not described

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
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<td>No information provided. Reported as randomised</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: “The placebo tablets, indistinguishable from the verum Euphyllin retard tablets (281.7 mg theophylline), were kindly provided by Byk Gulden Pharmazeutika, Konstanz, FRG.” (Page 217) Quote: “Verum and placebo tablets were randomised so that neither the patient nor the examining medical staff knew the real content of the administered tablets.” (Page 217)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>5 of 16 participants randomised were dropped out with insufficient information provided. Quote: “Five patients of 16 dropped out (transfer to other clinical departments, dismissal before the end of the study or insufficient compliance).” (Page 217)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study</td>
</tr>
</tbody>
</table>
## Methods

Randomised, double-blind, controlled trial  
Study type: single-centre study  
Location: Iran (Tehran)  
Study design: parallel  
Randomisation: not described  
Allocation concealment: not described  
Blinding: blinding of participants and key study personnel  
Follow-up period: 48 hours

## Participants

Randomised: 60 (intervention group: 30; control group: 30)  
Excluded (post-randomisation): not described  
**Gender** (women): 60 (100%)  
**Age** (years); mean (SD): 27.1 (3.45)  
**Baseline VAS score;** mean (SD): intervention group 9.20 (0.71); control group 9.07 (0.69)  
**Inclusion criteria:**  
- 18 to 40 years  
- ASA I and II  
- Headache after spinal anaesthesia for caesarean section  
**Exclusion criteria:** Cluster headache, convulsion, cerebrovascular accident, pre-eclampsia, eclampsia, high intracranial pressure, coagulopathy or previous neurologic disease

## Interventions

**Intervention group:** 200 mg hydrocortisone intravenously as a bolus and 100 mg hydrocortisone every 8 hours for 48 hours  
**Co-interventions:**  
- All patients were treated conventionally: complete bed rest, hydration (serum dextrose saline 3 L/4 h) and analgesics (acetaminophen 2 325 mg tablets every 6 hours and intravenous pethidine 50 mg every 12 hours)

## Outcomes

1. Number of participants with EBP performed  
2. Change in pain severity VAS score after 6, 24 and 48 hours  
3. Number of any possible adverse events

## Notes

- Post-dural puncture headache (PDPH): Quote “Headache after spinal anaesthesia”. (Page 416)  
- Visual analogue scale (VAS): 0 to 1 no headache; 2 to 4 mild headache, 5 to 7 moderate headache; 8 to 10 severe headache  
- Sample size calculation: not described

## Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided. Described as randomised.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
</tbody>
</table>
### Noyan 2007 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Parturient women and observer did not know which patient had received hydrocortisone&quot;. (Page 418)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No missing outcome data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study</td>
</tr>
</tbody>
</table>

### Rucklidge 2004

**Methods**
- Randomised, double-blind, placebo-controlled trial
- Study type: multicentre trial
- Location: UK
- Study design: parallel
- Randomisation: computer-generated random numbers
- Allocation concealment: central randomisation
- Blinding: blinding of participants and key study personnel
- Follow-up period: 48 hours

**Participants**
- Randomised: 18 (intervention group: 9; control group: 9)
- Excluded (post-randomisation): not described
  - Gender (women): 18 (100%)
  - Age (years); mean (SD): intervention group 24.1 (3.8); control group 29.3 (4.7)
  - Baseline VAS score: (graphical data)
  - Inclusion criteria: Women with PDPH following deliberate or accidental dural puncture associated with obstetric regional anaesthesia or analgesia
  - Exclusion criteria: Asthma, severe allergy or diabetes

**Interventions**
- **Intervention group:** intramuscular synthetic analogue of ACTH (Synacthen Depot®) 1 mg (1 ml)
- **Control group:** intramuscular saline 0.9% (1 ml)
- **Co-interventions:**
  - All patients were treated with simple oral analgesics and hydration
  - EBP was performed if requested by the patient

**Outcomes**
1. Number of participants with EBP performed
2. Change in pain severity VAS score after 6, 12, 24 and 48 hours
3. Number of any possible adverse events
### Notes
Post-dural puncture headache (PDPH): Quote “severe headache occurring within 48 h of dural puncture; exacerbation on sitting or standing with relief on lying or on abdominal compression; and the absence of focal neurological signs”. (Page 138)
Visual analogue scale (VAS): 0 = no pain and 10 = worst pain imaginable
The study reported data on neck stiffness and nausea as 2 side effects derived from the progression of the condition. These 2 side effects were not considered as adverse events related with the assessed intervention
Email contact with Dr. Steve Yentis on March 2010 for clarification about VAS numerical results
Sample size calculation: estimate VAS reduction = 30%, $\beta = 80\%$; $\alpha = 0.05$

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Parturients were randomly allocated to receive Synacthen Depot 1 mg (1 ml) or 0.9% saline (1 ml) according to computer-generated random numbers held at the Chelsea and Westminster Hospital, London”. (Page 138)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Parturients were randomly allocated to receive Synacthen Depot 1 mg (1 ml) or 0.9% saline (1 ml) according to computer-generated random numbers held at the Chelsea and Westminster Hospital, London”. (Page 138)</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: “The study agent was dispatched from the relevant pharmacy in a prefilled syringe and the contents were blinded to the parturient, investigator and midwife administering the drug”. (Page 138)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No missing outcome data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study</td>
</tr>
</tbody>
</table>

**Risk of bias**
Methods
Randomised, double-blind, placebo-controlled trial
Study type: single-centre study
Location: USA (New York)
Study design: parallel
Randomisation: table of random numbers
Allocation concealment: central randomisation
Blinding: blinding of participants and key study personnel
Follow-up period: not described

Participants
Randomised: 41 (intervention group: 20; control group: 21)
Excluded (post-randomisation): not described
Gender (women): not reported
Age (years): not reported
Baseline VAS score: not evaluated
Inclusion criteria: patients with PDPH after a spinal anaesthesia, with usual symptomatic treatment unsatisfactory and headache went through a 2 to 4 days course
Exclusion criteria: not described

Interventions
**Intervention group:** Intravenous caffeine sodium benzoate (CSB) (0.5 g/2 ml)
**Control group:** intravenous physiologic saline solution (2 ml)
**Co-interventions:** supplementary caffeine (0.5 g/2 ml) was administered if headache was not relieved after 1 to 2 hours

Outcomes
1. PDPH persistence of any severity at 1 to 2 hours
2. Number of participants with a conservative supplementary therapeutic option offered (CSB second dose demanded)

Notes
Post-dural puncture headache (PDPH): Quote "Aggravated by sitting or standing". (Page 308)
Sample size calculation: not described

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “After informed consent was obtained, the patients were treated in random fashion with initial intravenous injection A which was either: physiologic saline solution (2 ml) or CSB (0.5 gm / 2 ml).” (Page 308) Quote: “The solutions were prepared in the hospital pharmacy according to a list derived from a table of random numbers.” (Page 308)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “The solutions were prepared in the hospital pharmacy according to a list derived from a table of random numbers.”</td>
</tr>
</tbody>
</table>
Blinding (performance bias and detection bias)  
All outcomes  
Low risk  
Quote: “The syringes were coded so that the observers were not aware of the contents.”  

Incomplete outcome data (attrition bias)  
All outcomes  
Low risk  
No missing outcome data  

Selective reporting (reporting bias)  
High risk  
The study report fails to include results for a key outcome (number of any possible adverse events) that would be expected to have been reported for such a study.

EBP: epidural blood patch  
h: hour  
PDPH: post-dural puncture headache  
SD: standard deviation  
VAS: visual analogue scale

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilera 1988</td>
<td>Not RCT (case series)</td>
</tr>
<tr>
<td>Bart 1978</td>
<td>No individual pharmacological drug assessed</td>
</tr>
<tr>
<td>Basso 1985</td>
<td>Intervention was not aimed to treat PDPH</td>
</tr>
<tr>
<td>De las Heras 1997</td>
<td>Not RCT (case report)</td>
</tr>
<tr>
<td>Eldor 1990</td>
<td>Not RCT (case series)</td>
</tr>
<tr>
<td>Ergün 2008</td>
<td>Randomisation by alternation (odd hospital record numbers assigned to intervention and even numbers to control; information provided by the trialists)</td>
</tr>
<tr>
<td>Flaatten 1987</td>
<td>Intervention was not aimed at treating PDPH</td>
</tr>
<tr>
<td>Hakim 2005</td>
<td>Not RCT (clinical trial without control group)</td>
</tr>
<tr>
<td>Hodgson 1997</td>
<td>Not RCT (case report)</td>
</tr>
<tr>
<td>Lang 1993</td>
<td>The orthostatic component of headache not described</td>
</tr>
<tr>
<td>Study</td>
<td>Findings</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Naja 2009</td>
<td>No individual pharmacological drug assessed</td>
</tr>
<tr>
<td>Oedit 2005</td>
<td>No individual pharmacological drug assessed</td>
</tr>
<tr>
<td>Sandesc 2005</td>
<td>No individual pharmacological drug assessed</td>
</tr>
<tr>
<td>Schwalbe 1991</td>
<td>The orthostatic component of headache not described</td>
</tr>
<tr>
<td>Torres 1986</td>
<td>The orthostatic component of headache not described</td>
</tr>
<tr>
<td>van Kooten 2008</td>
<td>No individual pharmacological drug assessed</td>
</tr>
<tr>
<td>Widerlöv 1979</td>
<td>Intervention was not aimed at treating PDPH</td>
</tr>
<tr>
<td>Zenglein 1978</td>
<td>Intervention was not aimed at treating PDPH</td>
</tr>
</tbody>
</table>

PDPH: post-dural puncture headache
RCT: randomised controlled trial
**Comparison 1. Comparison 1: Caffeine versus placebo**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of participants with EBP performed (secondary outcome 3)</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.64 [0.31, 1.30]</td>
</tr>
<tr>
<td>2 Change in pain severity scores (secondary outcome 4)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
<td></td>
</tr>
<tr>
<td>2.1 Baseline VAS score</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>9.0 [-0.80, 18.80]</td>
</tr>
<tr>
<td>2.2 Change in pain severity VAS score after 4 hours</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-16.0 [-34.07, 2.07]</td>
</tr>
<tr>
<td>2.3 Change in pain severity VAS score after 24 hours</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>7.0 [-18.10, 32.10]</td>
</tr>
<tr>
<td>3 Number of participants showing improvements in pain severity scores (secondary outcome 5)</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>1.5 [1.02, 2.21]</td>
</tr>
<tr>
<td>3.1 Number of participants showing improvements in pain severity VAS score 4 hours</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>1.5 [1.02, 2.21]</td>
</tr>
<tr>
<td>4 Number of any possible adverse effects (secondary outcome 7)</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>1.0 [0.07, 14.90]</td>
</tr>
</tbody>
</table>

**Comparison 2. Comparison 2: Sumatriptan versus placebo**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of participants with EBP performed (secondary outcome 3)</td>
<td>1</td>
<td>10</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.82 [0.49, 1.38]</td>
</tr>
<tr>
<td>2 Change in pain severity scores (secondary outcome 4)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
<td></td>
</tr>
<tr>
<td>2.1 Baseline VAS score</td>
<td>1</td>
<td>10</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-26.0 [-55.14, 3.14]</td>
</tr>
<tr>
<td>2.2 Change in pain severity VAS score after 1 hour</td>
<td>1</td>
<td>10</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-18.0 [-55.73, 19.73]</td>
</tr>
<tr>
<td>3 Number of participants showing improvements in pain severity scores (secondary outcome 5)</td>
<td>1</td>
<td>10</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>1.0 [0.08, 11.93]</td>
</tr>
</tbody>
</table>
### Comparison 3. Comparison 3: Gabapentin versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Change in pain severity scores (secondary outcome 4)</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Baseline VAS score</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.20 [-0.17, 0.57]</td>
</tr>
<tr>
<td>1.2 Change in pain severity VAS score after 1 day</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.60 [-1.92, -1.28]</td>
</tr>
<tr>
<td>1.3 Change in pain severity VAS score after 2 days</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.60 [-2.87, -2.33]</td>
</tr>
<tr>
<td>1.4 Change in pain severity VAS score after 3 days</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.90 [-3.10, -2.70]</td>
</tr>
<tr>
<td>1.5 Change in pain severity VAS score after 4 days</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.6 [-1.74, -1.46]</td>
</tr>
<tr>
<td>2 Number of any possible adverse effects (secondary outcome 7)</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

### Comparison 4. Comparison 4: Theophylline versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)</td>
<td>1</td>
<td>11</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.42 [0.12, 1.40]</td>
</tr>
<tr>
<td>2 Change in pain severity (&quot;sum of pain&quot;) during the treatment period (secondary outcome 4)</td>
<td>1</td>
<td>11</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-12.0 [-17.19, -6.81]</td>
</tr>
<tr>
<td>3 Number of any possible adverse effects (secondary outcome 7)</td>
<td>1</td>
<td>11</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.83 [0.07, 10.20]</td>
</tr>
</tbody>
</table>

### Comparison 5. Comparison 5: Hydrocortisone versus control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of participants with EBP performed (secondary outcome 3)</td>
<td>1</td>
<td>60</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.33 [0.01, 7.87]</td>
</tr>
<tr>
<td>2 Change in pain severity score (secondary outcome 4)</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Baseline VAS score</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.13 [-0.22, 0.48]</td>
</tr>
</tbody>
</table>
### 2.2 Change in pain severity VAS score after 6 hours

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 Change in pain severity VAS score after 6 hours</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-3.86 [-4.48, -3.24]</td>
</tr>
</tbody>
</table>

### 2.3 Change in pain severity VAS score after 24 hours

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3 Change in pain severity VAS score after 24 hours</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-3.14 [-3.78, -2.50]</td>
</tr>
</tbody>
</table>

### 2.4 Change in pain severity VAS score after 48 hours

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4 Change in pain severity VAS score after 48 hours</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.24 [-1.64, -0.84]</td>
</tr>
</tbody>
</table>

### 3 Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Number of any possible adverse effects (secondary outcome 7)</td>
<td>1</td>
<td>60</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

---

#### Comparison 6. Comparison 6: ACTH versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of participants with EBP performed (secondary outcome 3)</td>
<td>1</td>
<td>18</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.86 [0.48, 1.53]</td>
</tr>
<tr>
<td>2 Number of any possible adverse effects (secondary outcome 7)</td>
<td>1</td>
<td>18</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

#### Comparison 7. Comparison 7: Caffeine sodium benzoate versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PDPH persistence of any severity at 1 to 2 hours (primary outcome)</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.29 [0.13, 0.64]</td>
</tr>
<tr>
<td>2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (IV, Fixed, 95% CI)</td>
<td>0.29 [0.13, 0.64]</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1: Caffeine versus placebo, Outcome 1: Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 1 Number of participants with EBP performed (secondary outcome 3)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favours caffeine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camann 1990</td>
<td>7/20</td>
<td>11/20</td>
<td>0.64 [0.31, 1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>20</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.64 [0.31, 1.30]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7 (Favours caffeine), 11 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.24 (P = 0.22)

Analysis 1.2. Comparison 1: Caffeine versus placebo, Outcome 2: Change in pain severity scores (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 2 Change in pain severity scores (secondary outcome 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Caffeine</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Baseline VAS score</td>
<td>Camann 1990</td>
<td>20</td>
<td>69 (13.42)</td>
<td>20</td>
<td>60 (17.89)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>20</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>9.00 [-0.80, 18.80]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.80 (P = 0.072)

2 Change in pain severity VAS score after 4 hours
Camann 1990
20 | 33 (26.83) | 20 | 49 (31.3) | -16.00 [-34.07, 2.07] |

**Subtotal (95% CI)** | **20** | **20** | **100.0 %** | **-16.00 [-34.07, 2.07]** |            |

Heterogeneity: not applicable
Test for overall effect: Z = 1.74 (P = 0.083)

3 Change in pain severity VAS score after 24 hours

(Continued . . .)
### Analysis 1.3. Comparison 1: Caffeine versus Placebo, Outcome 3 Number of participants showing improvements in pain severity scores (secondary outcome 5).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Caffeine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Camann 1990</td>
<td>18/20</td>
<td>12/20</td>
<td>1.50 [1.02, 2.21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>20</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.50 [1.02, 2.21]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (Caffeine), 12 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.06 (P = 0.040)
### Analysis 1.4. Comparison 1

**Comparison 1:** Caffeine versus placebo, **Outcome 4** Number of any possible adverse effects (secondary outcome 7).

**Review:** Drug therapy for treating post-dural puncture headache

**Comparison:** 1 Comparison 1: Caffeine versus placebo

**Outcome:** 4 Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Caffeine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camann 1990</td>
<td>1/20</td>
<td>1/20</td>
<td>1.00 [0.07, 14.90]</td>
<td>100.0 %</td>
<td>1.00 [0.07, 14.90]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>20</td>
<td>20</td>
<td>100.0 %</td>
<td>1.00 [0.07, 14.90]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (Caffeine), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

![Graph showing comparison](image)

### Analysis 2.1. Comparison 2

**Comparison 2:** Sumatriptan versus placebo, **Outcome 1** Number of participants with EBP performed (secondary outcome 3).

**Review:** Drug therapy for treating post-dural puncture headache

**Comparison:** 2 Comparison 2: Sumatriptan versus placebo

**Outcome:** 1 Number of participants with EBP performed (secondary outcome 3)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Sumatriptan</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connelly 2000</td>
<td>4/5</td>
<td>5/5</td>
<td>0.82 [0.49, 1.38]</td>
<td>100.0 %</td>
<td>0.82 [0.49, 1.38]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>5</td>
<td>5</td>
<td>100.0 %</td>
<td>0.82 [0.49, 1.38]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (Sumatriptan), 5 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.75 (P = 0.45)

![Graph showing comparison](image)
Analysis 2.2. Comparison 2: Sumatriptan versus placebo, Outcome 2: Change in pain severity scores (secondary outcome 4).

Comparison: 2 Comparison 2: Sumatriptan versus placebo
Outcome: 2 Change in pain severity scores (secondary outcome 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Sumatriptan</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Baseline VAS score</td>
<td>Connelly 2000</td>
<td>5 61 (24)</td>
<td>5 87 (23)</td>
<td>100.0 %</td>
<td>-26.00 [-55.14, 3.14]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>5</strong></td>
<td><strong>5</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>-26.00 [-55.14, 3.14]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.75 (P = 0.080)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in pain severity VAS score after 1 hour</td>
<td>Connelly 2000</td>
<td>5 47 (22)</td>
<td>5 65 (37)</td>
<td>100.0 %</td>
<td>-18.00 [-55.73, 19.73]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>5</strong></td>
<td><strong>5</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>-18.00 [-55.73, 19.73]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.94 (P = 0.35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi$^2$ = 0.11, df = 1 (P = 0.74), I$^2$ = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis 2.3. Comparison 2: Sumatriptan versus placebo, Outcome 3: Number of participants showing improvements in pain severity scores (secondary outcome 5).

Comparison: 2 Comparison 2: Sumatriptan versus placebo
Outcome: 3 Number of participants showing improvements in pain severity scores (secondary outcome 5)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Sumatriptan</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Connelly 2000</td>
<td>1/5</td>
<td>1/5</td>
<td>1.00 [ 0.08, 11.93 ]</td>
<td>100.0 %</td>
<td>1.00 [ 0.08, 11.93 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>5</strong></td>
<td><strong>5</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.00 [ 0.08, 11.93 ]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong> 1 (Sumatriptan), 1 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.0 (P = 1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 3.1. Comparison 3 Comparison 3: Gabapentin versus placebo, Outcome 1 Change in pain severity scores (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 3 Comparison 3: Gabapentin versus placebo

Outcome: 1 Change in pain severity scores (secondary outcome 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gabapentin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV/Fixed,95% CI</td>
<td>IV/Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Baseline VAS score</td>
<td>10 7.5 (0.428)</td>
<td>10 7.3 (0.423)</td>
<td>100.0 %</td>
<td>0.20 [-0.17, 0.57]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>10 10</td>
<td>100.0 %</td>
<td>0.20 [-0.17, 0.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.05 (P = 0.29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Change in pain severity VAS score after 1 day</td>
<td>10 4.1 (0.31)</td>
<td>10 5.7 (0.42)</td>
<td>100.0 %</td>
<td>-1.60 [-1.92, -1.28]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>10 10</td>
<td>100.0 %</td>
<td>-1.60 [-1.92, -1.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 9.69 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Change in pain severity VAS score after 2 days</td>
<td>10 1.8 (0.29)</td>
<td>10 4.4 (0.33)</td>
<td>100.0 %</td>
<td>-2.60 [-2.87, -2.33]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>10 10</td>
<td>100.0 %</td>
<td>-2.60 [-2.87, -2.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 18.72 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Change in pain severity VAS score after 3 days</td>
<td>10 0.3 (0.15)</td>
<td>10 3.2 (0.29)</td>
<td>100.0 %</td>
<td>-2.90 [-3.10, -2.70]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>10 10</td>
<td>100.0 %</td>
<td>-2.90 [-3.10, -2.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 28.09 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Change in pain severity VAS score after 4 days</td>
<td>10 0.1 (0.1)</td>
<td>10 1.7 (0.21)</td>
<td>100.0 %</td>
<td>-1.60 [-1.74, -1.46]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>10 10</td>
<td>100.0 %</td>
<td>-1.60 [-1.74, -1.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 21.75 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 260.84, df = 4 (P = 0.00), I² = 98%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Analysis 3.2. Comparison 3 Comparison 3: Gabapentin versus placebo, Outcome 2 Number of any possible adverse effects (secondary outcome 7).**

Review: Drug therapy for treating post-dural puncture headache

Comparison: 3 Comparison 3: Gabapentin versus placebo

Outcome: 2 Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gabapentin</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Dogan 2006</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>0.0 [ 0.0, 0.0 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Gabapentin), 0 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)

**Analysis 4.1. Comparison 4 Comparison 4: Theophylline versus placebo, Outcome 1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2).**

Review: Drug therapy for treating post-dural puncture headache

Comparison: 4 Comparison 4: Theophylline versus placebo

Outcome: 1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Theophylline</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Feuerstein 1986</td>
<td>2/6</td>
<td>4/5</td>
<td>100.0 %</td>
<td>0.42 [ 0.12, 1.40 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>6</strong></td>
<td><strong>5</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.42 [ 0.12, 1.40 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 2 (Theophylline), 4 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
### Analysis 4.2. Comparison 4
Comparison 4: Theophylline versus placebo, Outcome 2 Change in pain severity ("sum of pain") during the treatment period (secondary outcome 4).

**Review:** Drug therapy for treating post-dural puncture headache

**Comparison:** 4  Comparison 4: Theophylline versus placebo

**Outcome:** 2  Change in pain severity ("sum of pain") during the treatment period (secondary outcome 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Theophylline</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean(SD)</td>
<td>N  Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Feuerstein 1986</td>
<td>6  16 (3.91)</td>
<td>5  28 (4.73)</td>
<td>100.0 %</td>
<td>-12.00 [-17.19, -6.81]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>6  5</td>
<td>100.0 %</td>
<td>-12.00 [-17.19, -6.81]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 4.53 (P < 0.00001)

### Analysis 4.3. Comparison 4
Comparison 4: Theophylline versus placebo, Outcome 3 Number of any possible adverse effects (secondary outcome 7).

**Review:** Drug therapy for treating post-dural puncture headache

**Comparison:** 4  Comparison 4: Theophylline versus placebo

**Outcome:** 3  Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Theophylline</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Feuerstein 1986</td>
<td>1/6</td>
<td>1/5</td>
<td>100.0 %</td>
<td>0.83 [0.07, 10.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>6  5</td>
<td>100.0 %</td>
<td>0.83 [0.07, 10.20]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (Theophylline), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
Analysis 5.1. Comparison 5: Hydrocortisone versus control, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache
Comparison: 5: Comparison 5: Hydrocortisone versus control
Outcome: 1: Number of participants with EBP performed (secondary outcome 3)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hydrocortisone</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noyan 2007</td>
<td>0/30</td>
<td>1/30</td>
<td></td>
<td>0.33 [0.01, 7.87]</td>
<td>0.33 [0.01, 7.87]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>30</td>
<td>30</td>
<td>100.0%</td>
<td>0.33 [0.01, 7.87]</td>
<td>0.33 [0.01, 7.87]</td>
</tr>
<tr>
<td>Total events:</td>
<td>0 (Hydrocortisone), 1 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heterogeneity: not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

Analysis 5.2. Comparison 5: Hydrocortisone versus control, Outcome 2 Change in pain severity score (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache
Comparison: 5: Comparison 5: Hydrocortisone versus control
Outcome: 2: Change in pain severity score (secondary outcome 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hydrocortisone</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noyan 2007</td>
<td>N = 30, Mean(SD) = 9.2 (0.71)</td>
<td>N = 30, Mean(SD) = 9.07 (0.69)</td>
<td>0.13 [ -0.22, 0.48 ]</td>
<td>0.13 [ -0.22, 0.48 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>30</td>
<td>100.0%</td>
<td>0.13 [ -0.22, 0.48 ]</td>
<td>0.13 [ -0.22, 0.48 ]</td>
</tr>
</tbody>
</table>
| Heterogeneity: not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
2 Change in pain severity VAS score after 6 hours
| Noyan 2007        | N = 30, Mean(SD) = 2.77 (1.07) | N = 30, Mean(SD) = 6.63 (1.35) | -3.86 [-4.48, -3.24 ] | -3.86 [-4.48, -3.24 ] |
| Subtotal (95% CI) | 30             | 30      | 100.0%         | -3.86 [-4.48, -3.24 ] | -3.86 [-4.48, -3.24 ] |
| Heterogeneity: not applicable
Test for overall effect: Z = 12.27 (P < 0.00001)
3 Change in pain severity VAS score after 24 hours

(Continued...
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hydrocortisone</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noyan 2007</td>
<td>30 0.73 (0.74)</td>
<td>30 3.87 (1.63)</td>
<td>-3.14 [-3.78, -2.50]</td>
<td>100.0 %</td>
<td>-3.14 [-3.78, -2.50]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

- 30 30
- 100.0 % -3.14 [-3.78, -2.50]

**Heterogeneity:** not applicable

- Test for overall effect: Z = 9.61 (P < 0.00001)

4 Change in pain severity VAS score after 48 hours

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hydrocortisone</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noyan 2007</td>
<td>30 0.63 (0.61)</td>
<td>30 1.87 (0.93)</td>
<td>-1.24 [-1.64, -0.84]</td>
<td>100.0 %</td>
<td>-1.24 [-1.64, -0.84]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

- 30 30
- 100.0 % -1.24 [-1.64, -0.84]

**Heterogeneity:** not applicable

- Test for overall effect: Z = 6.11 (P < 0.00001)

- Test for subgroup differences: Chi² = 160.56, df = 3 (P = 0.00), I² = 98%

**Analysis 5.3. Comparison 5** Comparison 5: Hydrocortisone versus control, Outcome 3 Number of any possible adverse effects (secondary outcome 7).

**Review:** Drug therapy for treating post-dural puncture headache

**Comparison:** 5 Comparison 5: Hydrocortisone versus control

**Outcome:** 3 Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hydrocortisone n/N</th>
<th>Control n/N</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noyan 2007</td>
<td>0/30</td>
<td>0/30</td>
<td>0.0 [ 0.0, 0.0]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- 30 30
- 0.0 [ 0.0, 0.0]

**Total events:** 0 (Hydrocortisone), 0 (Control)

**Heterogeneity:** not applicable

- Test for overall effect: Z = 0.0 (P < 0.00001)
Analysis 6.1. Comparison 6 Comparison 6: ACTH versus placebo, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 6 Comparison 6: ACTH versus placebo

Outcome: 1 Number of participants with EBP performed (secondary outcome 3)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ACTH n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucklidge 2004</td>
<td>6/9</td>
<td>7/9</td>
<td></td>
<td>100.0%</td>
<td>0.86 [0.48, 1.53]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>9</strong></td>
<td><strong>9</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.86 [0.48, 1.53]</strong></td>
</tr>
</tbody>
</table>

Total events: 6 (ACTH), 7 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

Analysis 6.2. Comparison 6 Comparison 6: ACTH versus placebo, Outcome 2 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 6 Comparison 6: ACTH versus placebo

Outcome: 2 Number of any possible adverse effects (secondary outcome 7)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ACTH n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
<th>Risk Ratio IV/Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucklidge 2004</td>
<td>0/9</td>
<td>0/9</td>
<td></td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>9</strong></td>
<td><strong>9</strong></td>
<td></td>
<td><strong>0.0 [0.0, 0.0]</strong></td>
</tr>
</tbody>
</table>

Total events: 0 (ACTH), 0 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Analysis 7.1. Comparison 7 Comparison 7: Caffeine sodium benzoate versus placebo, Outcome 1 PDPH persistence of any severity at 1 to 2 hours (primary outcome).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 7 Comparison 7: Caffeine sodium benzoate versus placebo

Outcome: 1 PDPH persistence of any severity at 1 to 2 hours (primary outcome)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Caffeine sodium benzoate</th>
<th>Placebo</th>
<th>Risk Ratio (Fixed, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sechzer 1978</td>
<td>5/20</td>
<td>18/21</td>
<td>100.0 % 0.29 [0.13, 0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>21</td>
<td>100.0 % 0.29 [0.13, 0.64]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Caffeine sodium benzoate), 18 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 3.10 (P = 0.0019)

Analysis 7.2. Comparison 7 Comparison 7: Caffeine sodium benzoate versus placebo, Outcome 2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 7 Comparison 7: Caffeine sodium benzoate versus placebo

Outcome: 2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Caffeine sodium benzoate</th>
<th>Placebo</th>
<th>Risk Ratio (Fixed, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sechzer 1978</td>
<td>5/20</td>
<td>18/21</td>
<td>100.0 % 0.29 [0.13, 0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>21</td>
<td>100.0 % 0.29 [0.13, 0.64]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Caffeine sodium benzoate), 18 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 3.10 (P = 0.0019)
Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Anesthesia, Epidural explode all trees
#2 MeSH descriptor Anesthesia, Spinal explode all trees
#3 MeSH descriptor Injections, Spinal explode all trees
#4 MeSH descriptor Myelography explode all trees
#5 MeSH descriptor Spinal Puncture explode all trees
#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 MeSH descriptor Headache Disorders explode all trees
#10 headach* or cephalgia or (head near/2 pain) or (cranial near/2 pain)
#11 (#9 OR #10)
#12 (#8 AND #11)

Appendix 2. MEDLINE Ovid search strategy

1 exp Anesthesia, Epidural/
2 exp Anesthesia, Spinal/
3 Injections, Spinal/
4 exp Myelography/
5 exp Spinal Puncture/
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*)).mp.
7 myelogra*.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Headache Disorders/
10 (headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)).mp.
11 9 or 10
12 8 and 11
13 randomised controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 12 and 21

key:
p = title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type, ab = abstract, fs = floating subheading
Appendix 3. EMBASE Ovid search strategy

1 exp spinal anaesthesia/
2 exp lumbar puncture/
3 exp MYELOGRAPHY/
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 anesthes* or anaesth* or needle*)).mp.
5 myelogra*.mp.
6 1 or 2 or 3 or 4 or 5
7 exp "headache and facial pain"/
8 (headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)) (head adj2 pain) or (cranial adj2 pain)).mp.
9 7 or 8
10 6 and 9
11 random*.mp.
12 factorial*.mp.
13 (crossover* or cross over* or cross-over*).mp.
14 placebo*.mp.
15 (doubl* adj blind*).mp.
16 (singl* adj blind*).mp.
17 assign*.mp.
18 allocat*.mp.
19 volunteer*.mp.
20 crossover procedure/
21 double blind procedure/
22 randomised controlled trial/
23 single blind procedure/
24 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 10 and 24
key:
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

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 anesthes* or anaesth* 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 cephalalg*).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

HISTORY
Review first published: Issue 8, 2011

CONTRIBUTIONS OF AUTHORS
Conceiving the review (guarantor): Xavier Basurto (XB).
Screening search results: XB, Ivan Solà (IS).
Screening retrieved papers against inclusion criteria: XB, IS, Xavier Bonfill Cosp (XBC).
Appraising quality of papers: XB, IS.
Extracting data from papers: XB, IS.
Data management for the review: XB, Laura Martínez (LM).
Entering data into Review Manager (RevMan 5.1): XB, LM.
Interpretation of data: XB, IS, XBC, LM.
Statistical analysis: XB, IS, LM.
Writing the review: XB, IS, XBC, LM.
Comment and editing of review drafts: XB, IS, XBC, LM.
Responsible for reading and checking review before submission: XB, IS, XBC, LM.
Responsible for initiating and running the update of this review: XB

DECLARATIONS OF INTEREST
None known

SOURCES OF SUPPORT
Internal sources

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

External sources

- Agencia de Calidad para el Sistema Nacional de Salud, Ministerio de Sanidad, Política Social e Igualdad, Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of participants: “The use of a standardized diagnostic criteria for PDPH will not be required, but it should at least be described as orthostatic headache which worsens on standing and is improved by lying down.” The “it should at least be” has been added to emphasise the need to include only those RCTs that have used an orthostatic headache criteria to include participants.

- PaPaS Review Group Specialised Register electronic search eliminated.

- CINAHL search strategy included.

NOTES

Protocol title split from 'Drug therapy for preventing and treating post-dural puncture headache' into two separate titles; one on prevention (Basurto 2009) and this one on treatment.