Systematic Review

Opioids for the Prevention of Post-dural Puncture Headache in Obstetrics: A Systematic Review and Meta-analysis of Efficacy and Safety

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Background: Post-dural puncture headache (PDPH), or spinal headache, is the most common serious complication resulting from iatrogenic puncture of the dura during epidural or spinal anesthesia and cerebrospinal fluid (CSF) leak in pregnant women.

Objective: To analyze the effectiveness and safety of opioids as a prophylaxis approach in treating obstetric patients who underwent unintentional dural puncture during the initiation of neuraxial anesthesia.

Study Design: A systematice review and meta-analysis.

Setting: No restriction regarding study type.

Methods: PubMed, Embase, and the Cochrane library were searched for available papers published up to September 2020.

Results: According to the eligibility criteria, 10 studies were included with post-dural puncture headache (PDPH) incidence as the primary outcome and the number of epidural blood patch (EBP) required as the second outcome. The risk estimates of each study were reported as odds ratios (ORs). The results showed morphine does not decrease the incidence of PDPH (OR = 0.45, 95% CI: 0.15 - 1.34, $P = 0.153$, $I^2 = 74.4\%$, Pheterogeneity = 0.004) and opioids do not decrease the use of EBP (OR = 0.40, 95% CI: 0.08 - 1.95, $P = 0.259$, $I^2=73.7\%$, Pheterogeneity = 0.004). Fentanyl does not decrease the incidence of PDPH (OR = 0.35, 95% CI: 0.01-13.77, $P = 0.576$, $I^2 = 81.0\%$, Pheterogeneity = 0.022).

Limitations: The small number of included studies, high heterogeneity, and variety in study designs.

Conclusions: Exposure to opioids for any reason after the diagnosis of unintentional dural puncture is not associated with a reduced risk of PDPH and does not decrease the need for therapeutic EBP.

Key words: Epidural blood patch, headache, heterogeneity, iatrogenic injury, meta-analysis, opioids, patch, post-dural puncture, prophylaxis

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Post-dural puncture headache (PDPH), or spinal headache, is the most common serious complication resulting from iatrogenic puncture of the dura during epidural or spinal anesthesia and cerebrospinal fluid (CSF) leak in pregnant women (1). The overall incidence of PDPH after neuraxial procedures varies widely from 6% to 36% (2-7), mainly because of differences in populations, techniques of dural puncture, and reporting procedures (8). Over the past 2 decades,

with the introduction of pencil-point spinal needles for spinal anesthesia in pregnant women, the problem of PDPH in obstetrics has been more associated with an iatrogenic dural puncture during attempted epidural procedures. The overall incidence of epidural needles accidentally entering the subarachnoid is 0.5-4% when attempting epidural procedures with 16-18 gauge epidural needles, resulting in a headache rate of 45-80% (9). In many cases, the headache is mild in intensity and brief, without significant sequelae; however, PDPH is occasionally severe enough to last months or even years (10). These headaches can be extreme and debilitating, preventing ambulation and limiting interaction between mother and baby during the postpartum period, in addition to prolonging hospitalization, increasing emergency room visits, and health care costs (11-14).

The treatment options for PDPH vary greatly, with a highly variable level of evidence, including bed rest, analgesics, antiemetics, caffeine, theophylline, hydrocortisone, gabapentin, occipital nerve block, epidural blood patch (EBP), and epidural dextran (15-18). Nevertheless, many institutions have neither guidelines nor protocols for prophylaxis or treatment, making the management of PDPH quite heterogeneous (19). EBP is increasingly used for the management of patients with persistent PDPH and its prevention. EBP remains the most effective treatment for moderate-to-severe PDPH (17,20-23), but there are no proven interventions for preventing PDPH. As an invasive method, EBP is generally not recommended for preventive usage (24).

One systematic review indicates that opioids could be used as a prophylaxis for PDPH (25). Still, this previous review assessed only 3 studies (26-28), investigated PDPH of any severity as the primary outcome. A meta-analysis was not possible because of dose inequivalence and differences in baseline characteristics (25). Since the publication of this previous review, a randomized controlled trial (RCT) was carried out and tested the hypothesis that opioids would decrease the incidence and severity of PDPH or the need for EBP in the obstetric population (29). Therefore, a meta-analysis is necessary to analyze the prophylactic value and safety of opioids in patients with PDPH.

To our best knowledge, this is the first meta-analysis to analyze the effectiveness and safety of opioids as a prophylaxis approach in treating obstetric patients who underwent iatrogenic dural puncture during the initiation of epidural anesthesia.

Methods

Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (30). The relevant articles were searched based on the PICO principle (31). PubMed, Embase, and the Cochrane library were searched for available papers published up to September 2020 using the MeSH terms 'post-dural puncture headache' and 'opioids', as well as other relevant key words. The eligibility criteria were: 1) population: obstetric patients who underwent dural puncture during anesthesia; 2) interventions: opioids; 3) outcome: incidence of post-dural puncture headache and the number of epidural blood patch required; 4) study type: no restriction; and 5) language: English.

Data Extraction

The study characteristics (authors, year of publication, study design, country where the study was performed, sample size, and mean age in the treatment and control group), treatment parameters (type of delivery, the type of treatment that the patients received, dose of opioids, injection site, and duration of PDPH in both groups), the primary outcome (incidence of PDPH), and the secondary outcome (the number of EBP required) were extracted by 2 authors (Lan Wu and Shouming Chen) using a standardized form. Any discrepancy was solved by discussion until a consensus was reached.

Data Synthesis

The risk estimates of each study were reported as odds ratios (ORs). We extracted the number of patients with and without PDPH in the treatment and control groups to calculate the ORs that combined the effect size.

Quality of the Evidence

The level of evidence was assessed independently by 2 authors (Wu and Jiang) according to the Newcastle-Ottawa scale (NOS) for cohort studies (32) and the Cochrane Handbook for RCTs (33). Discrepancies in the assessment were resolved through discussion until a consensus was reached.

Statistical Analysis

All analyses were performed using STATA SE 14.0 (StataCorp, College Station, Texas, USA). The effects and corresponding 95% confidence intervals (CIs) were used to compare the outcomes. Statistical heterogene-

ity among the studies was calculated using Cochran's Q test and the I2 index. Due to the differences in the dosage of opioids and surgical approaches of each study, to avoid the effect of heterogeneity between each study, random-effects models were applied for the analysis, regardless of the results of Cochrane's Q test and I^2 index. Two sensitivity analyses were conducted. We did not assess potential publication bias by funnel plots and Egger's test because the number of studies included in this meta-analysis was smaller than 10, in which case the funnel plots and Egger's test could yield misleading results and are not recommended (34,35). *P*-values < 0.05 are considered statistically significant.

Results

Search Process and Characteristics of the Included Studies

Figure 1 presents the search process. A total of 141 records were identified, and 15 duplicates were excluded. Among the remaining 126 records, 80 records were excluded because they were of noneligible study types, not accessible, or in a language other than English. Forty-six full-text papers were assessed for eligibility and 36 were excluded (outcome, n = 5; study aim/design, n = 16; intervention, n = 15); therefore, 10 studies were included for the quantitative analysis.

Table 1 presents the characteristics of the 10 included studies (11 datasets) (26,28,29,36-42). There were 7 RCTs (8 datasets) (26,28,29,36-39) and 3 retrospective studies (40-42). There are 728 patients (28-194/study).

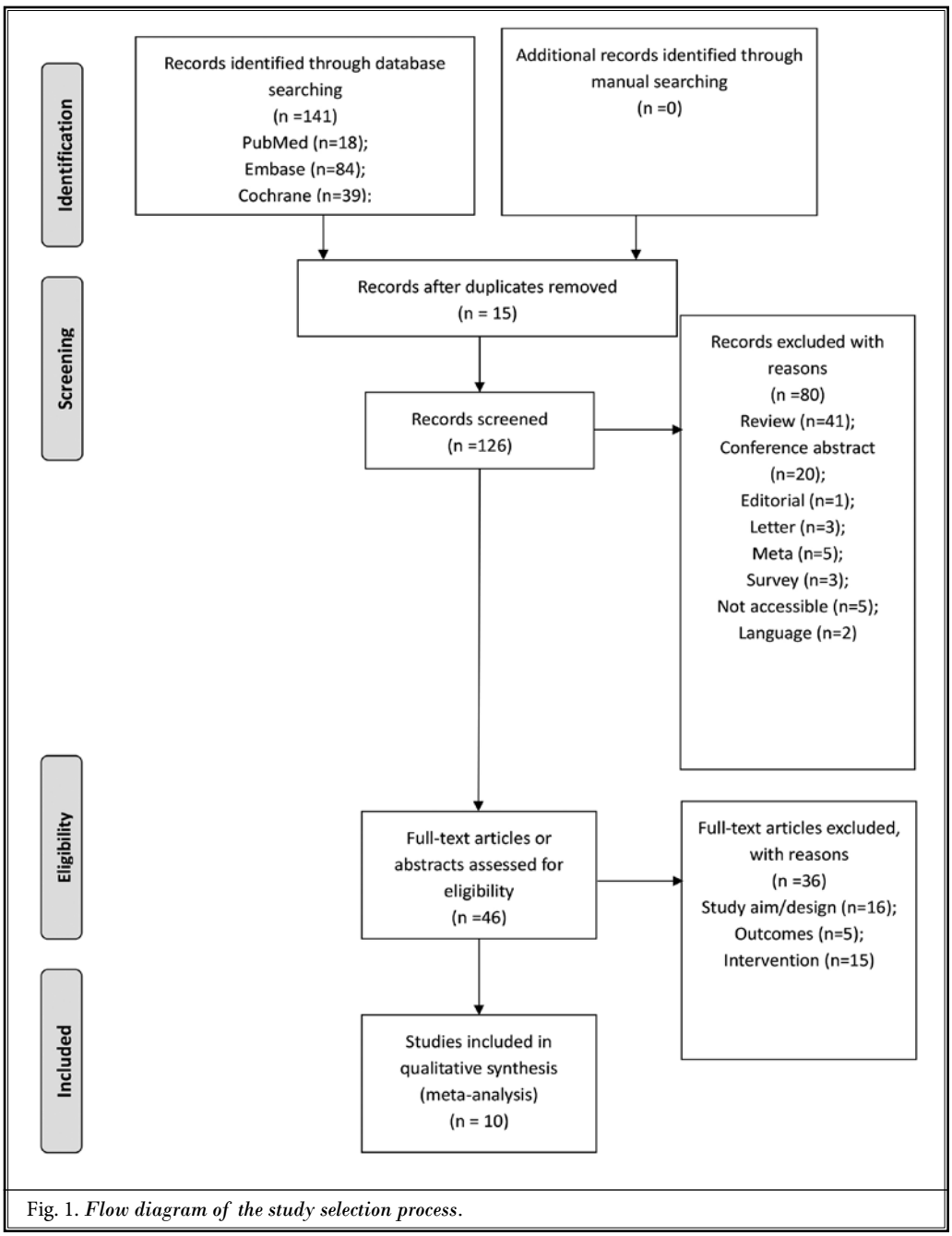

Fig. 1. *Flow diagram of the study selection process.*

Table 1. *Characteristics of the included studies.*

Author	Country	Study Design	Surgery	Treatment/control	Does of interventional analgesia	Injection site	Number	Age, y		Duration of PDPH	
								Treatment	Control	Treatment	Control
Abboud 1992	USA	RCT	Cesarean delivery	Morphine/saline	0.2 mg	Subarachnoid	82	30. 3± 1	29.6 ± 0.9	12.5 ± 1.6 hr	4.4 ± 0.5 hr
Akkamahadevi 2012	India	RCT	Cesarean or vaginal delivery	sufentanil + bupivacaine/fentanyl + bupivacaine	S:0.3 mcg/L/F:2.5 mcg/mL	Intrathecal	60	23.46	22.02	/	/
Al-metwalli 2008	Saudi Arabia	RCT	Vaginal delivery	Morphine/saline	3 mg	Intrathecal	50	28.4 ± 6.0	29.6 ± 5.4	3 (3-4) days	2 (1–3) days
Campbell 1995[a]	USA	RCT	Cesarean or vaginal delivery	sufentanil + bupivacaine/ bupivacaine	10 μg	Intrathecal	29	28.6 (7.1)	28.9 (5.5)	/	/
Campbell 1995[b]	USA	RCT	Cesarean or vaginal delivery	sufentanil/bupivacaine	10 μg	Intrathecal	28	29.5 (7.2)	28.9 (5.5)	/	/
Devcic 1993	USA	RCT	Cesarean delivery	Fentanyl + bupivacaine/ bupivacaine alone	20 μg	Subarachnoid	194	28.3	29.1	/	/
D'Angelo 1994	USA	RCT	Cesarean or vaginal delivery	sufentanil/bupivacaine	10 μg	Intrathecal	62	24 (0.9)	25 (0.9)	/	/
Peralta 2020	USA	RCT	Cesarean or vaginal delivery	Morphine/saline	0.15 mg	Intrathecal	61	33 (30-36)	32 (29-34)	418 (291-550) min	427 (286-540) min
Brinser 2019	USA	Retrospective cohort	Cesarean or vaginal delivery	Morphine/saline	3-4 mg	Intrathecal	80	28.5 ± 4.8	30.1 ± 6.0	/	/
Cesur 2009	Turkey	Retrospective cohort	Cesarean delivery	Morphine/meperidine or tramodol	3 mg	Intrathecal	52	27 ± 6	28 ± 8	44 ± 10 h	/
Cohen 1994	USA	Retrospective study	Caesarean delivery	fentanyl+bupivacaine+epinephrine/ meperidine	5 μg/mL	Intrathecal	30	27.3 (1.2)	29.5 (1.3)	/	/

Supplemental Digital Content presents the quality analysis. Among the RCTs, only Peralta et al (29) had a low risk of bias, while the 6 other studies (26,28,36-39) had at least one item with at least an unclear risk of bias. Among the cohort studies, 2 scored 5 points (40,41) and one which scored 6 points (42).

PDPH Incidence of Morphine

Five studies (26,29,37,40,41) could be included for the incidence of PDPH with morphine. The results showed that morphine does not decrease the incidence of PDPH (OR = 0.45, 95% CI: 0.15 - 1.34, P = 0.153, I^2 = 74.4%, Pheterogeneity = 0.004) (Fig. 2A and Supplementary Table 2). Similar results were observed when analyzing the RCTs (26,29,37) (OR = 0.59, 95% CI: 0.18 - 1.99, P = 0.396; I^2 = 65.2%, Pheterogeneity = 0.056) and retrospective studies (40,41) (OR = 0.27, 95% CI: 0.01 - 5.12, P = 0.380; I^2 = 89.6%, Pheterogeneity = 0.002) independently (Fig. 2B and Supplementary Table 2).

PDPH Incidence of Fentanyl

Two studies (28,42) could be included for the incidence of PDPH with fentanyl. The results showed that fentanyl does not decrease the incidence of PDPH (OR = 0.35, 95% CI: 0.01 - 13.77, P = 0.576, I^2 =

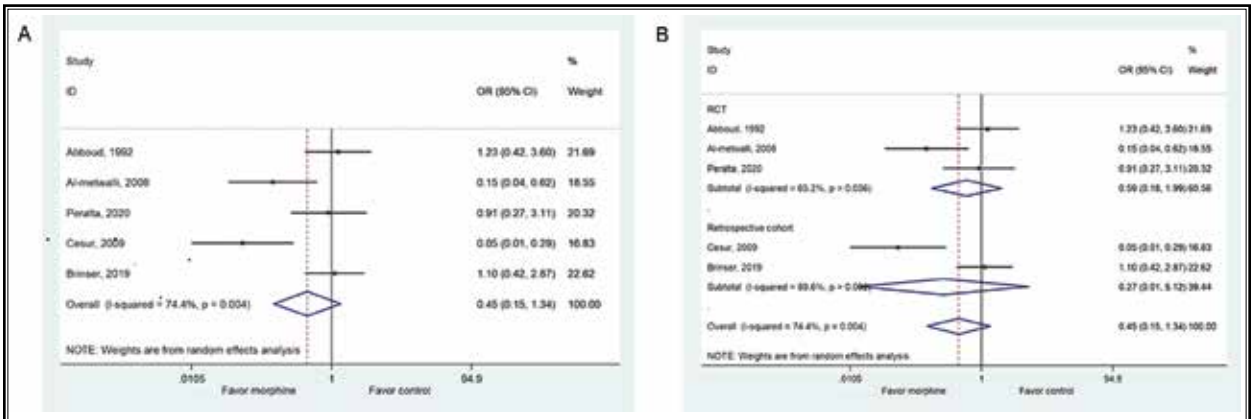

Fig. 2. *A) Forest plot of PDPH of morphine in the treatment vs. control groups; B) Forest plot of PDPH of morphine by study type in the treatment vs. control groups.*

81.0%, Pheterogeneity = 0.022) (Fig. 3 and Supplementary Table 2).

Number of EBP

Five studies (29,37,40-42) could be included for the number of EBP. The results showed that opioids do not decrease the use of EBP (OR = 0.40, 95% CI: 0.08 - 1.95, P = 0.259, I^2 = 73.7%, Pheterogeneity = 0.004) (Fig. 4 and Supplementary Table 2). Similar results are observed when analyzing the RCTs (29,37) (OR = 0.56, 95% CI: 0.04 - 8.79, P = 0.678; I^2 = 67.6%, Pheterogeneity = 0.079) and retrospective studies (40-42) (OR = 0.27, 95% CI: 0.02 - 4.24, P = 0.351; I^2 = 82.5%, Pheterogeneity = 0.003) independently (Fig. 4 and Supplementary Table 2).

Sensitivity analysis

The sensitivity analyses show that the results are robust (Fig. 5A and 5B).

Discussion

In the OBGYN setting, the ability to care for the newborn by the mothers could be compromised because of PDPH. Optimal management of PDPH is thus particularly important for delivering mothers. Drug therapy has been discussed for many years (25,29). To date, no meta-analysis has examined the prophylactic value and safety of opioids in patients with PDPH compared with EBP. Therefore, this meta-analysis aims to analyze the effectiveness and safety of opioids as a prophylaxis approach in treating obstetric patients who underwent iatrogenic dural puncture during the initiation of epidural anesthesia.

The results indicate that exposure to opioids, for

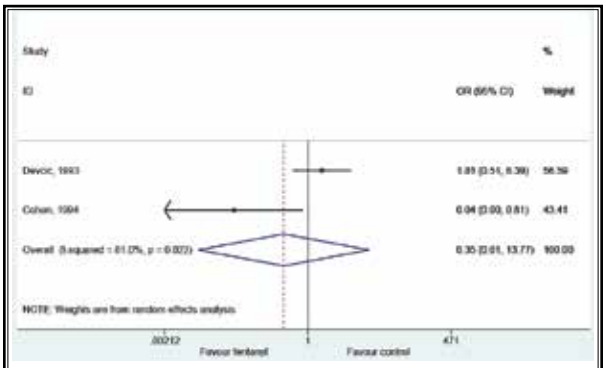

Fig. 3. *Forest plot of PDPH of fentanyl in the treatment vs. control groups.*

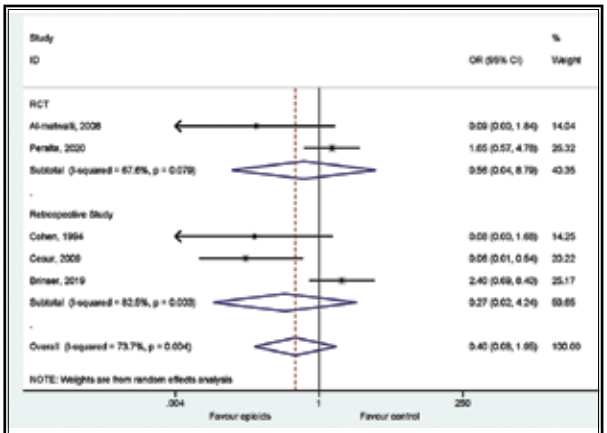

Fig. 4. *Forest plot of EBP by study type in the treatment vs. control groups.*

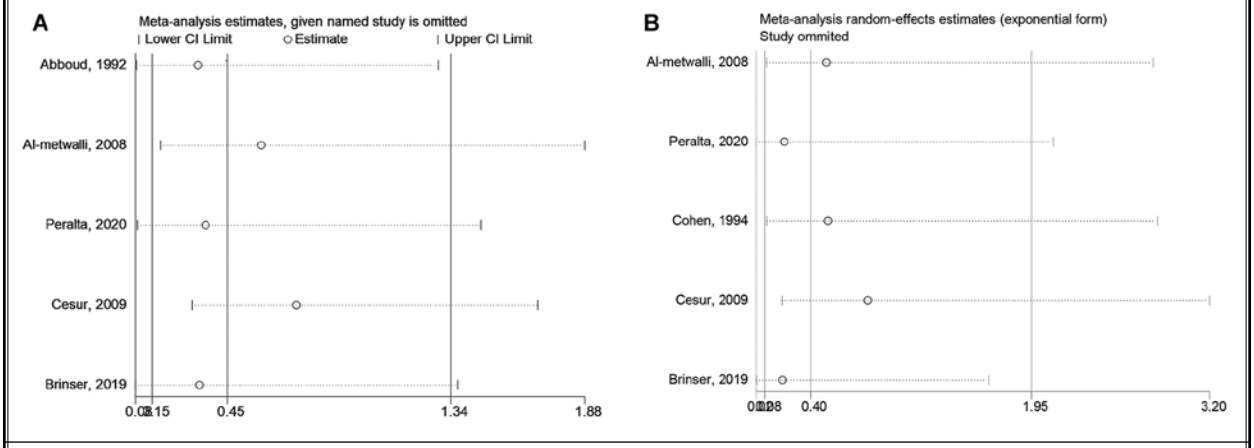

Fig. 5. *A) Sensitivity analysis of PDPH; B) Sensitivity analysis of EBP.*

any reason, after the diagnosis of unintentional dural puncture is not associated with a reduced risk of PDPH and does not decrease the need for therapeutic EBP. Although an overall protective effect of opioids was not observed in this study, its role as prophylaxis of PDPH should continue be investigated because of the small number of included studies and high heterogeneity.

One previous systematic review showed that opioids could be used for PDPH prophylaxis (25), but this previous review assessed only 3 studies (26,28,37), 2 of which met the criteria for inclusion in the present meta-analysis. Of note, this previous systematic review could not perform a meta-analysis because of the small number of studies and too wide variability in opioids dose, and differences in baseline characteristics (25). Nevertheless, this previous review suggested that opioids could be used to decrease the occurrence of PDPH, irrespective of severity, after lumbar puncture, especially in obstetric patients (25). In one of the 3 included studies, Abboud et al (26) showed that subarachnoid morphine did not decrease the occurrence of PDPH in obstetric patients, while another study showed that epidural morphine could prevent PDPH in high-risk obstetric patients (37). The third study included in the previous review (25) could not be included in this meta-analysis because it compared 2 types of needles (28). On the other hand, the present meta-analysis revealed no benefit of PDPH prophylaxis using opioids, either regarding the occurrence of PDPH or the use of EBP. It is the first meta-analysis to systematically review the effectiveness and safety of opioids for preventing PDPH in obstetric patients. Of note, regarding the occurrence of PDPH, 2 of the included studies reported benefits from morphine (37,41), while the other 3 did not (26,29,40).

This study has limitations and they have to be considered when looking at the results. Some studies were small. Nevertheless, they demonstrated that the estimated sample size had a low risk to influence the null hypothesis and a rigorous study design would eliminate such risk. Selection bias may become a concern for retrospective cohort studies because it is hard to distinguish between opioid administration for prophylaxis against PDPH, versus opioids administration for analgesia after cesarean delivery. Whether the route of opioids administration influences the successful prevention of PDPH should be investigated since one retrospective study did not distinguish between intrathecal and epidural morphine (40). Finally, although the sensitivity analyses showed that the results were robust, heterogeneity was high for all meta-analyses, which probably influenced the results.

In conclusion, exposure to opioids for any reason after recognized iatrogenic dural puncture is not associated with a reduced risk of PDPH or a decreased need for therapeutic EBP. Although an overall protective effect of opioids was not observed in this study, its role as prophylaxis of PDPH remains to be investigated.

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Supplementary 1a. *Cochrane criteria for the quality of RCTs*

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients and peraonnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abboud 1992 (26)	High	Unclear	Low	Unclear	High	Unclear	High
Al-metwalli 2008 (37)	Low	Unclear	Low	Low	Low	Unclear	Unclear
Peralta 2020 (29)	Low	Low	Low	Low	Low	Low	Low
Akkamahadevi 2012 (36)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Campbell 1995a (38)	Low	Unclear	Low	Low	High	Low	Unclear
Devcic 1993 (28)	Unclear	Unclear	Unclear	Low	Unclear	High	Unclear
D'Angelo 1994 (39)	Unclear	Unclear	Unclear	Low	High	Low	Unclear

Supplementary 1b. *Nos criteria for quality of cohort studies*.

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Cesur 2009 (41)	/	⋆	⋆	/	⋆	⋆	⋆	/	5
Brinser 2019 (40)	/	⋆	⋆	/	⋆	⋆	⋆	/	5
Cohen 1994 (42)	⋆	⋆	⋆	/	⋆	⋆	/	⋆	6

Supplementary Table 2. *Outcomes in the opioids vs. saline groups*.

	n	OR (95%CI)	*P*	I^2	Pheterogeneity
PDPH incidence of morphine	5	0.45 (0.15, 1.34)	0.153	74.4%	0.004
RCT	3	0.59 (0.18, 1.99)	0.396	65.2	0.056
Retrospective cohort	2	0.27 (0.01, 5.12)	0.380	89.6	0.002
PDPH incidence of fentanyl	2	0.35 (0.01, 13.77)	0.576	81.0	0.022
EBP	5	0.40 (0.08, 1.95)	0.259	73.7	0.004
RCT	2	0.56 (0.04, 8.79)	0.678	67.6	0.079
Retrospective cohort	3	0.27 (0.02, 4.24)	0.351	82.5	0.003

OR: odds ratio; CI: confidence interval; PDPH: post-dural puncture headache; RCT: randomized controlled trial; EBP: epidural blood patch.