Original Article

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Prophylactic Neuraxial Morphine Against Post-Dural Puncture Headache: A Meta-Analysis

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Objective: Reducing the risk of post-dural puncture headache (PDPH) remains a clinical challenge. This meta-analysis aims at investigating the effects of prophylactic neuraxial morphine on risk and severity of PDPH.

Methods: CENTRAL, EMBASE, and MEDLINE were searched for randomized controlled trials (RCTs) and non-RCTs that compared participants with or without neuraxial morphine prophylaxis against PDPH from inception till January 4, 2021.

Results: Of the seven eligible studies involving 3,949 participants (RCT = 4, non-RCT = 3) published between 1992 and 2020, six focused on parturients receiving spinal anesthesia or undergoing epidural procedures with an unintentional dural puncture and one investigated women subjected to spinal or epidural anesthesia with an inadvertent dural puncture. Our results demonstrated no association between the use of neuraxial morphine and risks of PDPH [relative risk (RR) = 0.76; 95% confidence interval (CI): 0.54 – 1.07, 3,949 participants] and epidural blood patch requirement (RR = 0.86, 95% CI: 0.58 – 1.29, 3,949 participants) as well as headache severity (mean difference = -0.32, 95% CI: -1.52 to 0.87, 191 participants). Consistently, subgroup analysis (i.e., RCT vs. non-RCT) and sensitive analysis revealed similar findings. Besides, use of neuraxial morphine increased the risk of pruritis (RR = 8.5, 95% CI: 3 – 24.12, 132 participants).

Conclusion: There was no evidence supporting the efficacy of prophylactic neuraxial morphine against post-dural puncture headache. Other pharmacological strategies for prophylaxis or headache alleviation should be initiated when dural puncture occurs especially in high-risk patients such as parturients.

Key words: spinal, epidural, neuraxial morphine, post-dural puncture headache, obstetric

Introduction

Neuraxial analgesia and anesthesia are common approaches to achieving procedure-related pain relief among parturients. The application of labor epidural analgesia or neuraxial anesthesia provides distinct advantages for this patient population because of effective labor pain control by the former and the avoid-

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ance of airway management in the latter taking into account the potential high risk of difficult airway during caesarean section.[1,2] Although previous studies support the use of neuraxial analgesia for labor pain by demonstrating its efficacy and safety in parturients without increasing their risks of cesarean delivery or instrumental vaginal delivery,[3,4] postdural puncture headache (PDPH) remains a potential iatrogenic complication of neuraxial blockade.[5] A previous meta-analysis[5] and a large-scale study involving 23,358 cases[6] showed an incidence of accidental dural puncture-related PDPH up to 50% – 88% in parturients. The occurrence of PDPH not only increases the length of hospital stay but it also impairs the quality of patient care and the satisfaction of patients.[7]

Management strategies for PDPH vary with symptom severity, ranging from conservative treatment to epidural blood patching (EBP). Because there is no consensus on the optimal treatment, the management approaches are highly heterogeneous.[8] For those in favor of EBP, issues still exist regarding the choice of patients, the post-procedural timing of implementation, and the treatment strategy for those with initial EBP failure.[9] Moreover, patients who refuse EBP and those with absolute (e.g., postpartum coagulopathy) or relative (i.e., fever, preeclampsia) contraindications for the procedure[9,10] pose another challenge to PDPH treatment. The COVID-19 pandemic also raised a concern regarding the use of EBP in those having contracted the disease.[11]

Taking into account the inadequacy of current evidence regarding the therapeutic strategies against PDPH,[9] prophylaxis may be a rational approach. Despite the promising findings from one published randomized controlled trial (RCT) and a large-scale retrospective study on 3,537 patients that showed the effectiveness of prophylactic intrathecal or epidural morphine for the prevention of PDPH,[12,13] several studies failed to demonstrate significant differences in the risk of PDPH between patients with neuraxial morphine prophylaxis and those without.[14-16] In addition, potential respiratory depression associated with the use of neuraxial morphine in this clinical setting is another crucial concern for clinicians.[17-19] Therefore, we aimed at exploring the prophylactic effectiveness of neuraxial morphine against PDPH by performing a meta-analysis of available studies.

Materials and Methods

This meta-analysis was reported according to the Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) guidelines[20] and was registered with PROSPERO (CRD42021228906).

Search strategy

To perform this analysis, comparative trials that reported the occurrence of PDPH with or without neuraxial morphine prophylaxis were identified from electronic databases including Embase, Medline, and Cochrane Central Register of Controlled Trials from inception to January 4, 2021. Only trials published in English were included. A sensitive search strategy was conducted by combining the following keywords with the Boolean Operators of “AND” and “OR”: ("Spinal" or "intraspinal" or "dural" or "intradural" or "epidural" or "lumbar*" or "theca*" or "intrathecal" or "subarachnoid*" or "sub arachnoid*" or "regional") AND (morphine or opioid*) AND ("postdural puncture headache" or "PDPH"). The search strategies and syntax for one of these databases (i.e., Embase) can be found in Table 1.

Study selection criteria and data extraction

The titles and abstracts of the acquired studies were examined independently by two reviewers to identify eligible articles compar-

Table 1. Search Strategy for Embase.

Database	#	Search syntax
Embase	1	(("Spinal" or "intraspinal" or "dural" or "intradural" or "epidural" or "lumbar*" or "theca*" or "intrathecal" or "subarachnoid*" or "sub arachnoid*" or "regional") Near/3 (puncture* or inject* or anesth* or anaesth* or needle*)):ti,ab,kw,de
	2	"anesthesia, epidural"/exp or "anesthesia, spinal"/exp or "Injections, Spinal"/exp or "lumbar puncture"/exp
	3	Morphine or opioid*
	4	"opiate agonist"/exp or "morphine derivative"/exp
	5	("postdural puncture headache" or "PDPH"):ti,ab,kw,de
	6	"postdural puncture headache"/exp
	7	(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6)

ing the risk of PDPH between patients receiving dural puncture with neuraxial morphine prophylaxis and those without. The criteria for eligibility of studies included: (1) adult patients (age ≥ 18 years) with dural puncture; (2) intervention group included the use of epidural or intrathecal morphine with no restrictions on dosage; (3) control group included placebo or no treatment. The exclusion criteria were (1) studies that focused on the pediatric population, (2) those in which information regarding primary outcomes was unavailable. The selected studies were independently investigated by two authors for the final analysis. Two reviewers independently performed the extraction of data that included: primary author, year of publication, sample size, patient characteristics, study setting, and outcomes (e.g., risk of PDPH). On encountering disagreements, a third author was involved to help in reaching a consensus. If data on primary or secondary outcomes were not available in a study, the corresponding author was contacted for further information.

Primary outcome and secondary outcomes

The primary outcome was the risk of PDPH and EBP requirement, while the secondary outcomes included changes in the severity of PDPH and the risks of other adverse events (e.g., pruritis or nausea). The definition of PDPH was according to the criteria of each trial.

Assessment of risk of bias for included studies

Two authors evaluated the risk of bias in the eligible randomized controlled trials (RCTs), including the overall risk of bias and the risk of bias of individual studies, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[21] The potential risk of bias was rated by assigning a rating rank of “low”, “high,” or “unclear” to each trial. For observational studies, quality assessment was performed by using the Newcastle-Ottawa Scale (NOS) based on three domains (i.e., study group selection, group comparability, and outcome of interest ascertainment).[22] The Selection, Comparability, and Outcome domains were assigned a maximum of four, three, and two stars, respectively. A higher number of stars represents a better quality of the study (i.e., the highest quality study is given nine stars). Any disagreements were solved through discussion.

Statistical analysis

Review Manager (RevMan 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all data analysis. For dichotomous outcomes (e.g., risk of PDPH), we calculated the risk ratios

(RR) with 95% confidence interval (CI) with the Mantel-Haenszel method using the random-effects model because clinical and methodological heterogeneity was expected among the studies. We evaluated the heterogeneity with the I^2 statistics, in which I^2 levels of 25%, 50% and 75% are considered to be of low, moderate, and high degrees of heterogeneity, respectively. We performed subgroup analyses of the design of studies (i.e., RCTs vs. non-RCTs) to identify potential contributors to heterogeneity. Besides, a post-hoc sensitivity analysis was performed by omitting certain studies from data synthesis to explore the robustness of our findings. When 10 or more studies reported a specific outcome, the probabilities of publication bias were assessed by visual inspection of the funnel plots. We used a two-tailed test in which a probability value $p < 0.05$ was considered statistically significant.

The reliability of conclusions drawn from the cumulative evidence was evaluated by trial sequential analysis (TSA) [TSA viewer version 0.9.5.10 Beta (www.ctu.dk/tsa)] to identify false-positive or false-negative findings from multiple testing and sparse data.[23] The required information size (RIS) and the trial sequential monitoring boundaries were computed for the primary outcomes. The variance was obtained from data retrieved from the included studies. The anticipated intervention effect is considered to reach a sufficient level of evidence when the cumulative Z curve crosses the TSA boundary where no further studies are needed, while insufficient evidence to reach a conclusion is implicated when the Z curve fails to cross the TSA boundaries or reach the RIS. We applied two-sided tests with a type I error, power, and relative risk reduction of 5%, 80%, 20%, respectively,[24] to dichotomous outcomes for the computation of RIS.

Results

Inclusion and exclusion of Studies

Figure 1 shows the reasons for study inclusion and exclusion. Of a total of 696 eligible records retrieved from the databases, 101 were

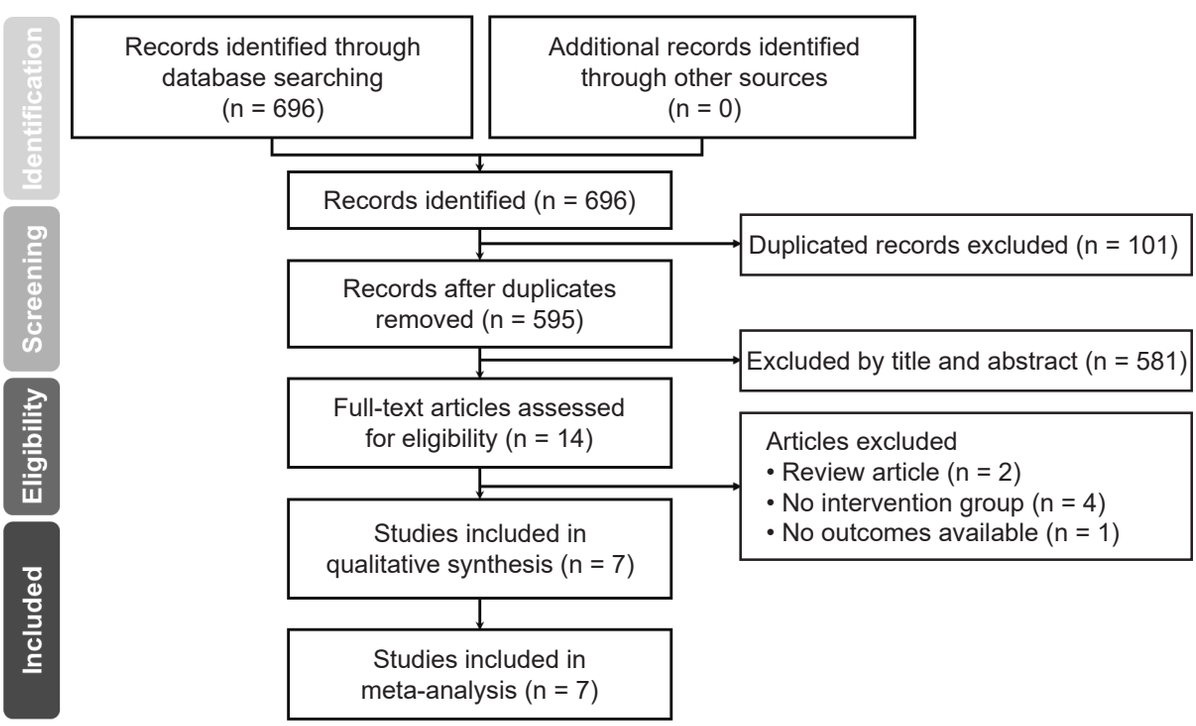

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for identifying eligible studies.

removed because of duplications and 581 were excluded after initial screening of the titles and abstracts. Of the 14 remaining eligible reports for full-test review, 7 were excluded because of no outcome available (n = 1), incompatible selection criteria (i.e., no intervention group) (n = 4), or being a review article (n = 2). Finally, a total of seven comparative studies[12-16,25,26] were included in the current meta-analysis (Fig. 1).

Characteristics of included studies

Seven comparative studies involving 3,949 participants published between 1992 to 2020 were analyzed. The study characteristics are demonstrated in Table 2. Of the seven studies, four were RCTs[12,14,16,26] and three were retrospective observational studies.[13,15,25] Six studies focused on parturients receiving spinal anesthesia or undergoing epidural procedures with an unintentional dural puncture,[12-16,26] while one study investigated women subjected to spinal anesthesia or epidural anesthesia with an inadvertent dural puncture.[25] The sample size ranged from 50 to 3,537. Although five studies indicated the duration of follow-up with a minimum of two days,[12-14,16,26] the other two studies did not specify this duration.[15,25] Three studies reported a dosage of intrathecal morphine ranging from 50 to 200 mcg,[14,16,26] while one study used epidural morphine at a dose of 3 mg[12] and the other applied epidural morphine or intrathecal morphine at a dose of 4 mg and 100 – 200 mcg, respectively.[25] On the other hand, two studies did not specify the dosage of opioids.[13,15]

Risk of bias assessment

The risks of bias of individual RCTs are summarized in Figure 2. The risks of bias caused by allocation concealment, blinding of outcome assessment, or other bias (e.g., information regarding conflict of interest was unavailable) were found in one,[14] two,[12,14] and three[12,14,26] of the RCTs, respectively. Although the registered information was unavailable in three RCTs,[12,14,26] we considered the risk of reporting bias to be low as the primary outcome was available in these studies. For non-RCTs (Table 3), we awarded nine stars to two studies,[13,15] and seven stars to one study which did not specify the duration of follow-up after dural puncture or mention the dropout rate.[25]

Primary outcome

Prophylactic effect of neuraxial morphine against post-dural puncture headache

Seven studies involving 3,949 patients (morphine group, n = 2,474 vs. control group,

Table 2. Characteristics of included studies.

Study	Setting	Sample size	Needle size	Route	Dosage of morphine	Follow-up (days)	Country
Abboud 1992[14*]	Parturients receiving spinal anesthesia for	82	25-G SN	IT	200 μg	3	United states
Al-metwalli 2008[12*]	Parturients with unintentional dural puncture	50	17-G EN	Epidural	3 mg	≥ 5	Saudi arabia
Brinser 2019[15]	Parturients with unintentional dural puncture	80	17-G EN	Epidural or IT	NA	NA	United states
Hein 2010[26*]	Nulliparous receiving CSE analgesia for labor pain	90	27-G SN	IT	50 μg, 100μg	4	Sweden
Martlew 2009[13]	Parturients receiving spinal anesthesia for CS	3,537	25-G SN	IT	Diamorphine[†]	≥ 2	United Kingdom
Peralta 2020[16*]	Postpartum patients with unintentional dural puncture	61	17-G EN	IT	150 μg	≥ 5	United states
Williams 2013[25]	Women with unintentional dural puncture	57	NA	Epidural or IT	4 mg[¶] or 100 – 200 μg[§]	NA	United Kingdom

*Randomized controlled trial; CSE: combined spinal epidural; CS: Caesarean section; G: gauge; EN: epidural needle; SN: spinal needle; IT: intrathecal; [†]dosage unknown; NA: not available; [¶]for epidural route; [§]for intrathecal route.

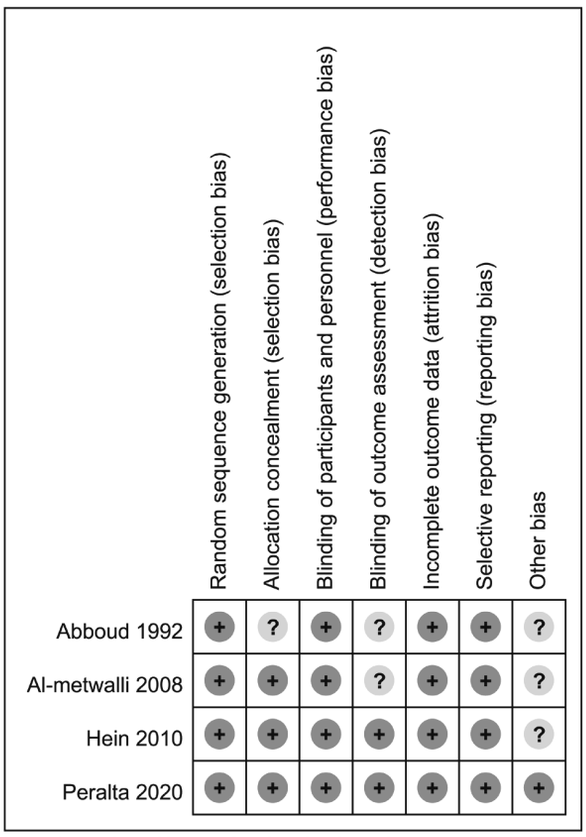

Fig. 2 Risks of bias of individual studies.

n = 1,475) were available for analysis of the prophylactic effect of neuraxial morphine against PDPH. A forest plot on the risk of PDPH is presented in Figure 3. The pooled RR was 0.76 (95% CI: 0.54 – 1.07, p = 0.11), demonstrating similar risks of PDPH between patients receiving neuraxial morphine and those without. In addition, RCTs and non-RCTs showed no significant difference in the risk of PDPH on subgroup analysis (p = 0.89). Subgroup analysis based on the route of opioid administration (i.e., only intrathecal vs. epidural or intrathecal) demonstrated that different routes of opioid administration had no impact on the risk of PDPH (Figure not shown). Nevertheless, there was a moderate to high heterogeneity among the included studies in our primary analysis (I^2 = 71%). Sensitivity analysis showed no significant effect on outcome through omitting certain trials. TSA demonstrated that the cumulative Z-curve crossed the futility boundary, suggesting sufficient evidence supporting these outcomes (Fig. 4).

Impact of neuraxial morphine on the risk of epidural blood patch requirement

The forest plot on seven available studies with a total of 3,949 patients (morphine group, n = 2,474 vs. control group, n = 1,475) shown in Figure 5 did not demonstrate statistical significance (RR = 0.86, 95% CI: 0.58 – 1.29, p = 0.48; I^2 = 26%) in the risk of EBP requirement following neuraxial morphine prophylaxis. Consistently, subgroup analysis and sensitivity analysis showed similar findings.

Secondary outcomes

Impact of neuraxial morphine prophylaxis on the severity of PDPH

Three studies involving a total of 191 patients (morphine group, n = 94 vs. control group, n = 97) were available for analysis. The forest plot demonstrated comparable levels of pain between the two groups (mean difference = -0.32, 95% CI: -1.52 to 0.87, p = 0.59; I^2 = 67%) (Figure not shown). Sensitivity analysis showed no significant influence on outcome by omitting certain trials.

Impact of neuraxial morphine prophylaxis on the risk of adverse events

Two studies with a total of 132 patients

Table 3. Quality of included studies assessed with Newcastle Ottawa scale (n = 3).

Study	Number of stars awarded in each domain			Total score (out of 9)
	Selection (Maximum: 4 ＊)	Comparability (Maximum: 2 ＊)	Outcome (Maximum: 3 ＊)	
Brinser 2019	＊＊＊＊	＊＊	＊＊＊	9
Martlew 2009	＊＊＊＊	＊＊	＊＊＊	9
Williams 2013	＊＊＊＊	＊＊	＊	7

(morphine group, n = 65 vs. control group, n = 67) were available for the analysis of adverse events. The forest plot demonstrated an increased risk of pruritis (RR = 8.5, 95% CI: 3 to 24.12, $p < 0.0001$; $I^2 = 0\%$), while the risk of nausea was similar (RR = 1.52, 95% CI: 0.55 to 4.18, $p = 0.42$; $I^2 = 67\%$) between the two groups (Figure not shown).

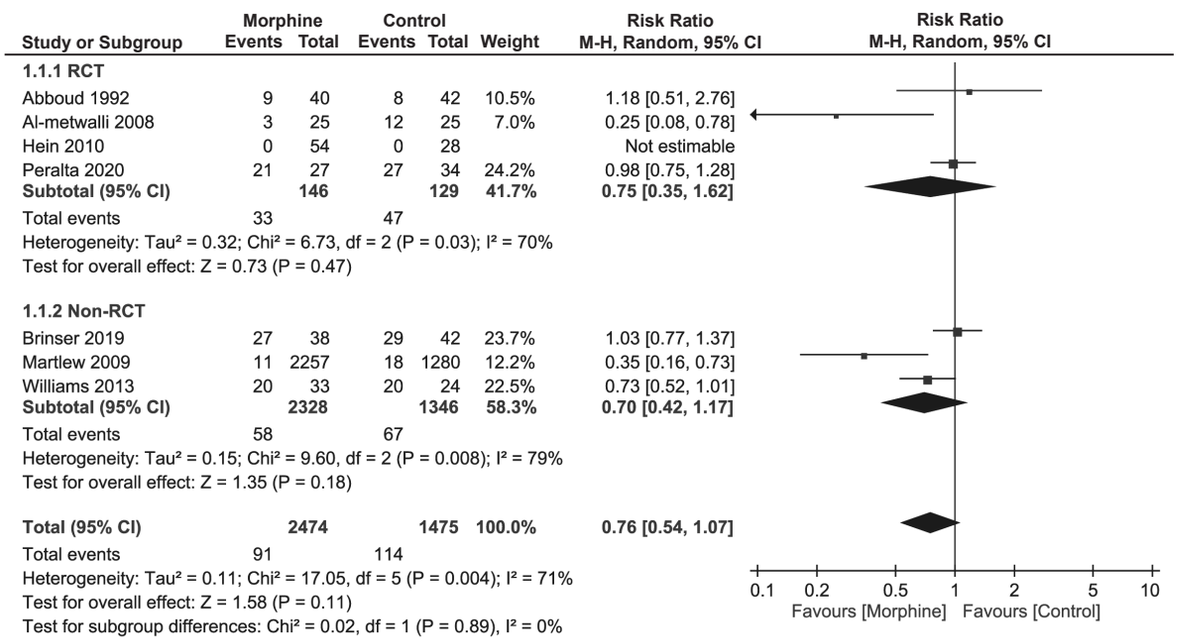

Fig. 3 Forest plot for comparing the risk of post-dural puncture headache with or without neuraxial morphine prophylaxis. CI: confidence interval; M-H: Mantel-Haenszel.

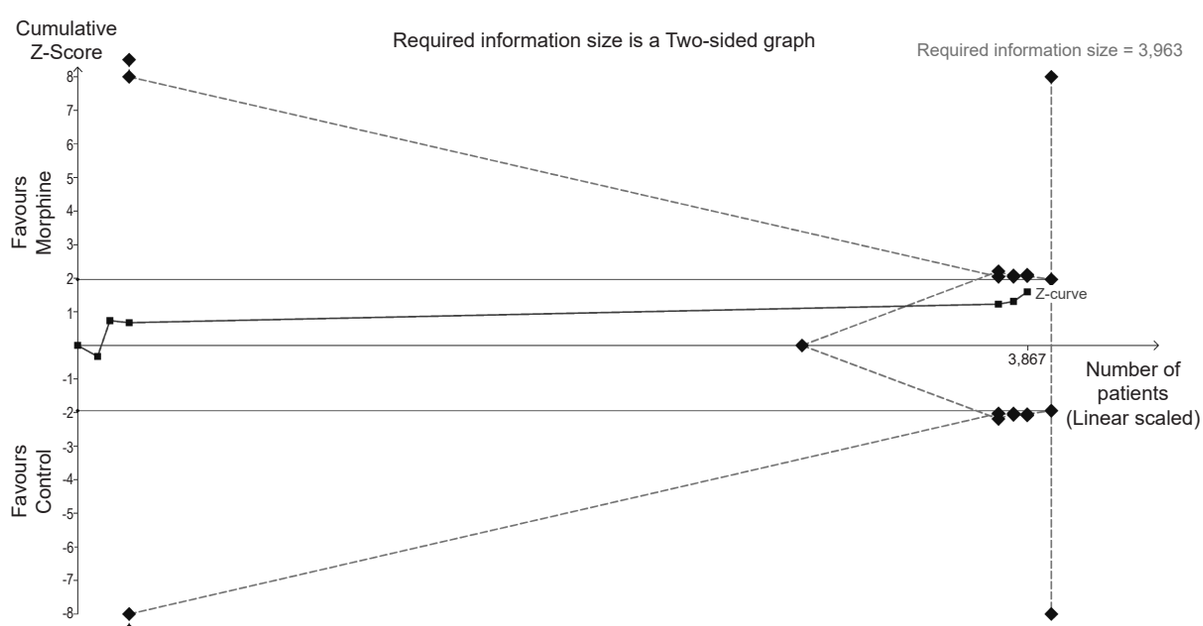

Fig. 4 Trial sequential analysis of the prophylactic effect of neuraxial opioid against post-dural puncture headache with the risk of type I error and power set at 5% and 80%, respectively. The variance calculated from the data obtained from the included trials with the relative risk reduction (RRR) set at 20%.

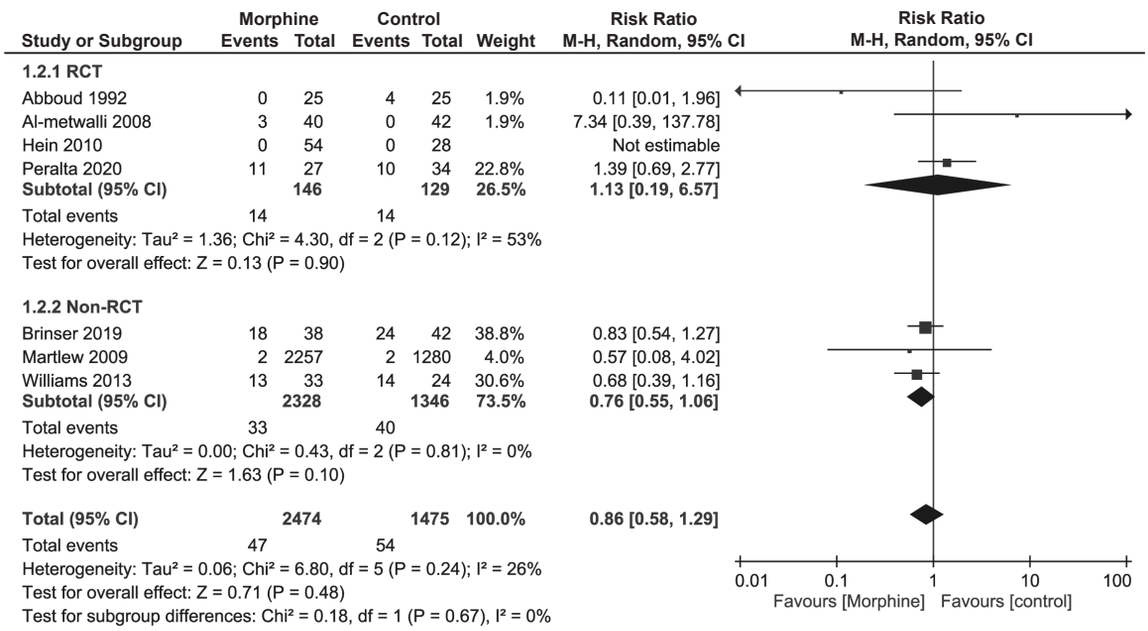

Fig. 5 Forest plot for comparing the risk of epidural blood patch requirement with or without neuraxial morphine prophylaxis. CI: confidence interval; M-H: Mantel-Haenszel.

Discussion

Because there are no consensual guidelines on the management of PDPH,[27,28] clarification of the effect of prophylactic neuraxial morphine on the risk of PDPH could facilitate the establishment of a standard protocol for those requiring spinal analgesia or anesthesia through dural puncture to minimize the clinical impact of this condition. However, current evidence supporting the prophylactic use of neuraxial morphine against PDPH remains insufficient. Through a meta-analysis of RCTs and observational studies, we showed that neuraxial morphine was associated with neither a prophylactic effect nor a reduction in EBP requirement in patients with dual puncture. Moreover, the severity of PDPH was not influenced by the application of neuraxial morphine. These findings highlighted that neuraxial morphine may not be indicated for PDPH prophylaxis or pain control.

Despite the routine application of neuraxial opioids in obstetric anaesthesia or analgesia, the adverse side-effect of respiratory depression, particularly in patients with cardiopulmonary diseases, pre-existing respiratory conditions (e.g., obstructive sleep apnea), and concomitant administration of systemic opioids[18,29] remain important clinical concerns. The onset of respiratory depression can be early, late, or biphasic;[30,31] while early-onset respiratory depression could appear as soon as 30 to 90 minutes after opioid administration due to its rapid vascular uptake,[32] delayed depression of the respiratory drive may occur up to 6 to 18 hours following neuraxial morphine injection[33] because of its rostral spread to the brainstem through the cerebrospinal fluid (CSF). The process has been reported to cause a maximum depression between 6.5 and 7.5 hours after morphine administration.[34,35] A previous large-scale study on a total of 8,927 obstetric and 12,434 non-obstetric patients reported an incidence of 0.26% – 3% for intrathecal morphine with a dose range of 0.15 – 0.8 mg as well as an incidence of between 0% and 2.8% for epidural morphine injection with a dose range of 2 – 5 mg.[19] Therefore, current practice guidelines recommend a low-dose neuraxial morphine with multimodal analgesia

in the setting of obstetric anaesthesia or analgesia.[18] For determining the degree of respiratory monitoring (i.e., intensity, frequency, and duration) in parturient patients receiving neuraxial opioids, risk stratification and perioperative risk assessment are recommended.[18]

A previous report showed a reduction in PDPH by 36% (from 48% to 12%) through the administration of epidural morphine at a dose of 3 mg at the end of delivery, followed by a booster dose at 24 hours via an in situ epidural catheter.[12] In this way, the finding endorsed the use of a relatively high dose of neuraxial morphine for PDPH prophylaxis that may increase the risk of respiratory depression and also the associated untoward side-effects. As RCTs addressing the impact of prophylactic neuraxial morphine on the risk of PDPH were rare, a previous meta-analysis[36] was unable to provide pooled evidence for this issue. Through incorporating RCTs and non-RCTs into a meta-analysis involving 3,949 participants, we found that neuraxial morphine had no significant impact on the risk of PDPH. In addition, there was no difference in the risk of EBP requirement between patients receiving neuraxial morphine and those without. Therefore, for patients with dural puncture, other strategies instead of neuraxial morphine may be indicated for reducing the risk of PDPH.

Two previous meta-analyses have demonstrated the inability of routine bed rest after dural puncture to prevent PDPH,[37,38] while the role of fluid supplementation remains unclear.[37] Pooled evidence from previous meta-analyses suggested the effectiveness of several strategies including the insertion of an intrathecal catheter following dural puncture, the use of atraumatic needles, a lateral decubitus position during lumbar puncture, and the application of prophylactic epidural blood patch for reducing the risk of PDPH.[36,39-42] On the other hand, although the effectiveness of some approaches such as continuous epidural saline pumping, intrathecal normal saline administration, and prophylactic dexamethasone following dural puncture have not systematically analyzed, they have been shown to be effective against PDPH in several RCTs.[43-45]

Although two previous studies in Israel[28] and UK[27] reported that most hospitals (e.g., 71%) perform EBP for PDPH after failure of conservative measures, a recent prospective international study involving 24 countries reported a different set of criteria that justify the use of EBP in patients with increasing intensity of PDPH after initial diagnosis.[46] Nevertheless, regardless of its indication, the application of EBP for PDPH may be associated with immediate (e.g., risk of accidental dural puncture) and subsequent long-term complications (i.e., 3 months) such as backache, headache, and analgesic use.[46,47] Besides, the necessity of EBP appears questionable taking into account the similar outcome (i.e., mild headache) between patients receiving EBP and those without seven days after the onset of PDPH.[46] Therefore, it is possible that prophylactic pharmacological interventions, which may prevent or reduce the severity of PDPH, may reduce the need for EBP and also its associated short- and long-term complications. Although the application of neuraxial morphine may be the missing piece of the jigsaw puzzle, we found no significant association between its prophylactic use and the severity of PDPH.

This meta-analysis had several limitations that need to be considered for accurate interpretation of its findings. First, because all studies included in the present study were conducted in the relatively young female population, the results cannot be extrapolated to other subgroups of patients (e.g., male or elderly). Second, the high heterogeneity among the included studies arising from variations in parameters including the dose of morphine, the size of needle used, and the route of drug administration may blemish the reliability of the primary outcome. Third, such a small sample size makes subgroup analyses and sensitivity

analyses even more challenging to interpret. Finally, the possibility of a dose-dependent response still exists,[16] taking into consideration the effectiveness reported in one of the included studies that adopted a higher dose (i.e., 3 mg).[12] Further large-scale trials focusing on dosage effect are warranted to support this finding.

Conclusion

The current meta-analysis demonstrated no significant association of the prophylactic use of neuraxial morphine with the risk of post-dural puncture headache, the requirement for epidural blood patch, and headache severity in women undergoing nueraxial analgesic or anesthetic procedures. Therefore, the results of the present study did not support neuraxial morphine prophylaxis against post-dural puncture headache, although a dose-dependent effect cannot be ruled out. Further large-scale trials are warranted to support the findings.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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