ANESTHESIOLOGY

Prophylactic Intrathecal Morphine and Prevention of Post–Dural Puncture Headache

A Randomized Double-blind Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Epidural morphine has been suggested to be effective for preventing post–dural puncture headache, but the effects of intrathecal morphine in reducing the incidence of this complication is unknown

What This Article Tells Us That Is New

- In a single-center, randomized, double-blind study, there was no evidence that intrathecal morphine prevented post–dural puncture headache

ABSTRACT

Background: Prophylactic epidural morphine administration after unintentional dural puncture with a large-bore needle has been shown to decrease the incidence of post–dural puncture headache. The authors hypothesized that prophylactic administration of intrathecal morphine would decrease the incidence of post–dural puncture headache and/or need for epidural blood patch after unintentional dural puncture.

Methods: Parturients with an intrathecal catheter *in situ* after unintentional dural puncture with a 17-g Tuohy needle during intended epidural catheter placement for labor analgesia were enrolled in this randomized, double-blind trial. After delivery, subjects were randomized to receive intrathecal morphine 150 μg or normal saline. The primary outcome was the incidence of post–dural puncture headache. Secondary outcomes included onset, duration, and severity of post–dural puncture headache, the presence of cranial nerve symptoms and the type of treatment the patient received.

Results: Sixty-one women were included in the study. The incidence of post–dural puncture headache was 21 of 27 (78%) in the intrathecal morphine group and 27 of 34 (79%) in the intrathecal saline group (difference, −1%; 95% CI, −25% to 24%). There were no differences between groups in the onset, duration, or severity of headache, or presence of cranial nerve symptoms. Epidural blood patch was administered to 11 of 21 (52%) of the intrathecal morphine group and 10 of 27 (37%) of subjects in the intrathecal saline and (difference 15%; 95% CI, −18% to 48%).

Conclusions: The present findings suggest that a single prophylactic intrathecal morphine dose of 150 μg administered shortly after delivery does not decrease the incidence or severity of post–dural puncture headache after unintentional dural puncture. This study does not support the clinical usefulness of prophylactic intrathecal morphine after an unintentional dural puncture.

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Unintentional dural puncture is a known risk of neuraxial procedures, occurring in approximately 0.51% to 1.5% of epidural catheter placement attempts with any size epidural needle in obstetric patients.[1–4] The incidence of post–dural puncture headache after unintentional dural puncture is between 50% and 80%.[3–5] Post–dural puncture headache can be a significant cause of maternal morbidity in the obstetric patient.[6,7] In addition to interfering with the mother's ability to care for her newborn, treatment of post–dural puncture headache can increase health care costs by prolonging the length of hospitalization and increasing emergency room visits in the postpartum period.[8,9]

Several strategies exist to treat post–dural puncture headache, but currently there are no proven interventions for preventing or reducing the likelihood of post–dural puncture headache after unintentional dural puncture. A randomized, controlled trial evaluated the use of epidural morphine (3 mg after delivery, and 3 mg 24 h later) for the prevention and treatment of post–dural puncture headache in obstetric patients.[10] The incidence of post–dural puncture headache rate was reduced from 48% to 12% (difference, −36%; 95% CI, −7.6% to −64%) after administration of epidural morphine compared with saline placebo. After an unintentional dural puncture with a large-bore (usually 16- to 18-gauge) needle, the large dural tear may facilitate intrathecal translocation of epidural morphine, increasing the risk for respiratory depression.[11–13] Although we are not aware of any reports of respiratory arrest in this setting, it remains a theoretical concern because of the large differential dose between epidural and spinal morphine.[14]

At many maternity centers, it is common practice to place an intrathecal catheter at the time of the unintentional dural puncture. The incidence of intrathecal catheter

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placement after unintentional dural puncture is unknown. In a single United States tertiary care institution, 73% of 235 parturients over a 5-yr period had an intrathecal catheter placed after an unintentional dural puncture.[15] In the United Kingdom, a 2005 study of maternity units found that placement of intrathecal catheter after unintentional dural puncture was common in 59% of the units, whereas a 2018 study in Canada found that 30% of anesthesia providers placed an intrathecal catheter after unintentional dural puncture.[16,17] Neuraxial labor analgesia is maintained with a continuous intrathecal infusion of a long-acting amide local anesthetic (*e.g.*, bupivacaine) and lipid-soluble opioid (*e.g.*, fentanyl). Given that the administration of epidural morphine may have unpredictable adverse effects after a puncture with a large bore needle, and that the use of intrathecal catheters after unintentional dural puncture is a common practice, we undertook this randomized, double-blind trial to test the hypothesis that the prophylactic administration of intrathecal morphine after unintentional dural puncture in obstetric patients would decrease the incidence and severity of post–dural puncture headache. We hypothesized that postpartum women randomized to receive intrathecal morphine would have a reduced incidence of post–dural puncture headache or need for epidural blood patch compared with women randomized to receive saline.

Materials and Methods

The study was approved by the Institutional Review Board (IRB) for human subjects at Northwestern University (Chicago, Illinois; STU00043549, approval date June 6, 2011). The protocol was registered at ClinicalTrials.gov (NCT01977898), Principal Investigator Feyce M. Peralta, registration date November 7, 2013. Sixteen patients were recruited between November 18, 2011, when the first patient was recruited, and November 7, 2013, the date of the trial registration. There were no revisions made to the protocol between the date of study approval and the date of trial registration. The study was a randomized, controlled, parallel group trial of pregnant women admitted to Prentice Women's Hospital. This article adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Inclusion criteria were postpartum patients after vaginal delivery with an unintentional dural puncture and a functioning intrathecal catheter for labor analgesia, age 18 yr or older, and ability to read and comprehend the English language. A functioning intrathecal catheter was defined by satisfactory labor analgesia endorsed by the patient after placement. Exclusion criteria were a previous post–dural puncture headache, body mass index greater than 40 kg/m^2, history of obstructive sleep apnea, and patients who underwent cesarean delivery. Patients undergoing cesarean delivery were excluded because they receive intrathecal morphine for postoperative analgesia as standard of care and would, therefore, not be eligible for randomization.

A convenience sample of eligible women were screened and approached shortly after delivery after the patient had met the criteria to be discharged to the postpartum unit. Women meeting inclusion criteria provided informed written consent for study participation. Subjects were randomly allocated to receive either preservative-free morphine 150 μg (treatment group) or an equal volume of saline (control group) as an intrathecal bolus just before removal of the intrathecal catheter. Before the study commencement, two-group block randomization (1:1) using randomly selected block sizes of four and eight was performed by an investigator (R.J.M.) using a computer-generated allocation list.[18] The allocation list was kept in the pharmacy serving the labor and delivery unit. Group allocation was assigned by the pharmacist, who prepared and labeled the syringe as "IT morphine study drug." The anesthesiologist injecting the study drug, the study nurse collecting follow-up data, and the patient were unaware of group assignment.

The study drug was administered using a standardized procedure. After thoroughly sanitizing the catheter port a 3-ml syringe was attached and a volume of 1 ml of cerebrospinal fluid was aspirated. The study drug (0.3 ml) was then administered through the intrathecal catheter followed by the aspirate to flush the study drug through the catheter (dead space 0.3 ml). The intrathecal catheter was then removed. If the anesthesiologist was unable to aspirate from the catheter, the intrathecal drug was administered and flushed with 1.0 ml of preservative free saline to ensure drug delivery.

Respiration was monitored visually for rate and level of sedation by nursing personnel every hour for a period of 12 h and then every 2 h for a period of 12 h as per standard of care at our institution. This frequency and modality of monitoring are consistent and greater than those recommended after low-dose (≤ 0.15mg) intrathecal morphine.[13] On postpartum days 1 to 5, all patients were visited daily by a research nurse while on the postpartum ward, and they were called by phone after discharge from the hospital. Patients were assessed for the presence of a post–dural puncture headache using the International Headache Society definition of a headache that occurs after a dural puncture, worsens within 15 min after sitting or standing, and improves within 15 min after lying, with at least one of the following: neck stiffness, tinnitus, hyperacusis, photophobia, or nausea.[19] The headache develops within 5 days after dural puncture and resolves (numeric rating scale for pain = 0) either spontaneously within 1 week or within 48 h after effective treatment. Patients were also asked to assess the headache pain using the numeric rating scale 0 to 10, where 0 represents no pain and 10 represents the worst pain imaginable. They were also questioned regarding the presence of a backache, signs and symptoms of cranial nerve injury, and current headache treatments. Side effects of intrathecal morphine, including nausea, vomiting, pruritus, and urinary retention, were recorded. Patients who

developed a post–dural puncture headache were followed for 3 days after the resolution of their headache.

Treatments for post–dural puncture headache were based on a previously described treatment protocol.[20] Mild postural headaches (defined as a verbal rating score for pain less than 4) were treated with conservative therapy including oral hydration and increased oral caffeine intake. If the headache did not resolve or per patient request, oral analgesics were provided as needed. Moderate postural headaches (defined as verbal rating score for pain of 4 to 6 without limitation of childcare ability) received the same conservative therapy. Patients with moderate postural headaches with limiting childcare abilities and patients experiencing severe postural headaches (defined as verbal rating score for pain greater than 6) were advised to undergo a therapeutic epidural blood patch. This treatment consisted of the epidural injection of 20 ml of autologous blood over 2 to 3 min through an epidural needle, injected at the level or one level below the presumed unintentional dural puncture. The patient was positioned in the sitting position for the procedure and then repositioned supine for a period of 1 h after the epidural blood patch. An epidural blood patch was not performed for at least 24 h after the unintentional dural puncture. If the epidural blood patch failed to relieve the headache after 24 h, or if the headache recurred after successful treatment, the epidural blood patch was repeated.

Statistical Analysis

The primary outcome was the incidence of post–dural puncture headache. The primary outcome was compared between groups using a chi-squared statistic. Secondary outcomes included the onset, duration, and severity of post–dural puncture headache, the presence of cranial nerve symptoms, backpain, and the type of treatment the patient received (hydration, oral analgesics, epidural blood patch). Results are summarized as proportions (95% CI) and median (interquartile range, 1st to 3rd, quartile). Secondary nominal outcomes were compared using a chi-square statistic and interval outcomes using the Mann–Whitney *U* test. Imbalances in preoperative characteristics of the patients in the study groups were assessed by examining the mean standardized difference and 95% CI of the standardized difference. Standardized differences were determined using Hedges' *g* for continuous variables and Cliff's delta for ordinal or dichotomous data. CI for differences in proportions were calculated using the Pearson–Klopper method. Differences in medians and 95% CI interval of the median difference were calculated using a 10,000-sample bootstrap. Analyses were performed by intent to treat. All analyses were two-sided, and a $P < 0.05$ was required to reject the null hypothesis.

The incidence of post–dural puncture headache is estimated to be approximately 50% after unintentional dural puncture.[3,4] Assuming that a relative decrease of at least 50% would be necessary to support the clinical usefulness of this treatment, we determined that a sample size of 64 patients in each group would be required to achieve 80% power to detect this difference between intrathecal morphine and saline administration. Group sample sizes of 64 achieve 80% power to detect a difference between the group proportions of 0.25. The proportion in the treatment group is assumed to be 0.5 under the null hypothesis and 0.25 under the alternative hypothesis. The proportion in the control group is 0.5. A superiority trial test was performed using the two-sided Fisher's exact test. The significance level of the test was targeted at 0.05. The sample size was calculated using PASS 11, version 11.0.01, release date November 3, 2010 (NCSS Inc., USA).

After enrolling and randomizing 63 participants, an unplanned interim analysis was undertaken because of increasing difficulty with recruitment of patients for this study. The interim analysis was not planned *a priori*. At that time, the post–dural puncture headache rate was 78% in the intrathecal morphine group and 79% in the intrathecal saline group. To estimate the probability of achieving superiority of intrathecal morphine over saline if study recruitment continued until the planned enrollment of 128 subjects, a conditional power analysis using Bayesian estimation was performed. Using the previous probability estimates of a 0.75 probability of not having a post–dural puncture headache in the intrathecal morphine group and 0.50 in the saline group, the number of subjects in each group that would not have a post–dural puncture headache in the remaining sample was estimated and the probability of accepting the null hypothesis and the alternate hypothesis was determined. The analysis demonstrated that after achieving the original estimated sample size, the probability of demonstrating superiority of intrathecal morphine compared with the intrathecal saline group was 0.039 and the probability of demonstrating superiority of intrathecal saline compared with morphine was 0.021. Because of the likely improbability of demonstrating superiority of the intrathecal morphine treatment, even if the original sample size was achieved, we elected to stop study enrollment on January 31, 2019. This estimation was made using the PredProbs.calc – Version 1.5.0.0 (https://biostatistics.mdanderson.org/SoftwareDownload/). Data were analyzed using RStudio version 1.2.1335 (Integrated Development for R. RStudio, Inc., USA; URL: http://www.rstudio.com/) and R version 3.6.1, release date July 5, 2019 (The R Foundation for Statistical Computing, Austria).

Results

Enrollment began November 2011 and ended January 2019. Patient recruitment and follow-up are shown in figure 1. One hundred thirty-six patients were approached, and 68 consented for participation. Five patients were excluded after consent before randomization, two patients withdrew consent, and three had nonfunctioning intrathecal catheters. After randomization, one patient in each group was

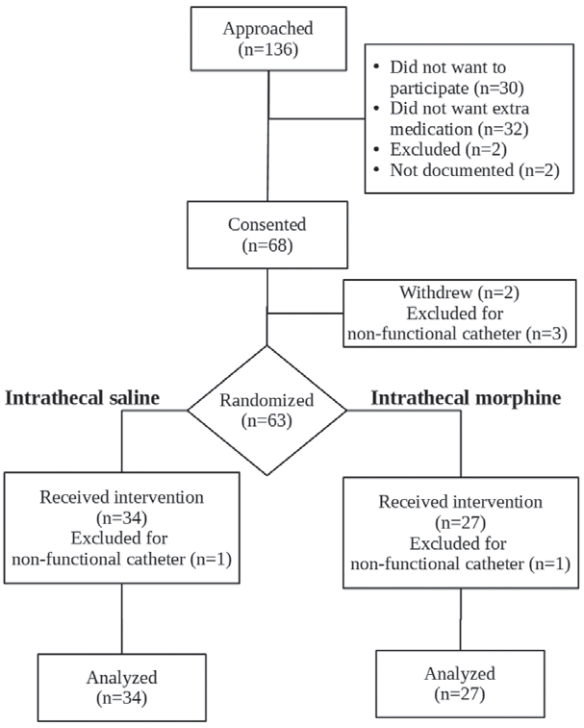

Fig. 1. Consort flow diagram of patient flow in the study.

excluded because of concerns for a nonfunctioning intrathecal catheter. Sixty-one patients were included in the analysis. In all, 311 patient assessments were required by the study design and 297 of 311 (95%) assessments were completed. In the saline group, three patients had only three assessments and six patients had four assessments. In the morphine group, two patients had only three assessments. There were no missed assessments in patients who had not endorsed a post–dural puncture headache in a prior assessment; therefore, the incidence of post–dural puncture headache would not have changed had all assessments been completed. In four saline patients and two morphine patients, the reported duration of the headache may have been impacted by the missing assessments.

Standardized differences greater than 0.1 were found for age, race, ethnicity, catheter insertion depth, and intrapartum intrathecal infusion volume (table 1). Although extremes of age have been shown to influence the incidence, but not the treatment, of post–dural puncture headache, the range and difference in age seen in this study would not have likely had an influence on the incidence of post–dural puncture headache. Race, ethnicity, and catheter insertion depth have not been associated with the incidence of post–dural puncture headache. The difference in the intrathecal infusate volume between the saline and morphine groups (3.3 ml administered over many hours) is less than the amount of intrathecal saline that has been demonstrated to reduce the

Table 1. Characteristics of Women Randomized to Intrathecal Saline and Morphine Groups

	Saline (n = 34)	Morphine (n = 27)	Standardized Difference* (95% CI)
Age, yr	32 (29 to 34)	33 (30 to 36)	0.45 (–0.06 to 0.97)
Race, n (%)			
White	26 (76)	24 (89)	
African American	5 (15)	1 (4)	–0.12 (–0.31 to 0.08)
Asian	3 (9)	2 (7)	
Hispanic ethnicity, n (%)	3 (9)	7 (26)	0.17 (–0.03 to 0.35)
Body mass index, kg/m^2	28.9 (25.5 to 33.9)	29.1 (25.3 to 33.0)	0.02 (–0.49 to 0.53)
Gestational age, w	39 (38 to 40)	39 (38 to 40)	0.01 (–0.50 to 0.53)
Nulliparous, n (%)	4 (12)	5 (18)	0.07 (–0.25 to 0.12)
Loss of resistance method			
Air	17 (50)	16 (59)	–0.09 (–0.34 to 0.16)
Saline	17 (50)	11 (41)	
Intrathecal catheter depth (cm)			
Insertion†	11 (9.5 to 11)	11 (10 to 12)	0.11 (–0.42 to 0.63)
Removal‡	11 (9.5 to 11)	11 (10 to 12)	0.03 (–0.49 to 0.55)
Intrathecal catheter dwell time, min	427 (286 to 540)	418 (291 to 550)	0.06 (–0.45 to 0.57)
Intrathecal infusion volume, ml	16.2 (6.9 to 27.0)	12.9 (8.0 to 19.0)	–0.31 (–0.82 to 0.21)
Unable to aspirate before administering study drug, n (%)	6 (18)	4 (15)	–0.03 (–0.21 to 0.17)
Mode of delivery			
Vaginal	29 (85)	24 (89)	–0.03 (–0.21 to 0.13)
Instrumented	5 (15)	3 (11)	

Data presented as median (interquartile range, 1st to 3rd quartile) or n (%) of column.

*Standardized difference reported as Hedge's g for interval data and Cliff's delta for dichotomous data. †Missing one value for catheter depth at insertion in saline group. ‡Missing four values of catheter depth at removal in saline group and two in the morphine group.

incidence of post–dural puncture headache (10 ml administered as a bolus) in one observational study.[21]

The overall incidence of post–dural puncture headache was 79% (95% CI, 68% to 89%). The incidence of post–dural puncture headache was 78% in the intrathecal morphine group and 79% in the intrathecal saline group (difference, −1%; 95% CI, −25% to 24%; table 2). Most patients presented with post–dural puncture headache by postoperative day 2 and the median (1st, 3rd, quartile) duration of the post–dural puncture headache was 3 d (2 d to 3.5 d) in the intrathecal morphine and 2 d (1 d to 3 d) in the intrathecal saline (difference, 1d; 95% CI, −1 to 1 d). The difference in the median numeric rating scale headache pain score was −0.5 (95% CI, −4 to 1). There was no difference in type of treatment of post–dural puncture headache. Epidural blood patch was administered to 52% of subjects in the intrathecal morphine and 37% of the intrathecal saline group (difference 15%; 95% CI, −18% to 48%). No patient received an epidural blood patch before 24 h after unintentional dural puncture.

Cranial nerves symptoms were reported by 11 patients, one patient reported diplopia, and 10 reported aural fullness. The incidence of backpain was 41% in the morphine group and 62% in the saline group (difference, −21%; 95% CI, −49 to 7). The median (1st, 3rd, quartile) numeric rating score for back pain was 1 (1 to 3) in the morphine and 1 (1 to 3) in the saline groups. All patients received an intrathecal infusion of a local anesthetic and opioid (fentanyl) mixture for labor analgesia, so many of them reported pruritus and/or nausea. In addition, some of the patients with post–dural puncture headache had nausea. No patients had a new onset of pruritus and or nausea that we could directly associate with the intrathecal morphine. There were no adverse events related to the study intervention, intrathecal morphine, or saline, in any subject in the study.

Discussion

The important finding of this study was the lack of effectiveness of prophylactic intrathecal morphine given *via* an *in situ* intrathecal catheter after an unintentional dural puncture during initiation of neuraxial labor analgesia. A second unexpected finding of the study was the high rate of post–dural puncture headache after placement of an intrathecal catheter for labor analgesia at the level of the unintentional dural puncture. Based on our findings, the use of prophylactic intrathecal morphine *via* an intrathecal catheter placed after an unintentional dural puncture does not appear to be a clinically effective strategy for reducing the incidence or severity of post–dural puncture headache.

Previous reports have extolled the use of neuraxial opioids after an unintentional dural puncture for the prevention and treatment of post–dural puncture headache. Case reports have suggested a benefit when epidural morphine was administered prophylactically after unintentional dural puncture,[22,23] as well as for treatment of post–dural puncture headache.[24] In the only randomized trial examining the prophylactic administration of epidural morphine after unintentional dural puncture, Al-metwalli[10] demonstrated

Table 2. Post–Dural Puncture Headache Outcomes by Study Group

	Morphine (n = 27)	Saline (n = 34)	Difference in Proportions (95% CI)	*P* Value
Post–Dural puncture headache, n (%)*	21 (78)	27 (79)	−1% (−25 to 24%)	0.877
First presenting day, n (%)†				
1	9 (43)	11 (41)	2% (−31 to 35%)	
2	8 (38)	8 (29)	9% (−23 to 41%)	0.691
3	1 (5)	4 (15)	−10% (−31 to 11%)	
4	3 (14)	4 (15)	−1% (−25 to 24%)	
Number of headache days, n (%)†				
1	4 (19)	8 (30)	−11% (−40 to 18%)	
2	5 (24)	9 (33)	−9% (−39 to 21%)	
3	7 (33)	4 (15)	18% (−11 to 47%)	0.610
4	4 (19)	5 (18)	1% (−26 to 28%)	
5	1 (5)	1 (4)	1% (−15 to 18%)	
Cranial nerve symptoms†				
None	13 (62)	24 (88)	−26% (−55 to 4%)	
Visual	1 (4)	0 (0)	4% (−9 to 17%)	0.223
Auditory	7 (28)	3 (12)	16% (−8 to 40%)	
Greatest reported pain (0 to10)‡	7 (3 to 8.5)	7.5 (5 to 8)	−0.5% (−4 to 1%)	0.499
Type of treatment, n (%)†				
Hydration	1 (5)	1 (3)	2% (−17 to 13%)	
Oral analgesics	9 (43)	16 (60)	−17% (−51 to 16%)	0.463
Epidural blood patch	11 (52)	10 (37)	15% (−18 to 48%)	
Repeat epidural blood patch, n (%)†	1 (9)	1 (10)	−1% (−22 to 20%)	0.525

Data presented as median (interquartile range, 1st to 3rd quartile) or n (%) of *fraction of number of cases per group, †fraction of number of cases with post–dural puncture headache per group. ‡Numerical rating scale, 0 = no pain, 10 = worst pain imaginable.

a decrease in post–dural puncture headache from 48 to 12% when epidural morphine 3 mg was administered at the end of delivery and again at 24 h *via* the *in situ* epidural catheter. The difference between our results and those of Al-metwalli is surprising, given that spinal and epidural morphine presumably work by similar mechanisms. In addition to the route of morphine administration, the two studies differed in the total dose and timing of administration, the Al-metwalli protocol included a second morphine dose after 24 h. Similar to our findings, in a retrospective analysis of 80 patients exposed to either epidural or intrathecal morphine after an unintentional dural puncture, Brinser *et al.*[25] reported no difference in the incidence of post–dural puncture headache with morphine exposure (48.2%) compared with no exposure (51.8%). After controlling for a history of preeclampsia and mode of delivery the adjusted odds ratio for a post–dural puncture headache was 1.24 (95% CI, 0.13 to 2.33) with neuraxial morphine exposure.

We chose to administer intrathecal morphine 150 μg because this is the current dose given to parturients receiving intrathecal morphine as a component of spinal for cesarean delivery at our institution. This dose also has a predictable side effect profile and history of safety in this population.[26,14] Therefore, our intrathecal dose roughly corresponds to the analgesic benefit of the epidural morphine dose administered by Al-metwalli, although in the current study we did not repeat dosing at 24 h.[10]

The etiology(s) of post–dural puncture headache is likely multifactorial. The classic explanation is that loss of cerebrospinal fluid causes a decrease in subarachnoid pressure. In the upright position, the brain sags in the skull, resulting in tension on pain-sensitive blood vessels in the brain.[27] Another possible cause is the compensatory vasodilation that accompanies loss of cerebrospinal fluid, resulting in a "vascular-type" headache.[27] The mechanism by which neuraxial morphine might prevent the onset of post–dural puncture headache after unintentional dural puncture is not clear. Al-metwalli, in discussing the mechanism by which epidural morphine administration might protect against the development of post–dural puncture headache, did not have a ready explanation.[10] He suggested a possible volume effect with the injection of morphine into the epidural space (in the Al-metwalli study, epidural morphine was injected in 10-ml saline), but this seems unlikely, because the dwell time of saline in the epidural space is short, and intermittent saline injections have not been shown to be efficacious in treating post–dural puncture headache. A second proposed mechanism is the central effects of μ-opioid receptor agonism as morphine migrates rostrally from the neuraxial lumbar injection. This, too, seems an unlikely mechanism because systemic opioid analgesia provides little relief for post–dural puncture headache. Thus, we can think of no compelling reason why neuraxial opioids should work to prevent post–dural puncture headache.

The effect of placement of an intrathecal catheter through the dural rent after unintentional dural puncture with a large-bore Tuohy needle on the incidence of post–dural puncture headache is controversial. Almost all studies on the topic are retrospective, and none employed a randomized, controlled study design. Several meta-analyses have been performed in the past decade and were inconclusive.[1,28] The most recent meta-analysis, published in 2017, included 1,044 patients in 13 studies. The pooled risk ratio for post–dural puncture headache in the intrathecal catheter compared with replacement epidural catheter group was of 0.823 (95% CI, 0.700–0.967), but the heterogeneity was quite large.[29] The rate of epidural blood patch was also reduced, (risk ratio, 0.616; 95% CI, 0.443 to 0.855). Conversely, in a crossover study that included 34 maternity units in the United Kingdom, institutions were randomized to treating all patients who had an unintentional dural puncture with either an intrathecal catheter or replacement epidural catheter for a 6-month period, and then crossed over to the other treatment for 6 months for a 2-yr study.[30] The placement of an intrathecal catheter did not result in a lower post–dural puncture headache or epidural blood patch rate compared with replacement epidural (intrathecal catheter 72% *vs.* epidural catheter 62%, $P = 0.2$ for post–dural puncture headache). Our rate of post–dural puncture headache, 79%, was unexpectedly high, but similar to the rate reported in this crossover study. The current evidence from observational studies does not suggest that placement of an intrathecal catheter increases the risk for post–dural puncture headache.[1,29,30]

Some clinicians elect to leave intrathecal catheters in place for 24 h after delivery, citing data which suggest that this may be more beneficial than the immediate removal of the catheter after delivery.[31,32] In our routine practice, we remove the intrathecal catheter shortly after delivery because of safety concerns, and we elected to continue this practice in the current study. It is possible that by removing the catheter shortly after the intrathecal morphine administration much of the drug may not remain in the cerebrospinal fluid but egress through the dural hole. This could explain the lack of efficacy seen in the study and the lack of increase in the incidence of pruritus and nausea in the group receiving intrathecal morphine. Thus, it is possible that leaving the catheter in place for 24 h and administering a second dose of morphine before catheter removal may have produced different results. We did not identify adverse effects or safety concerns in our study. However, the study is underpowered to adequately address the most worrisome concern, delayed respiratory depression after intrathecal morphine administration.[14]

The results of our study should only be interpreted in the context of its limitations. Our sample size is small, and we stopped the study before meeting our original estimated sample size. We recruited over a 7-yr period with approximately 12,000 deliveries per year, but were only

able to recruit 68 patients for participation. Nevertheless, our futility analysis suggests that the probability of rejecting the null hypothesis at the estimated sample size was low. Nevertheless, our study design was rigorous; patients and nurses evaluating outcomes were blinded to the study group. We arbitrarily chose a morphine dose; it is possible that higher doses, or repeated administration, may be effective.

In conclusion, our findings suggest that a single intrathecal morphine dose of 150 μg administered shortly after delivery does not decrease the incidence or severity of post–dural puncture headache after unintentional dural puncture. Our study does not support the clinical usefulness of prophylactic intrathecal morphine after an unintentional dural puncture.

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Competing Interests

The authors declare no competing interests.

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