Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday February 7th, 2019
1800 HOURS

LOCATION:
Pan Chancho Private Dining Room
44 Princess Street

PRESENTING ARTICLES:
Dr. Marta Cenkowski & Dr. Fraser Johnson

SPONSORED BY:
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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

Section Editor: **Richard Brull**

Addition of Neostigmine and Atropine to Conventional Management of Postdural Puncture Headache: A Randomized Controlled Trial

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BACKGROUND: Postdural puncture headache (PDPH) lacks a standard evidence-based treatment. A patient treated with neostigmine for severe PDPH prompted this study.
METHODS: This randomized, controlled, double-blind study compared neostigmine and atropine (n = 41) versus a saline placebo (n = 44) for treating PDPH in addition to conservative management of 85 patients with hydration and analgesics. The primary outcome was a visual analog scale score of ≤3 at 6, 12, 24, 36, 48, and 72 hours after intervention. Secondary outcomes were the need for an epidural blood patch, neck stiffness, nausea, and vomiting. Patients received either neostigmine 20 μg/kg and atropine 10 μg/kg or an equal volume of saline.
RESULTS: Visual analog scale scores were significantly better ($P < .001$) with neostigmine/atropine than with saline treatment at all time intervals after intervention. No patients in the neostigmine/atropine group needed epidural blood patch compared with 7 (15.9%) in the placebo group ($P < .001$). Patients required no >2 doses of neostigmine/atropine. There were no between-group differences in neck stiffness, nausea, or vomiting. Complications including abdominal cramps, muscle twitches, and urinary bladder hyperactivity occurred only in the neostigmine/atropine group ($P < .001$).
CONCLUSIONS: Neostigmine/atropine was effective in treating PDPH after only 2 doses. Neostigmine can pass the choroid plexus but not the blood–brain barrier. The central effects of both drugs influence both cerebrospinal fluid secretion and cerebral vascular tone, which are the primary pathophysiological changes in PDPH. The results are consistent with previous studies and clinical reports of neostigmine activity. (Anesth Analg 2018;127:1434–9)

KEY POINTS

- **Question:** Can neostigmine and atropine improve postdural puncture headache (PDPH) treatment when added to conventional management?
- **Findings:** Neostigmine plus atropine improved PDPH after only 2 doses without recurrence of headache or need for an epidural blood patch.
- **Meaning:** Neostigmine plus atropine is a simple pharmacological treatment for PDPH.

Postdural puncture headache (PDPH) is a complication of spinal anesthesia or lumbar puncture and is an unpleasant experience for the patient as well as the anesthetist. It is thought to result from meningeal traction related to low cerebrospinal fluid (CSF) pressure or cerebral vasodilation as an indirect effect of decreased CSF pressure.[1] We encountered a case of PDPH in a patient who had failed conservative management and was scheduled for an epidural blood patch (EBP) procedure. However, the EBP was cancelled following resolution of the PDPH within an hour of receiving neostigmine and atropine for the management of postoperative ileus.[2] The dramatic response to neostigmine in the patient with PDPH and postoperative ileus are in line with the central effects of neostigmine, which can pass through the choroid plexus but not the blood–brain barrier, and atropine on CSF secretion and cerebral vascular tone that are the primary pathophysiological changes associated with PDPH.[3–17] The clinical experience with neostigmine prompted this comparison of the efficacy of neostigmine and conservative management for the treatment of PDPH. The decision was supported by the well-known pharmacologic profile, safety, and ready availability of neostigmine.

METHODS

This prospective, randomized, controlled, double-blind trial was performed after approval by the Research and Ethics

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Trial registration: The trial was registered at Pan African Clinical Trial Registry (www.pactr.org, PACTR201510001299332). On October 9, 2015. The principal investigator was A.A.A.M.

Reprints will not be available from the authors.

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Committee of Faculty of Medicine at Beni-Suef University on March 25, 2014. Written informed consent was obtained from all trial participants, and the study period extended from October 15, 2015 to September 8, 2017. The trial was registered at the Pan African Clinical Trial Registry (www.pactr.org, PACTR201510001299332) on October 9, 2015 with Ahmed Abdelaal Ahmed Mahmoud as the principal investigator. The trial was registered after completing a pilot study of 20 patients to calculate the sample size of this trial and before enrollment of the first patient. The pilot study was performed from March 26, 2014 to June 3, 2015, and the patient data were not included in this trial.

As noted below, 90 patients of 20 to 40 years of age with American Society of Anesthesiology physical status II because of pregnancy and diagnosed with PDPH following intrathecal spinal anesthesia for elective cesarean delivery were included. Diagnosis of PDPH was based on the International Headache Society criteria (https://doi.org/10.5167/uzh-89115). Patients with PDPH and a visual analog scale (VAS) score <5, a history of chronic headache, cluster headache, migraine, convulsions, cerebrovascular accident, signs of meningismus, preeclampsia, eclampsia, coagulopathy, previous neurological diseases, and severe bleeding (>20% of blood volume); undergoing treatment with vasopressors, bronchial asthma, arrhythmia, and any type of heart block; weighing <50 kg; and with any contraindication of oral intake were excluded.

Intrathecal spinal anesthesia was performed after giving an intravenous (IV) fluid preload with 10 mL/kg Ringer's lactate by an anesthesiologist not involved in the trial. Intrathecal blocks were performed in the seated position using 2.5-mL hyperbaric 0.5% bupivacaine (12.5 mg) at L3–L4 using a 22-gauge Quincke spinal needle (B. Braun, Melsungen, Germany), which is the smallest available spinal needle in our institution because of cost and availability considerations. Parturients with postoperative PDPH and a VAS score of ≥5 were randomly allocated to receive either slow IV injection of 20 µg/kg neostigmine and 10 µg/kg atropine in 20 mL of 0.9% saline given over 5 minutes every 8 hours (n = 41) or 20 mL of 0.9% saline IV every 8 hours (n = 44). The intervention was continued until achieving a VAS score ≤3 or for a maximum of 72 hours. Patient in the neostigmine group who achieved VAS scores ≤3 before 72 hours were given 20 ml of saline 0.9% IV every 8 hours to maintain blinding. Both groups received conservative management, which consisted of nursing in the supine position, hydration with continuous infusion of 30 mL/kg/day Ringer's lactate solution, 1 g paracetamol plus 135 mg caffeine every 6 hours. Ketoprofen (100 mg) suppositories were given twice daily for 5 days as a part of a routine postoperative pain management protocol.

Randomization was performed using sealed opaque envelopes that contained random numbers generated by online application (https://www.randomizer.org/). The study was double blinded. Participants were not aware of their group assignment, and the medications were prepared by an anesthetist who was not involved in the trial. The anesthetist who assessed the participants after the intervention was blinded to the group allocation. Following World Health Organization recommendations, participants were instructed to withhold breastfeeding for 24 hours after the last dose of neostigmine/atropine.[18] A breast pump was used to relieve breast engorgement, ie, pump and dump. Participants were asked to report the severity of their headache after sitting upright for 15 minutes, using a 10-cm VAS at 0, 6, 12, 24, 36, 48, and 72 hours. The presence of neck stiffness, nausea and vomiting, diarrhea, abdominal cramps, muscle cramps, muscle twitches, bronchospasm, and urinary bladder hyperactivity were recorded throughout the study period as yes or no. Participant age, weight, height, body mass index, and the time interval between dural puncture and the occurrence of PDPH were also recorded. Conservative management of PDPH using oral medications continued throughout. An EBP was performed during the study if the VAS was ≥5 after 72 hours following parturient approval and consent, or if requested by the parturient at any time. Subsequent management after the study period, including EBP and adverse effects, were recorded. The primary outcome was the VAS at 24 hours. Additional predetermined outcomes were the requirement for an EBP, neck stiffness, nausea and vomiting, and any adverse effects associated with the neostigmine/atropine mixture.

Statistical Analysis

The aim of this study was to determine the differences in the VAS primary outcome and the secondary outcomes including the need for an EBP, neck stiffness, and nausea and vomiting in the neostigmine/atropine and control groups. Results were expressed as means ± SD, medians with interquartile range, or numbers and percentages of participants as appropriate. The Hodges–Lehmann estimate was used to calculate the median difference for VAS values between the experimental and placebo groups. The primary outcome (VAS) in the 2 study groups was compared by linear mixed-effects (between-within group) repeated measures model with adjustment of baseline as covariate to assess differences over time and the group-by-time interaction.

Categorical data (neck stiffness and nausea and vomiting) were evaluated by χ^2 or Fisher exact test when appropriate. A binary logistic regression was performed to compare neck stiffness and nausea and vomiting between groups at 72 hours with adjustment for baseline variable at 0 hour as covariate. We selected the time point 72 hours as a priority point being the point at which blood patch is deemed necessary to manage PDPH after failure of the medical treatment in the study groups.

Patient age, weight, height, body mass index, and onset of headache were compared by the independent Student *t* test. The Shapiro–Wilk test was used to verify the normality of continuous data distributions. *P* values <.05 were considered significant. Statistical analysis was performed using the statistical package for the social sciences version 22 (SPSS Inc, Chicago, IL).

A pilot study was performed prior to patient recruitment to estimate an appropriate sample size. The pilot study included 20 subjects, 10 in each arm. The smallest effect size *d* that would lead to a clinically significant difference was found to be equal to 0.63. Effect size was derived by software after entering mean difference and SD to calculate the sample size. An estimated mean VAS of 7.15 in the placebo group and 5.64 in the neostigmine group, with a pooled SD of 2.41, were used in the sample sized calculation. A sample size of 34 participants

Table 1. Demographic Characteristics and Headache Onset in Participants Treated With N or P

	N Group (n = 41)	P Group (n = 44)	Standardized Difference
Age (y)	30.22 ± 6.03	28.7 ± 6.15	0.25
Weight (kg)	80.63 ± 12.61	83.86 ± 14.95	−0.23
Height (m)	1.63 ± 0.07	1.64 ± 0.08	−0.13
Body mass index (kg/m^2)	30.2 ± 5.34	31.33 ± 6.15	−0.2
Onset of headache (h)	23.24 ± 8.15	26.02 ± 12.85	−0.26

Values are mean ± SD. Unpaired Student *t* test was used to compare group means (all $P > .05$).

Abbreviations: n, number of patients; N, neostigmine/atropine; P, placebo.

Table 2. VAS Scores for PDPH in N and P Group Participants Before and at 6, 12, 24, 36, 48, and 72 h After Intervention

	N Group (n = 41)	P Group (n = 44)	Median Difference (95% CI)[a]
Before intervention	8 (8–9)	9 (7–9)	0 (−1 to 1)
6 h after intervention	3 (2–4)	6 (4–7)	3 (2 to 4)
12 h after intervention	2 (1–3)	5 (4–6)	3 (2 to 3)
24 h after intervention	2 (0–3)	5 (4–6)	3 (2 to 4)
36 h after intervention	1 (0–2)	5 (4–6)	4 (3 to 4)
48 h after intervention	1 (0–2)	5 (4–6)	4 (3 to 4)
72 h after intervention	1 (0–2)	5 (4–6)	4 (3 to 4)

Values are median (interquartile range).

Abbreviations: CI, confidence interval; N, neostigmine/atropine; P, placebo; PDPH, postdural puncture headache; VAS, visual analog scale.

[a]Hodges–Lehmann estimate was used to derive median differences (95% CI) between the 2 groups.

Table 3. Secondary Outcomes of N and P Groups Treatment of PDPH

	N Group (n = 41)	P Group (n = 44)	*P* Value
Need for EBP, n (%)	0 (0)	7 (15.9)	.008
Neck stiffness (yes/no), n (%)			
Before intervention	15 (36.6)	12 (27.3)	
6 h after intervention	15 (36.6)	12 (27.3)	
12 h after intervention	13 (31.7)	12 (27.3)	
24 h after intervention	13 (31.7)	9 (20.5)	
36 h after intervention	12 (29.3)	8 (18.2)	
48 h after intervention	10 (24.4)	8 (18.2)	
72 h after intervention	10 (24.4)	8 (18.2)	.48
Nausea and vomiting (yes/no), n (%)			
Before intervention	7 (17.1)	11 (25)	
6 h after intervention	6 (14.6)	8 (18.2)	
12 h after intervention	5 (12.2)	5 (11.4)	
24 h after intervention	5 (12.2)	4 (9.1)	
36 h after intervention	4 (9.8)	4 (9.1)	
48 h after intervention	4 (9.8)	4 (9.1)	
72 h after intervention	4 (9.8)	4 (9.1)	.92

χ^2 Test was used to compare the 2 groups at 72 h.

Abbreviations: EBP, epidural blood patch; N group, neostigmine/atropine group; P group, placebo group; PDPH, postdural puncture headache.

provided a 2-tailed $\alpha = .05$, 80% power ($\hat{a} = .2$), and an allocation ratio = 1. Forty-five participants were included to account for possible protocol violations or loss of data. The sample size calculation was performed with G*Power software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany).[19]

RESULTS

During the study period, 3462 parturients had cesarean deliveries, 619 (17.9%) had general anesthesia, and 2843 (82.1%) had spinal anesthesia. Of those with spinal anesthesia, 312 (11%) developed PDPH. Only 98 patients, 31.4% of 312 patients who developed PDPH and 3.5% of the spinal anesthesia patients, reported a VAS score ≥5 and were assessed for study eligibility. Two patients were excluded because of a history of migraine headache, and 6 patients refused participation. Of the remaining 90 participants, 45 were assigned to the neostigmine/atropine group and 45 were assigned to the placebo group. Four participants in the neostigmine/atropine group and 1 in the placebo group were excluded because they were treated at other hospitals and discontinued the study intervention. Forty-one participants in neostigmine/atropine group and 44 in the placebo were evaluated (Consort Flowchart and Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/C542). The participant characteristics and the onset of headache are shown in Table 1. None of the between-group differences were significant.

The estimated mean difference of the main outcome, VAS, between groups was −2.56 (95% confidence interval [CI], −3.09 to −2.02, $P < .001$), which indicates a significant difference between groups with a significant overall treatment effect. As shown in Table 2, the median difference (with 95% CI) for VAS between the neostigmine/atropine and the placebo group at all the measurements from 0 to 72 hours was derived by Hodges–Lehmann estimate. The reduction in VAS after intervention from baseline at all predetermined evaluations from 6 to 72 hours was significant in both groups (linear mixed-effects repeated measures model with baseline covariate adjustment, $P < .001$). The VAS was significantly lower in the neostigmine/atropine group than in the placebo group at each measurement between 6 and 72 hours, $P < .001$ (Supplemental Digital Content 2, Figure 2, http://links.lww.com/AA/C543). There was no interaction between group and time ($P = .259$).

All patients in the neostigmine/atropine group achieved a VAS ≤ 3 after 2 doses; none experienced a recurrent headache, and none received an EBP because they failed to report a VAS ≥ 5. Seven patients in the placebo group (15.9%) were treated for persistent PDPH and a VAS ≥ 5 after 72 hours ($P = .008$; Table 3). Six of the 7 cases treated with EBP had an adequate response (VAS < 5); 1 case required a second EBP. No EBP-related complications were reported. There were no differences in the incidence of neck stiffness and nausea and vomiting in the 2 groups at 72 hours following intervention (Table 3).

Binary logistic regression found no differences in the incidence of neck stiffness (odds ratio, 2.33; 95% CI, 0.33–16.18; $P = .39$) or nausea and vomiting (odds ratio, 1; 95% CI, 0.199–5.01; $P > .99$; Table 4).

The incidence of abdominal cramps (8 participants, 19.5% versus none, $P = .002$), muscle twitches (6 participants, 14.6% versus none, $P = .008$), and urinary bladder hyperactivity (5 participants, 12.2% versus none, $P = .016$) was higher in the experimental group than in the placebo group. The occurrence of diarrhea, bronchospasm, and muscle cramps was comparable in the 2 groups (Table 5).

Table 4. Neck Stiffness and Nausea and Vomiting in the N and P Groups 72 h After Treatment

	N Group (n = 41)	P Group (n = 44)	Odds Ratio (95% CI)	*P* Value
Neck stiffness (yes/no), n (%)				
72 h after intervention	10 (24.4)	8 (18.2)	2.33 (0.33–16.18)	.391
Nausea and vomiting (yes/no), n (%)				
72 h after intervention	4 (9.8)	4 (9.1)	1 (0.199–5.01)	>.99

P > .05, binary logistic regression with baseline covariate adjustment.
Abbreviations: CI, confidence interval; N, neostigmine/atropine; P, placebo.

Table 5. Treatment-Associated Side Effects in the N and P Groups

	N Group (n = 41)	P Group (n = 44)
Diarrhea, n (%)	None	None
Abdominal cramps, n (%)	8 (19.5)	None[a]
Muscle cramps, n (%)	2 (0.05)	None
Muscle twitches, n (%)	6 (14.6)	None[a]
Bronchospasm, n (%)	None	None
Urinary bladder hyperactivity, n (%)	5 (12.2)	None[a]

χ^2 or Fisher exact test was used.
Abbreviations: N, neostigmine/atropine; P, placebo.
[a]*P* < .05.

DISCUSSION

This is the first randomized controlled trial to examine the addition of neostigmine and atropine to conservative treatment for PDPH. For ethical reasons, all patients received conservative treatment. Those not treated with neostigmine/atropine received a saline placebo. Neostigmine significantly lowered VAS scores, shortened the duration of PDPH and avoided the need for EBP. No >2 doses were needed to reach the study end point. Other secondary outcomes were comparable between the 2 groups. Treatment-associated muscle twitches, abdominal cramps, and hyperactivity were more frequent in the neostigmine/atropine group.

Neostigmine is a quaternary amine anticholinesterase that increases acetylcholine levels.[20] In animal studies,[10–13] neostigmine was found to have an initial direct stimulatory action on depolarization of cerebrospinal ganglia and resulted in cerebral vasoconstriction.[14] This effect of neostigmine antagonizes the cerebral vasodilation associated with PDPH and explains the rapid improvement of a headache. The central vascular action of neostigmine was confirmed by functional magnetic resonance imaging in the study of the vascular activity of anticholinergics on cognitive function and the ability of neostigmine to reverse it.[21] Those results suggested that neostigmine restored the normal vascular tone of cerebral vessels. In line with that, neostigmine was reported to be effective in the treatment of migraine headaches, which may share some pathophysiological mechanisms with PDPH.[22,23]

Neostigmine does not cross the blood–brain barrier but can enter the CSF because the blood–brain and blood–CSF barriers are anatomically distinct.[3–6] Systemic neostigmine can enter the CSF but is not be able to enter the brain parenchyma through the blood–brain barrier.[3–6] The presence of neostigmine in CSF would be expected to increase the level of acetylcholine in CSF and subsequently in the brain through inhibition of cholinesterase. The increased level of acetylcholine would produce cerebral vasoconstriction.[10,24] Neostigmine produces intracerebral vasoconstriction[10,24] with clinically relevant effects[21–23,25–27] that include migraine relief[22,23] and treatment of central cholinergic syndrome.[26,27] At least 2 mechanisms can explain neostigmine-induced intracerebral vasoconstriction. Neostigmine has a biphasic effect on sympathetic ganglia, ie, depolarization followed by hyperpolarization.[10–13] Hyperpolarization that results in vasoconstriction reflects sympathetic regulation of the blood supply to cerebral vessels.[14] An increase in central acetylcholine[3–6,21–23,25,26] can maintain cerebral vasoconstriction[10,24] initiated by the direct stimulation of the cerebrospinal ganglia.[10–13] Entry of neostigmine into the CSF[3–6] can provide the analgesic effects that have been observed following the direct administration of neostigmine neuroaxially.[9]

The choroid plexus is the primary source of CSF.[28,29] Sympathetic inhibition can reduce CSF secretion by about 30%.[8,30–32] Sympatholysis, as with neostigmine-induced late hyperpolarization of cerebrospinal ganglia,[10–13] can increase secretion by 30%. As the effect of neostigmine on cerebrospinal ganglia fades, ganglion function is restored, but another mechanism can increase CSF secretion. Acetylcholine inhibits choroid plexus secretion,[8,30–32] and in addition to its anticholinesterase activity, neostigmine inhibits the uptake of acetylcholine by the choroid plexus[7] because it competes with acetylcholine for the same transport system.[7,33] That mechanism can account for an increase in CSF secretion in response to neostigmine and can help to explain the rise in CSF pressure following neostigmine/atropine administration reported in a series of 12 patients with cerebral aneurysms.[34]

Atropine crosses the blood–brain barrier and is a parasympatholytic[20] that was found to inhibit parasympathetic cholinergic cerebral vasodilatation in an animal study.[17] Block of the sphenopalatine parasympathetic ganglion by atropine has been reported successful in treating PDPH by reversing PDPH-associated cerebral vasodilation.[35,36] Atropine increases CSF secretion by antagonizing the effect of acetylcholine[8] on the choroid plexus, possibly by its effect on muscarinic receptors in the choroid plexus[8,30] and possibly on nicotinic acetylcholine receptors.[37]

Recent studies[38–40] discovered that CSF is predominantly drained by cerebral vessels on the brain surface and not by the subarachnoid villi. Considering the combined effects of neostigmine and atropine on cerebral vasoconstriction,[3–6,8,17,21–23,25,26] neostigmine may act to increase CSF pressure by reducing CSF absorption by vessels on the brain surface. The possible pathways and mechanisms by which the neostigmine/atropine combination acts to resolve PDPH are shown in the Figure.

Following World Health Organization recommendations, breastfeeding was withheld for 24 hours after the last dose of neostigmine/atropine[18] for the safety of the newborn. As no participants required >2 doses, breastfeeding was resumed within a relatively short average time of 36 hours after the start of the study intervention. The clinical side effects associated with neostigmine/atropine were primarily cholinergic effects of neostigmine such as abdominal cramps, muscle twitches, and urinary bladder hyperactivity.

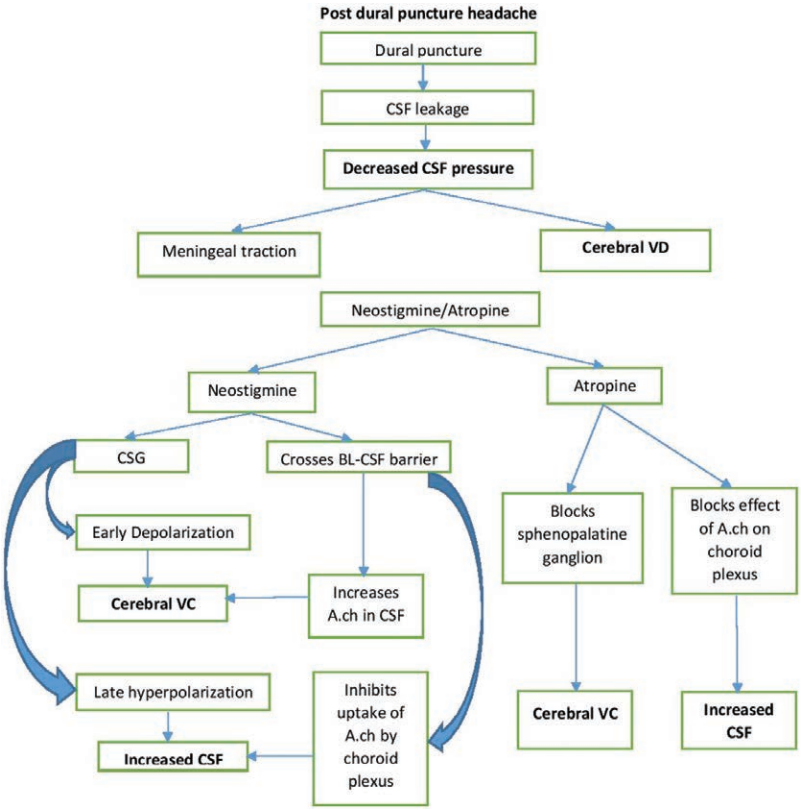

Figure. Pathophysiology of postdural puncture headache and the mechanisms of action of neostigmine and atropine treatment. BL-CSF, blood-cerebro-spinal fluid barrier; CSF, cerebrospinal fluid; CSG, cervical sympathetic ganglia; VC, vasoconstriction; VD, vasodilation.

These effects were clinically transient, self-limiting, and well tolerated. None require any medical intervention. The addition of atropine probably minimized the cholinergic side effects of neostigmine. Dilution of the medications in 20 mL of normal saline and slow administration over 5 minutes probably decreased the occurrence of clinically significant side effects associated with either neostigmine or atropine.

A 22-gauge cutting spinal needle is not consistent with the standard practice for providing spinal anesthesia for elective cesarean delivery in the developed world. However, this is the type of spinal needle used at our institution based on cost and availability considerations. The size and type of the needle may not directly influence the effect of neostigmine/atropine in PDPH, but the use of this needle may increase not only the incidence of PDPH in our institution but also the severity of PDPH experienced by our patients.

PDPH after cesarean delivery is a disabling condition that limits the ability of the new mother to resume walking or breastfeed in a semirecumbent position. In addition to delayed hospital discharge, patients may require an EBP or the prolonged use of analgesics that are not free of side effects. The use of neostigmine/atropine significantly accelerated the recovery from PDPH.

Limitations and Future Research

As this was the first study to evaluate neostigmine/atropine in PDPH, ethical reasons prevented investigation of neostigmine/atropine alone. All participants received routine conservative care including analgesics. This limitation was partially compensated by the randomized, controlled, double-blind design of the trial. All study participants were of American Society of Anesthesiology physical status II because of pregnancy. Clinical parameters could be measured without the use of invasive monitors. Future studies in either animals or critical patients in whom the use of invasive monitors is planned or required can include the measurement of cerebral blood flow (an indirect measure of cerebral vascular resistance), CSF pressure, or plasma and CSF neostigmine concentration by chromatography.[41] The effect of neostigmine on intracranial pressure should be studied in neurosurgery patients in whom increased pressure related to increased CSF may be detrimental.

A combination of neostigmine and atropine was effective in managing PDPH by lowering the associated VAS score and preventing headache persistence. The required 2 doses were well tolerated. ■

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DISCLOSURES

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Contribution: This author helped search the database, design the study, and write the primary and final manuscript.
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Contribution: This author helped invent the main idea of research.
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Epidural Labor Analgesia: Continuous Infusion Versus Patient-Controlled Epidural Analgesia With Background Infusion Versus Without a Background Infusion

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Abstract: **The purpose of this study was to compare the total epidural dose of 3 commonly used labor epidural modalities. After local institutional review board approval, 195 laboring parturients received an epidural catheter for labor analgesia. All patients received an initial bolus of 0.1% ropivacaine (10 mL) and fentanyl (100 μg). Maintenance of labor analgesia consisted of ropivacaine 0.1% with fentanyl 2 μg/mL. Patients were then randomly assigned into 3 groups: Group 1 (continuous epidural infusion [CEI]), continuous infusion at 10 mL/h; group 2 (CEI + patient-controlled epidural analgesia [PCEA]), CEI at 5 mL/h with a demand dose of 5 mL allowed every 20 minutes with a 20 mL/h maximum dose; group 3 (PCEA), demand doses only of 5 mL every 15 minutes with a 20 mL/h maximum dose. Measured variables included total epidural dose, total bolus requests and boluses delivered, number of staff interventions, pain Visual Analog Scale (VAS; 0–100), modified Bromage scores, stage I and II labor duration, delivery outcome, and maternal satisfaction after delivery. No differences were noted with respect to pain VAS, modified Bromage scores, stage I and II labor duration, number of staff interventions, delivery outcome, and maternal satisfaction score. Total infusion dose was lower in demand dose only PCEA compared with CEI and CEI + PCEA groups ($P = < .01$). Demand dose–only PCEA results in less total epidural dose compared with CEI and CEI + PCEA without affecting labor duration, motor block, pain VAS, maternal and neonatal outcomes, and maternal satisfaction.**

Perspective: ***This article compares 3 commonly used labor epidural delivery modalities (traditional continuous epidural infusion, patient-controlled epidural analgesia with a background infusion, and demand dose–only patient-controlled epidural analgesia). Benefits in epidural dose reduction with demand dose only PCEA does not translate into improved maternal and neonatal outcome.***

Key words: *Labor analgesia, continuous epidural, patient-controlled epidural analgesia, maternal outcome.*

Epidural analgesia is the most effective way of providing pain relief in labor.[16] Continuous epidural infusion (CEI) has become the most popular form of providing labor analgesia because it has the advantage of providing continuous analgesia.[15] However, CEI can result in progressive regression in the block requiring reactivation (administration of a bolus dose), with resultant increase in the anesthesiologist's workload.[2,7,10] On the other hand, a high CEI delivery rate (>15 mL/h) can result in a dense motor block requiring the infusion to be stopped.[2,4,10]

Patient-controlled epidural analgesia (PCEA) was first described by Gambling in 1988 and has increased in popularity.[3,8] As labor pain patterns change throughout labor, PCEA allows the patient to self-manage her labor pain, with the advantage of eliminating the problems of overdosing and underdosing commonly associated with CEI.[8]

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PCEA can be provided as demand dose only or in combination with a continuous background infusion. The purpose of this study is to determine whether continuous epidural infusion or patient-controlled epidural analgesia with or without a continuous background infusion is most advantageous in reducing labor pain with minimal motor block and staff intervention, while using the least amount of medication.

Methods

With local investigation review board (IRB) approval, this prospective, randomized, double-blinded study enrolled 195 parturients who requested labor epidural analgesia. All study subjects provided written consent. Patients were randomly assigned by computer program into 1 of the 3 treatment groups: Group 1, CEI; group 2, CEI + PCEA; and group 3, PCEA.

American Society of Anesthesiologists (ASA) Physical Status 1 or 2 parturients who requested labor analgesia at 2–6 cm of cervical dilation at term (37–42 weeks of gestation) with a singleton fetus in the vertex presentation were included into the study. Exclusion criteria included patients who received parenteral analgesics within 1 hour before the epidural block, history of chronic opioid use or chronic pain syndrome, fetal presentation other than vertex, patients with a known history of allergy, sensitivity, or any other reaction to amide local anesthetics, preeclampsia, parturients with any known contraindications to epidural analgesia, and a history of cesarean delivery.

A research coordinator not involved in data collection assigned patients to a study group using a computer-generated randomization table, and set up the epidural pumps in all groups. The patient and the person collecting the data were blinded to the type of epidural delivery modality. The PCEA button was connected to the epidural pump in all patients to blind the data collector and patient as to study group. However, in the CEI group, the pump was unable to indicate when a bolus dose was requested. All epidural catheters were placed in sterile fashion at the L3-4 or L4-5 intervertebral space using the loss of resistance technique to saline. Labor analgesia was initiated in all patients with a bolus of 0.1% ropivacaine (10 mL) and fentanyl (100 μg). Maintenance of labor analgesia consisted of ropivacaine 0.1% with 2 μg/mL fentanyl. Group 1 (CEI) had continuous infusion at 10 mL/h; group 2 (CEI + PCEA), continuous infusion at 5 mL/h with a demand dose of 5 mL allowed every 20 minutes with a 20 mL/h maximum dose; and group 3 (PCEA), demand doses only of 5 mL every 15 minutes with a 20 mL/h maximum dose. All patients were given the same instructions regarding the use of the PCEA button.

Oxytocin was administered at the discretion of the obstetrician. As per study protocol, vital signs (blood pressure, heart rate, pulse oximetry, and fetal heart rate) were recorded at baseline, and every 5 minutes for 15 minutes after the initial bolus and every hour thereafter until delivery.

Treatment for breakthrough pain was defined as pain Visual Analog Scale (VAS) >30 mm (100 mm unmarked line anchored at the left end with no pain and at the right end with worst pain imaginable), and a bolus of 10 mL of epidural medication was administered through the pump. No additional medication was given if the pain VAS <30 mm. If after 15 minutes pain VAS >30, additional 10 mL of the epidural medication was given. If the pain VAS was still >30, a bolus of 5 mL 1.5% lidocaine was administered to rule out a misplaced epidural catheter. If the patient still had a pain VAS >30 despite breakthrough pain intervention, then the patient was assumed to have a misplaced epidural catheter and was excluded from the study, no further data were collected, and the epidural catheter was replaced.

Demographic data included age, height, weight, gravity, parity, cervical dilation was recorded at the time of enrollment. Vital signs, pain VAS, and modified Bromage scores (0 = complete motor block, unable to move feet or knees, 1 = almost complete block, able to move feet only, 2 = partial block, just able to move knees, 3 = detectable weakness of hip flexion, and 4 = no motor weakness with no detectable weakness of hip flexion while supine with full flexion of knees) were collected during the following time periods; baseline (before epidural insertion), 5, 10, and 15 minutes after epidural insertion, and at hourly intervals until delivery. Our primary outcome data was total epidural dose. Secondary outcome data included total bolus requests and boluses delivered, stage I duration (defined as the time from epidural insertion to complete cervical dilatation) and II labor duration (defined as the time from complete cervical dilatation to delivery), number of staff interventions, delivery outcome (vaginal, instrumental vaginal, cesarean), and visual maternal satisfaction (0–100; 0 = totally dissatisfied, 100 = totally satisfied) were recorded after delivery upon removal of the epidural.

Sample Size Calculation

In a study comparing the role of continuous background infusion with PCEA, Ferrante[6] found the total cumulative bupivacaine doses were: 76.3 ± 10.3 mg for CEI, 47.6 ± 6.0 mg for CEI + PCEA, and 40.4 ± 5.8 mg for PCEA. Using a computer-generated statistical program,[9] sample size was determined using ANOVA with 3 treatment groups. At an $\alpha = 0.05$, power of 80%, minimal detectable difference of 6 mg ropivacaine, and a standard deviation of residual of 10.3; the calculated sample size is 57 patients per group for a total of 171 patients. To allow for patients who may not complete the study, a total of 195 patients were studied.

Data Collection and Statistical Considerations

Subjects were excluded from data analysis if there were protocol violations. Data from all the other subjects were analyzed. Normally distributed data are reported as mean ± SD. Variables not following a normal distribution are reported as median with range in parentheses. Normally distributed data were analyzed using ANOVA,

Table 1. Demographic Data

	Group 1 (CEI)	Group 2 (CEI + PCEA)	Group 3 (PCEA)	P Value
Number (n)	62	64	63	—
Age (yr)	27.8 ± 5.7	29.6 ± 6.6*	28.7 ± 5.6	.03
Height (cm)	164.1 ± 6.7	163.3 ± 11.0	165.3 ± 7.7	.44
Weight (kg)	85.2 ± 18.6	84.0 ± 18.0	83.0 ± 14.2	.77
Gravidy	2 (1–8)	2 (1–7)	2 (1–6)	.25
Parity	0 (0–3)	1 (0–3)	0 (0–4)	.88
Nulliparas (n)	33	30	32	.77
Multiparas (n)	29	34	31	.77
Gestation (wk)	39.2 ± 1.4	39.1 ± 1.4	39.2 ± 1.4	.91
Base cervical dilation (cm)	3.3 ± 1.3	3.4 ± 1.3	3.5 ± 1.3	.64

Abbreviations: CEI, continuous epidural infusion; PCEA, patient-controlled epidural analgesia; CEI + PCEA, PCEA + continuous epidural infusion.

NOTE. Base cervical dilation indicates baseline cervical dilation at epidural insertion. Data are mean ± SD or median with range in parentheses.

*$P < .05$ compared with group 1.

with intergroup comparison using the *t* test; non-normal data were analyzed using the Kruskal-Wallis tests with intergroup comparison using the Mann-Whitney test and nominal data using χ^2. A value of $P < .05$ is considered significant in the 3-group comparison tests, while all simultaneous intergroup comparisons are considered significant at $P < .02$ to adjust for the multiple comparisons.

Results

From December 2005 through September 2006, 195 patients were enrolled into the study; 6 were excluded due to misplacement of the epidural catheter resulting in inadequate analgesia, or malfunction of the epidural infusion device. Therefore, 189 patients completed the study.

Demographic data are reported in Table 1. No differences were noted except that patients were older in group 2 compared with group 1 (Table 1). Infusion data among the 3 groups are compared in Table 2. Numbers of PCA attempts were not recorded in group 1 as the pump was programmed in a continuous mode. Total epidural ropivacaine dose and fentanyl dose delivered were significantly less in group 3 compared with groups 1 and 2 (Table 2). There were no differences in PCEA bolus requests, and PCEA boluses delivered between both PCEA groups (groups 2 and 3). There were no differences in the number of staff interventions and number of intervention boluses given among the 3 groups (Table 2).

Table 3 presents maternal and neonatal outcome data. There were no differences with respect to stage I, stage II and combined labor epidural duration, maternal delivery outcome (vaginal, forceps, vacuum/suction, cesarean section), overall maternal satisfaction score, and neonatal outcome (1- and 5-minute Apgar scores and birth weight).

No differences were noted in median pain VAS (Fig 1) in the specific measured time intervals as described in the methods section described above. Likewise, no significant motor block was demonstrated at any time in any study groups in the specific measured time intervals.

Discussion

Patient-controlled epidural analgesia offers many advantages over CEI and is a safe, convenient, and highly effective way to maintain labor analgesia.[4,10,18] Compared with CEI, PCEA reduces anesthesia work-load and the number of interventions, improves analgesia and patient satisfaction, and reduces local anesthetic doses.[1,5,6,11,14,18] In our study, PCEA was associated with decreased drug utilization only when used without a background infusion,

Table 2. Infusion Data

	Group 1 (CEI)	Group 2 (CEI + PCEA)	Group 3 (PCEA)	P Value
Total ropivacaine dose (mg)	64.5 (0–216)	51.5 (10–172)	40.0 (0–120)*	< .01
Total fentanyl dose (μg)	129.0 (0–432)	103.0 (20–344)	80.0 (0–240)*	< .01
PCEA bolus requests (n)	—	15.5 (0–150)	10.0 (0–104)	—
PCEA boluses delivered (n)	—	5.0 (0–21)	5.0 (0–24)	—
PCEA volume delivered (mL)	—	25.0 (0–105)	25.0 (0–120)	—
Staff interventions (n)	0.5 (0–6)	0 (0–8)	0 (0–6)	.57
Intervention bolus (mL)	2.5 (0–50)	0 (0–65)	0 (0–50)	.58

Abbreviations: CEI, continuous epidural infusion; PCEA, patient-controlled epidural analgesia; CEI + PCEA, PCEA + continuous epidural infusion.

NOTE. Data are reported as median with ranges in parentheses.

*$P < .02$ compared with group 1.

Table 3. Maternal and Neonatal Outcome

	Group 1 (CEI)	*Group 2 (CEI + PCEA)*	*Group 3 (PCEA)*	*P Value*
Count (n)	62	64	63	—
Stage I duration (min)	296 ± 216	240 ± 179	236 ± 137	.15
Stage II duration (min)	45.5 ± 40.5	55.0 ± 45.5	44.9 ± 41.2	.38
Total stage 1 and 2 (min)	341.8 ± 233.9	294.5 ± 200.7	280.3 ± 160.6	.25
Vaginal delivery (%)	49 (79%)	52 (81%)	51 (81%)	1.00
Forceps (%)	2 (3%)	1 (2%)	2 (3%)	.80
Vacuum/suction (%)	2 (3%)	2 (3%)	1 (2%)	.81
Cesarean section (%)	9 (15%)	9 (14%)	9 (14%)	.99
Satisfaction score (0–100)	100 (50–100)	100 (30–100)	100 (50–100)	.30
1-min Apgar score	9 (6–10)	9 (4–9)	9 (6–9)	.40
5-min Apgar score	9 (8–10)	9 (7–9)	9 (8–10)	.24
Birth weight (g)	3501 ± 1362	3357 ± 498	3423 ± 457	.65

Abbreviations: CEI, continuous epidural infusion; PCEA, patient-controlled epidural analgesia; CEI + PCEA, PCEA + continuous epidural infusion; Stage I duration, time from epidural insertion to complete cervical dilation; Stage 2 duration, time from complete cervical dilatation to delivery.

NOTE. Data are mean ± SD or median with range in parentheses.

with no differences in regard to patient satisfaction, motor block and outcome.

In a meta-analysis of randomized controlled trials comparing demand dose only PCEA (without a background infusion) with CEI, van der Vyer et al[16] found that patients on PCEA were less likely to require anesthetic interventions, required lower doses of local anesthetic, with less motor block than those who received CEI. Contrary to this, our study showed the total epidural dose required was less in the demand dose only PCEA group, but the number of interventions were not decreased and we found no significant motor block in any group. The low incidence of motor block in all groups in our study is likely explained by the use of a lower concentration of ropivacaine solution. Van der Vyer[16] found that by reducing the concentration of local anesthetic sufficiently, the difference in motor block between PCEA and CEI becomes insignificant. However, our study was powered to detect differences in total epidural dose and not differences in the number of staff interventions.

Depending on the specific outcome variable of interest, studies are conflicting as to whether PCEA with a background infusion compared with without a background infusion is superior.[3,4,6,10] In other studies comparing CEI + PCEA and demand dose only PCEA using 0.16% ropivacaine plus 0.5 μg/mL sufentanil for labor and delivery, Bremerich et al[3] found that periods of VAS >40 mm during all stages of labor were significantly more frequent in parturients receiving demand dose only PCEA compared with parturients receiving CEI + PCEA but found no differences with respect to total epidural dose administered, duration of PCEA use during labor and delivery, neonatal outcome, overall pain scores and adverse events.[3] In our study, we found no differences in pain VAS, VAS >40, or in anesthetic staff interventions among the 3 groups.

Ferrante noticed that PCEA with or without a continuous background infusion provided a 35% dose-sparring effect compared with CEI.[6] Similarly, our study showed a reduction of 38% with the use of demand dose only PCEA compared with CEI ($P < .02$ which is considered statistically significant when adjusting for multiple comparisons). Even though not statistically significant, we did show a 22% reduction with demand dose only PCEA compared with CEI + PCEA ($P = .05$, which is not statistically significant when adjusting for multiple comparisons), and a 20% reduction with CEI + PCEA compared with CEI ($P = .30$). Boselli et al[1] showed similar dose reductions results comparing PCEA with different background infusions. Carvalho et al[4] compared four different types of PCEA regimens using 0.0625% bupivacaine and 0.35 μg/mL sufentanil. Either 10 or 15 mL CEI was combined with a demand dose of 6 mL–8 minute lockout, or a 12 mL–16 minute lockout. They found that all 4 PCEA regimens provided excellent analgesia with no differences in pain VAS, motor block, labor duration and maternal satisfaction. However, more requests to stop the epidural infusion for perceived motor weakness was found in the group with the 15 mL/h continuous infusion and 12 mL PCEA bolus.[4] Effectively they showed that combining CEI and demand doses offered no advantage.

Regression of sensory block over time, need for regular

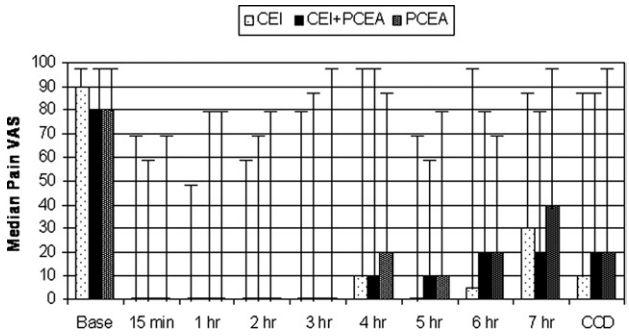

Figure 1. Median pain VAS at specific measured time intervals. CEI indicates continuous epidural infusion; CEI + PCEA, PCEA + continuous epidural infusion; PCEA, patient-controlled epidural analgesia; Base, baseline pain VAS before epidural insertion; CCD, complete cervical dilation. Data are displayed as median pain scores with error bars representing maximum pain.

rescue medication, and excessive motor block are all recognized complications of CEI.[2,7,8,10] Consequently, timed intermittent bolus dosing to deliver a background infusion of drug compared with standard CEI when either are used with or without PCEA have been studied. In comparing a CEI of ropivacaine (2 mg/mL) with fentanyl (2 μg/mL) at 10 mL/h to an intermittent 10 mL hourly bolus of the same solution, Fettes et al[7] found that regular intermittent epidural administration is associated with reduced need for epidural rescue medication, less epidural drug use, and equivalent pain relief when compared with CEI. Fettes[7] concluded that intermittent boluses result in more uniform spread, giving more reliable analgesia than CEI. Hogan[11] has shown that epidural spread is much more uniform when larger volumes are given with corresponding higher injectate pressures. Likewise, low pressure continuous infusions are associated with uneven distribution in the epidural space.[11] Similarly, Wong et al[17] compared programmed intermittent epidural bolus (PIEB) every 30 minutes beginning 45 minutes after the intrathecal injection) in multiparous patients with CEI (12-mL/h infusion) in laboring parturients, and found that PIEB combined with PCEA provided similar analgesia, but with a smaller bupivacaine dose, fewer manual rescue boluses, and better patient satisfaction compared with CEI.

With respect to maternal satisfaction, Saito et al[13] compared CEI to PCEA and found maternal satisfaction tended to be higher in the PCEA group. Nikkola et al,[12] on the other hand, found no advantages in terms of maternal satisfaction in comparing PCEA over intermittent bolus epidural analgesia. Satisfaction is very subjective, and other factors such as patient expectations, staff communication, health care team skills, and obstetric outcome are far more important than just analgesia.[16] Most parturients will find any pain relief during labor and delivery satisfactory and consequently have high satisfaction scores no matter the epidural delivery modality.[3] In our study, maternal satisfaction scores among all groups were high.

Despite the potential advantages of PCEA with or without CEI for labor analgesia, PCEA has not been widely adopted. Carvalho et al[5] performed an anonymous survey to determine CEI and PCEA practices among California hospitals and found that only 25% of California hospitals use PCEA in labor, with greater use among hospitals with dedicated obstetric anesthesia coverage and larger numbers of deliveries. All anesthesiologists surveyed used a continuous background infusion with PCEA (CEI + PCEA), with a median reported infusion rate of 6 mL/h (range, 3–15).[5] Reasons Carvalho gave for not using PCEA included; increased cost for PCEA setup, clinician preference, safety concerns, uncertainty in PCEA settings, and the inconvenience of change from conventional CEI. Carvalho[5] concluded that more staff education regarding PCEA use is needed to encourage increased utilization.

A limitation in our study is that we combined both nulliparous and multiparous patients, which has widened the standard deviations with respect to ropivacaine and fentanyl total dose as well as labor duration.

In conclusion, the benefit in reduction in total local anesthetic dose with demand dose only PCEA does not translate to improved maternal and neonatal outcome compared with CEI and CEI + PCEA.

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