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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Accepted for publication July 12, 2018.

Funding: Departmental.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

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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DOI: 10.1213/ANE.0000000000003734

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.

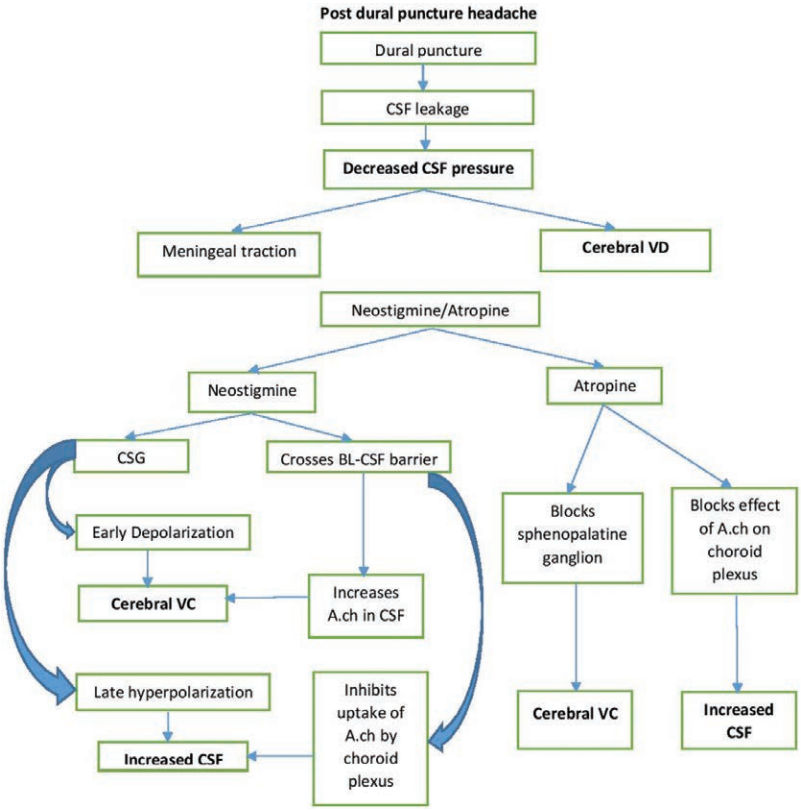

Figure. Pathophysiology of postdural puncture headache and the mechanisms of action of neostigmine and atropine treatment. BL-CSF, blood-cerebro-spinal fluid barrier; CSF, cerebrospinal fluid; CSG, cervical sympathetic ganglia; VC, vasoconstriction; VD, vasodilation.

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. ■

ACKNOWLEDGMENTS

The authors thank Prof Ahmed Mukhtar, Professor of Anesthesiology, Cairo University, for his guidance and support during writing the manuscript.

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