Original Article

Evaluation of the Preventive Effects of Neostigmine Plus Atropine on Post-Dural Puncture Headache

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Abstract

Background: Post-dural puncture headache (PDPH) is one of the most common side effects of spinal anesthesia. Several strategies and drugs have been suggested for the treatment and/or prevention of this headache. The aim of this study is evaluating the effects of intravenous prescription of neostigmine plus atropine 15 minutes after dural puncture on incidence and severity of PDPH during 5 days of follow-up in the setting of lower limb orthopedic surgeries.

Materials and Methods: In a randomized, controlled, double-blind clinical trial, 99 patients of lower limb orthopedic surgeries were randomized into study (49 patients) and control groups (50 patients). Fifteen minutes after dural puncture, participants in the two groups intravenously took neostigmine (40 μg/kg) plus atropine (20 μg/kg) and placebo (normal saline), respectively. Side effects of the studied drugs and incidence, severity, and duration of PDPH were evaluated 5 days after surgery.

Results: A total of 20 patients in the study group and 31 in the control group showed a headache-with-PDPH profile during 5 days of follow-up (P-value = 0.035). The mean duration of PDPH was 1.15 ± 0.48 and 1.32 ± 0.54 days in the study and control groups, respectively (P-value = 0.254).

Conclusion: Preventive administration of 40 μg/kg neostigmine plus 20 μg/kg of atropine may be effective in reducing the incidence and severity of PDPH after spinal anesthesia in lower limb orthopedic surgeries.

Keywords: Atropine, neostigmine, PDPH, preventive

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Introduction

Post-dural puncture headache (PDPH) or spinal (or post-spinal) headache is one of the most common side effects of spinal anesthesia[1] with an incidence of 6–36%. The incidence of this complication was reported to be 76–85% after accidental dural puncture in epidural anesthesia.[2] It usually starts within several hours after spinal anesthesia, but sometimes, it can be delayed for up to 2 weeks, which usually resolves within a few days.[3-5] The usual symptoms of PDPH other than headache are photophobia, neck stiffness, nausea and vomiting, diplopia, tinnitus, and dizziness.[6] The headache is usually throbbing and severe, starting from the forehead and extending to the occiput, and is aggravated by standing or sitting.[7] This is due to meningeal traction associated with cerebrospinal fluid (CSF) pressure reduction or dilation of cerebral arteries as an indirect effect of lowering CSF pressure as a result of CSF leakage from the punctured dura.[8] Current treatments or preventive measures for PDPH other than bed rest and hydration include theophylline, sumatriptan, caffeine, etc.[7,9,10] In resistant or severe cases, epidural blood patch (EBP) is a well-described technique used to provide relief of pain.[11]

The co-administration of neostigmine and atropine is a common treatment for terminating the effects of non-depolarizing muscle relaxants in the setting of general anesthesia with

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minimal side effects.[12-14] In a recent clinical trial, it has been documented that the use of neostigmine and atropine for PDPH can eliminate the need for EBP;[15] this effect has been questioned;[16] and data on the use of neostigmine plus atropine in PDPH is limited, and there is no study on the preventive effects of this drug combination on PDPH.

This study is a randomized, controlled, double-blind clinical trial and aimed to evaluate the preventive effects of neostigmine plus atropine on the PDPH in the setting of lower-limb orthopedic surgeries.

Materials and Methods

This randomized, controlled, double-blind clinical trial was done at the Anesthesiology Department, St Kashani hospital, Isfahan, Iran, after approval by the Research and Ethics Committee of the Isfahan University of Medical Sciences.

During the preoperative visit, 182 patients were evaluated, 58 of them did not have inclusion criteria, and 8 refused to participate in the study, so 116 patients entered the study [Figure 1]. Written informed consent was obtained from all of them. The trial was registered at the Iranian Registry of Clinical Trial (https://en.irct.ir/trial/52041) on November 9, 2020, with the IRCT registration number: IRCT20200825048515N11.

The inclusion criteria were 18–65 years old, American Society of Anesthesiologists classification (ASA) of I and II, a surgery duration of less than 2 hours, no contraindication of neuraxial anesthesia and no allergy to study drugs, no history of any chronic headache, migraine, cluster headaches, or opioid addiction, and candidate for lower limb orthopedic surgeries.

Patients did not have anything by mouth (NPO) since 8 hours before surgery and took 2 ml/kg/h intravenous fluids. In the operating room, basal vital signs (heart rate, blood pressure, and SpO2) were measured and patients were prepared for spinal anesthesia after preloading by intravenous 15 cc/kg/30 min of Ringer's lactate solution. Dural puncture in all participants was performed by an expert anesthesiologist using a Quinke No. 23 spinal needle in the L3-L4 or L4-L5 intervertebral space in a sitting position. Bupivacaine 0.5%, 10 to 15 mg, was used to create the block. After spinal anesthesia, patients were randomly allocated to two groups (n = 50 for each group) by computer-generated random numbers; odd numbers were in the intervention group, and even numbers were in the control group.

Fifteen minutes after spinal anesthesia, participants in the study group intravenously received a mixture of 40 μg/kg neostigmine plus 20 μg/kg atropine; in the control group, patients took placebo equivalently.

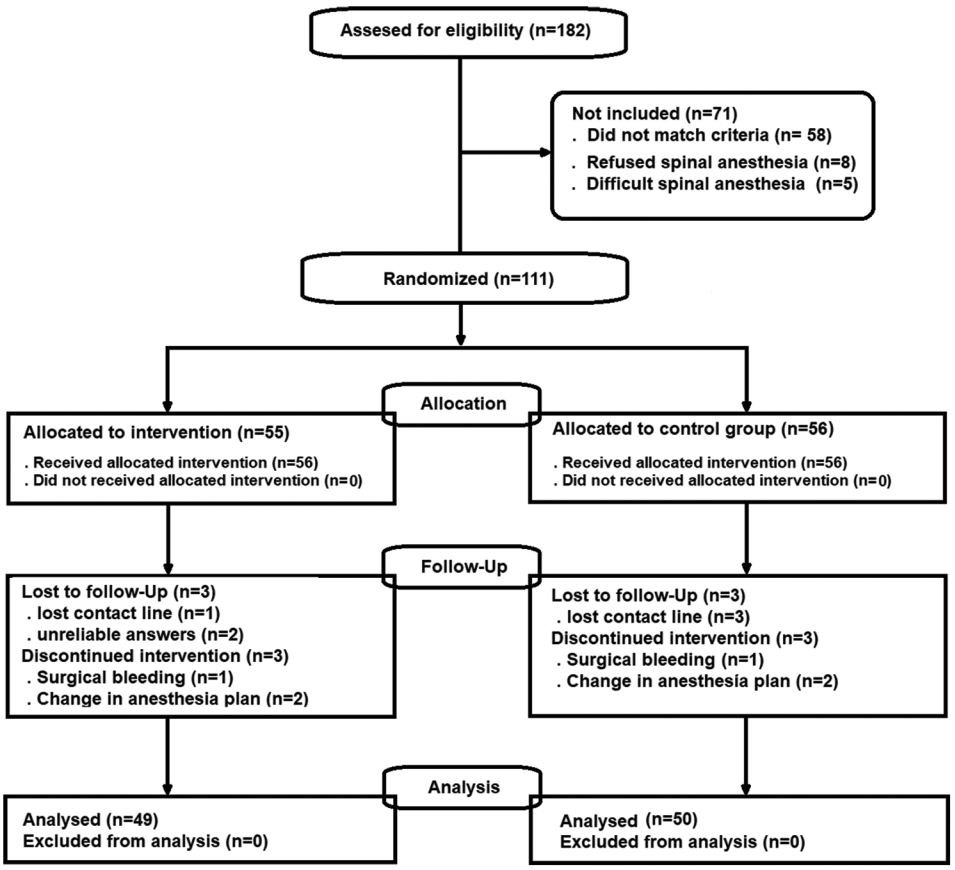

Figure 1: Flowchart of the study

The study drug and placebo (normal saline) were prepared by a co-worker in similar syringes. Each ml of the drug mixture of the study group had 200 μg neostigmine and 100 μg atropine.

The syringes were coded by the co-worker and provided to the executor. Based on the computer-generated random numbers, the executor prescribed 0.2 ml/kg coded syringes to the study or control group. The codes were reopened after statistical analysis. The patient, executor, and analyzer of the data were unaware of the patient's group until the end of the statistical analysis.

Fentanyl 1–2 μg/kg and/or midazolam 10–30 μg/kg was used for sedation during surgery. Hypotension was treated with isotonic fluid infusion and bolus injections of ephedrine (5 mg) or phenylephrine (20 μg).

Patients followed up for 5 days after surgery with any throbbing headache starting from the forehead and spreading to the occiput which was exacerbated by sitting or standing, or headaches plus photophobia, nausea, or vomiting, were recorded as PDPH. Its severity was measured by the visual analogue scale (VAS), with a score of 1 as mild, ignorable pain and 10 as the worst possible pain.

The treatment protocol for managing PDPH was hydration (recommended to drink tea and coffee or intravenous infusion of isotonic fluids), bed rest, intravenous acetaminophen (15 mg/kg), and eventually morphine (0.05 mg/kg). An EBP was considered for treating severe and unbearable headaches that did not respond to the previous treatments and lasted for more than 24 hours.

Demographic data (age, weight, and gender), types of operation, ASA physical status, duration of surgery, duration of anesthesia, and post-anesthesia care unit (PACU) stay time were recorded.

The heart rate, systolic blood pressure (SBP), and SpO2 were measured every 5 minutes during surgery, and episodes of bradycardia, tachycardia, hypertension (SBP more than 130 mmHg), and hypotension (SBP less than 90 mmHg) were recorded too.

Mean differences between groups were compared using independent sample t-tests and one-way analysis of variance (for repeated measurements), and post-hoc comparisons at various points in time were made by using Bonferroni's type I error rate correction for multiple tests of significance. Categorical variables were analyzed by the Pearson Chi-square test and by Fisher's exact test when the anticipated number was <5. The Mann–Whitney U-test was used as appropriate. $P < 0.05$ was set as statistically significant. All statistical analyses were performed using SPSS 20.

Results

After excluding 5 patients before and 12 of them after randomization [Figure 1], the statistical analysis was finally done on 99 participants.

The participants included 55 females and 44 males, and of them, 29 women were in the control group and 26 in the study group (*P*-value = 0.601). The minimum and maximum ages of participants in this study were 18 and 92 years, respectively; Also, they were 45 and 95 kg in weight, and 140 and 186 cm in height. The statistical analysis by independent sample t-tests did not show a significant difference in frequency distribution of patients in these two groups for age, weight, and height [Table 1].

Surgeries performed on patients included hip fracture, femur fracture repair surgery, knee replacement, and ankle and leg surgeries. Statistical analysis by the Chi-square test did not find significant differences between the two groups in the frequency distribution of the type of operation [Table 2].

The mean of prescribed fentanyl and midazolam during surgery, respectively, were 50.5 ± 41.9 μg and 1.3 ± 0.9 mg. Two groups had no significant differences in intraoperative dose of fentanyl (*P*-value = 0.721) and midazolam (*P*-value = 0.619).

The doses of drugs used to induce spinal anesthesia (bupivacaine) were 10 mg in 5 patients, 12.5 mg in 15 patients, and 15 mg in the others. Statistical analysis did not show significant differences between the two groups in the dose of bupivacaine (*P*-value = 0.130).

In the comparison, the two groups showed a *P* value of less than 0.05 in the mean heart rate before spinal anesthesia. In the first 30 minutes after intravenous administration of the studied drugs, none of the patients had bradycardia, but three in the study group had transient tachycardia (*P*-value = 0.076).

Participants did not have cardiac arrhythmias (other than tachycardia and mild bradycardia). There were no significant differences between the two groups in SBP before spinal anesthesia, mean heart rate, SBP, and SpO2 during surgery by analysis of variance [Table 3].

The incidence of headache in the control group was significantly higher than in the study group as per the Chi-square test. Sixty-two percent (31) of participants in the control group and 40% (20) in the study group showed headaches with a PDPH profile during 5 days of follow-up (*P*-value = 0.035)

In order, acetaminophen (15 mg/kg/q6h) or morphine (0.05 mg/kg/q6h) were used for relieving pain in VAS 3 to 6 and 7 to 10 in the post-operative period (*P*-value = 0.507).

The headaches in this study lasted between 1 to 3 days, and the most severe one had VAS = 8. The mean duration of PDPH in suffering participants was, respectively,

Table 1: Demographic characteristics of participants in the study (mean±SD)

	Control group	Study group	*P* by *t*-test
Age (year)	56.1±20.8	51.6±20.9	0.273
Weight (kg)	74.8±9.7	76.7±8.7	0.310
Height (cm)	166.5±12.8	167.5±10.3	0.666

Table 2: Distribution of kind of surgery in two groups of study

Kind of surgeries	Hip	Femur	Knee	Leg and lower parts	Others	*P* (Chi-Square test)
Control group	26% (13)	8% (4)	18% (9)	44% (22)	4% (2)	0.261
Study group	20.4% (10)	12.2% (6)	10.2% (5)	42.8% (21)	14.3 (7)	

Table 3: Hemodynamic indexes during surgery in two groups of study

	Control group	Study group	*P* (ANOVA)
Basal heart rate (beat/min)	78.6±8.3	82.1±8.7	*0.040
Basal SBP (mmHg)	130.1±7.9	132.9±12.8	0.197
Heart rate 15 minutes after studied drugs (beat/min)	78.9±8.2	79.4±11.4	0.782
Mean of heart rate during surgery (beat/min)	84.2±6.7	86.7±9.6	0.139
Mean of heart rate during surgery (mmHg)	135.4±10.6	135.6±12.2	0.944
SpO_2 during surgery (%)	98.3±1.6	98.8±1.2	0.453

*Significant difference

1.32 ± 0.54 and 1.15 ± 0.48 days in the control and study groups (*P*-value = 0.254).

Therapies used in patients with headaches included: supportive measures such as bed rest, drinking fluids, tea, and coffee, as well as intravenous acetaminophen and eventually morphine. In no case was an epidural patch required.

In the control group, 26 out of 31 patients needed drugs to control headache, for which morphine was prescribed in 4 patients due to insufficient improvement of PDPH with acetaminophen. In the study group, only 2 patients needed drug treatment to control headaches. In one case, oral acetaminophen provided an adequate response, but the other received opioids in addition to acetaminophen (*P*-value < 0.001).

Discussion

This study was a randomized double-blind clinical trial, performed to assess the preventive effects of an intravenous mixture of neostigmine and atropine on PDPH after spinal anesthesia in lower-extremity surgeries. The study revealed that neostigmine (40 μg/kg) plus atropine (20 μg/kg) can decrease the incidence of PDPH in this setting. This result aligned with Mahmood and co-workers' study that examined a similar mixture of neostigmine and atropine for the treatment of PDPH and concluded that their mixture is effective in treating PDPH after two doses.[15]

Neostigmine is a quaternary amine cholinesterase inhibitor that is frequently used in anesthesia practice for terminating the effects of non-depolarizing muscle relaxants.[17]

Acetylcholine is an inhibitor of CSF secretion in choroid plexus, and increasing levels of acetylcholine in neuromuscular junction is the general effect of anti-choline esterase drugs, but neostigmine by competing with acetylcholine in a transport system for entrance into the choroid plexus decreases the level of acetylcholine in the choroid plexus;[18,19] the net effect will be more CSF secretion.

In addition, neostigmine has a direct stimulatory action on cerebrospinal ganglia and induces some degrees of cerebral vasoconstriction.[20] This effect of neostigmine opposes cerebral vasodilation in PDPH and may be one of the mechanisms for preventing headache after dural puncture. Functional magnetic resonance imaging studies confirmed the effect of neostigmine in restoring the normal vascular tone.[21]

The increase of CSF secretion and opposition to cerebral vasodilation are suggested mechanisms of neostigmine for relieving PDPH.[15]

Atropine can be effective in the prevention and treatment of PDPH by two mechanisms, first, by inhibiting the sphenopalatine ganglion and causing cerebral vasoconstriction and, second, by blocking the effect of acetylcholine on the choroid plexus and increasing CSF secretion[22]

The incidence of PDPH after neuraxial procedures was reported in a wide range from less than 2% by Plewa[23] and up to 36% by Patel and cowriters[4] to more than 75%;[2] in the current study, about 50% of participants suffered from PDPH, and this relatively high incidence of PDPH may be due to the particular reason of the relatively large size of the needles (gauge 23) which were used in our study; however, it helped to highlight the effects of studied drugs in preventing PDPH.

The groups did not have significant differences in the mean of heart rate and SBP during surgery. There were no statistical differences in tachycardia, bradycardia, and other arrhythmias in the first 30 minutes after the injection of the studied drugs, these findings can indicate an acceptable safety of these drugs in this setting.

In Mahmoud's study,[15] seven patients required epidural blood patch (EBP) to control headache, whereas in the present study, no patient underwent EBP. The main reason for this difference is probably related to the type of patients studied; the participants in Mahmoud's study were pregnant women who had cesarean section under spinal anesthesia, and this group of patients have faster ambulation compared to the patients in the present study (ambulation is a potent factor in

aggravating PDPH). In addition, pregnancy is a risk factor for PDPH and its severity[24]

Conclusion

Intravenous administration of a mixture of 40 μg/kg neostigmine and 20 μg/kg of atropine 15 minutes after dural puncture may be significantly effective in the reduction of the incidence and severity of PDPH up to 5 days after surgery in patients who undergo lower-limb surgeries.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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