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ORIGINAL ARTICLE

Prophylactic Intravenous Injection of Neostigmine with Atropine versus Ondansetron on Post-dural Puncture Headache Incidence and Severity among Elective Cesarean Section Cases

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ABSTRACT

Background: Post-dural puncture headache (PDPH) is a debilitating condition that appears after puncturing the dura mater. The headache is severe, throbbing, frontal, radiates to the occiput; increases by standing, and decreases by lying down.

Objectives: This study aimed to compare the effect of ondansetron compared to neostigmine on reducing the incidence of PDPH in parturients undergoing spinal anesthesia for elective cesarean section.

Methods: Fifty-one parturients undergoing spinal anesthesia for elective cesarean section were allocated randomly into three equal groups; Group (n = 17) parturients received intravenous injection of 0.9% normal saline after delivery of the fetus as controls, Group (n = 17) parturients received intravenous injection of neostigmine and atropine after delivery of the fetus, Group (n = 17) parturients received intravenous injection of ondansetron after delivery of the fetus.

Results: The incidence of headache, and median of VAS was higher among controls as compared to the neostigmine and the ondansetron group. Also, were higher in the neostigmine group compared to the ondansetron group. The control group (47.1%) required significantly more post-operative analgesia than the ondansetron group (11.8%; p=0.01). The patient's heart rate increased during spinal anesthesia, but it reduced throughout delivery and after drug infusion. The occurrence of headache and median visual analogue scale score at 48 and 7 days were postpartum differed significantly among the three groups.

Conclusions: Intravenous injection of 0.08 mg/kg ondansetron is more effective in lowering the incidence and severity of post-dural puncture headache compared to 20g/kg neostigmine plus 10g/kg atropine intravenous injection in parturients undergoing spinal anesthesia for elective cesarean section.

Keywords: Neostigmine; Atropine; Ondansetron; Post-dural puncture headache

INTRODUCTION

The hazards associated with general anesthesia are avoided, hospital stays are shortened, postoperative pain is managed, and death rates are decreased in the use of spinal anesthesia after a cesarean section [1, 2]. Spinal anesthesia has some benefits, but it also comes with risks including neurotoxicity, back pain, and post-dural puncture headache (PDPH) [3].

Post-dural puncture headache occurs when the dura mater is pierced, and it is extremely painful. Pain is intense, frontal, throbbing, and radiates to the occiput; it is more severe when standing and less severe when lying down. Common negative reactions include

sensitivity to light, nausea, vomiting, neck stiffness, and ringing in the ears. It often begins within 2 days but can be delayed for up to 2 weeks; after a few days, it resolves on its own (5). First-line treatments for PDPH include bed rest, fluid replacement, oral caffeine, and non-narcotic pain relievers. When conventional methods fail, an epidural blood patch is used [6].

Many strategies were used to prevent PDPH including changing needle gauge and tip configuration [7], intravenous dexamethasone [8], intravenous injection of neostigmine and atropine, intravenous injection of ondansetron, intravenous opioid, epidural morphine, and prophylactic epidural blood patch [9].

Neostigmine has an anticholinesterase effect. It has limited brain penetration but can cross the choroid plexus. The key alterations in PDPH are CSF leakage and cerebral vascular dilatation, both of which are affected by the central effects of neostigmine and atropine [10].

Studies have shown that the 5-HT3 receptor antagonist ondansetron may reduce the occurrence of PDPH by inhibiting the dilation of cerebral arteries. Preventative treatment of nausea and vomiting with ondansetron is common practice [11]. The purpose of this study was to examine the effectiveness of intravenous injections of neostigmine with atropine versus ondansetron following delivery of the fetus to reduce the incidence of post-dural puncture headache (PDPH) in pregnant women undergoing spinal anesthesia for elective cesarean birth.

METHODS

Fifty-one pregnant women who had an elective C-section under spinal anesthesia were enrolled in our prospective randomized, controlled, double-blind clinical trial. The study was conducted over six months, from the beginning of July 2021 till the end of December 2021 at Anesthesia, Intensive Care, and Pain Management Department in collaboration with the Gynecology and Obstetrics Department, Zagazig University Hospitals, Egypt. After receiving approval from the local ethics committee and obtaining informed consent from parents. The work was done in conformity with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies.

Sample size

Assuming the mean visual analogue scale score in neostigmine with atropine group versus ondansetron group was 4 ± 2 versus 6 ± 3, at 80% power and 95% CI the estimated sample will be 51 cases, so 17 cases in each group using Open Epi.

Randomization and blinding

Pregnant women were assigned at random using computer-generated randomization tables in 3 equal groups: Group C included 17 parturients as controls. Group N included 17 parturients who received neostigmine plus atropine. Group O included 17 parturients who received ondansetron.

Inclusion criteria

Women with a BMI between 25 and 35 kg/m2 and a physical status of (II) or (III) according to the American Society of Anesthesiologists (ASA) were considered for cesarean delivery under spinal anesthesia.

Exclusion criteria

Cases with preeclampsia and eclampsia, in whom spinal anesthesia is contraindicated such as coagulopathy or spine deformities, prior PDPH, migraine, or persistent headache history, and chronic use of analgesics, drug abuse or smoking, or who had hypersensitivity to any of the used drugs, either Advanced cardiac, renal or hepatic diseases.

Withdrawal criteria

Mothers can discontinue participation in the study at any time without repercussions to their medical or surgical care. Presence of intraoperative bleeding more than 1 liter of blood.

All patients underwent through the following:

Patients were evaluated by recording their characteristics and vital signs (age, height, weight, BMI and SPO2), obtaining a medical history (including a list of any current medications), conducting a physical examination of all major body systems, and requesting routine investigations (such as a complete blood count, sedimentation rate, bleeding time).

Procedure:

An 18-gauge IV line was used to provide anesthetics and fluids, while a second 18-

gauge IV line was utilized to give the study drugs. A preload dose of lactated ringer solution (8-10 ml/kg) was given before the spinal anesthetic injection.

Technique of spinal anesthesia

After skin sterilization with 10% betadine, the parturients were seated. To numb the skin and subcutaneous tissues, an injection of 2 cm of lidocaine 2% was given. Using a para-median technique, a 22 G spinal needle was inserted into the L3-L4 intervertebral region with the bevel facing laterally to administer spinal anesthetic. Once the subarachnoid space has been located and confirmed by seeing cerebrospinal fluid (CSF) freely pouring from the needle, the procedure can continue, subarachnoid injection of hyperbaric bupivacaine (0.5%) in an injection of 2.5 ml (12.5 mg), then withdraw the needle. To prevent supine hypotension, the operation table was angled to the left by 15 degrees. A pinprick test showed that feeling was impaired at the T4 dermatome. Motor block was evaluated using the Bromage scale every 5 minutes for the first 15 minutes following spinal anesthesia[12].

When a T4 sensory block and a 3 bromage score were verified, surgery was started. One milliliter of blood loss was treated intraoperatively with 3 milliliters of ringer solution, and bleeding of more than 1 liter (20 percent) resulted in the withdrawal of the pregnant woman data collected during the investigation. After fetal delivery and cord clamping, the first intravenous line was used to begin infusing the research medicines. The research medication was administered via the second intravenous line. Both investigators and data collectors were blinded to the injected agents:

After fetal delivery, those in Group C received an intravenous injection of 5 ml of 0.9% normal saline. In Group N: neostigmine (20µg/kg) in addition to atropine (10µg/kg) with a total volume equal to 5 cc were injected IV after delivery of the fetus. In Group O: ondansetron (0.08mg/kg) (completed with normal saline till total volume reached 5 cc) was injected IV after delivery of the fetus.

Vital signs monitoring

Baseline, post-spinal anesthetic, post-delivery, 10 minutes, 20 minutes, and 30 minutes after infusion of the research medications, and post-operative MAP, HR, and SpO2 values were obtained.

Assessment of PDPH

Patients were followed for 2 weeks and queried about headache occurrences. Patients who had previously reported a headache sat quietly for three minutes in the hospital. Before being asked open-ended questions about how they felt. When PDPH ran into the International Headache Society, its presence was confirmed [13]. Mild headaches will be listed between 0 and 3, moderate headaches between 4 and 6, and severe headaches between 8 and 10 [14].

A second anesthesiologist who was unaware of the study medicines began following patients via phone. Bed rest, excess fluid intake, caffeinated beverages, and first-line analgesics including oral paracetamol 500mg as needed were implemented for patients whose headaches registered a VAS score of 3 or higher. When the mentioned treatments failed, oral theophylline 250 mg was administered. From each parturients the following data were collected, parturients characteristics' (Name, age, gestational age, BMI, gravidity, parity, ASA physical status, previous cesarean section), duration of surgery, volume of blood loss during surgery, intraoperative vital signs (heart rate, mean arterial pressure and SpO2 %): baseline, 10 minutes, 20 minutes, 30 minutes, and at the end of surgery; after infusion of the study drug; after spinal anesthetic; after birth of the infant; at the end of operation. Vital signs were monitored in the PACU at 15-minute intervals for a total of 2 hours. Number of patients requiring oral paracetamol and theophylline; frequency of postoperative nausea and vomiting; VAS score at 6, 12, 24, 48, and 14 days postoperatively to assess the severity of PDPH; frequency of postoperative neck stiffness at 6, 12, 24, 48, and 14 days postoperatively; and frequency of other adverse effects of the study drugs, such as dizziness, drowsiness, tiredness, or constipation.

STATISTICAL ANALYSIS

A version of SPSS software (IBM, 2020) was used for statistical analysis. Tables with the data were shown. The means, medians, standard deviations, and ranges were used to display numerical data. Portions and frequencies were used to display qualitative data. The variables' variance homogeneity and distributional properties were assessed using the Levene and Kolmogorov-Smirnov tests. To examine qualitative factors, Pearson's chi-squared test ($\chi 2$) was employed. Separate quantitative variables were analyzed when applicable using the Kruskal Wallis test (KW) and one-way ANOVA (F). Analysis of the dependent quantitative variables was done using repeated measures ANOVA (F). One might classify a p-value as highly statistically significant (HS) at <0.05, statistically non-significant (NS), and highly statistically significant (S) at <0.001.

RESULTS

The study initially included 70 scheduled for elective cesarean section. Among them 19 cases were excluded (8 cases didn't meet the inclusion criteria, 9 cases declined to participate and 2 cases excluded due to other reasons).The remaining 51 parturients were randomly with allocated into 3 equal groups (17 cases). (figure1).

As regarding the basic characteristics and clinical data of the parturients, there was no statistically significant difference with among the three studied groups as regard the age, gestational age, BMI, gravidity, parity, ASA score and previous CS (table1).

Regarding the surgical data, there was no statistically significant difference in the duration of operation or the volume of blood lost during surgery between the three groups tested (table2).

Table 3 showed that there was no statistically significant difference in intraoperative heart rate between the three examined groups at baseline, immediately after spinal anesthesia, immediately after delivery, or after drug infusion at 10, 20, 30 minutes until the completion of the operation ($p > 0.05$). There was a statistically significant rise in HR immediately following spinal anesthesia in each group when compared to their baseline value. The HR then reduced again, thus there was no statistically significant difference between the baseline value and the value immediately after delivery, after infusion of the study medicines at 10, 20, 30 minutes, or at the end of the operation (P0.05).

There was no statistically significant difference in intraoperative mean arterial blood pressure between the three studied groups at baseline, immediately after spinal anesthesia, immediately after delivery, or after drug infusion at 10, 20, 30 minutes until the end of surgery ($p > 0.05$).

While there was a statistically significant reduction in MAP immediately following spinal anesthesia in each group compared to its baseline level. Then MAP climbed again, thus there was no statistically significant difference between the baseline level and the level immediately after delivery, following infusion of the study medicines at 10,20,30 minutes, or at the completion of surgery ($p > 0.05$) (table4).

There was no statistically significant difference in intraoperative oxygen saturation between the three examined groups at baseline, immediately after spinal anesthetic, immediately after delivery, or after medication infusion at 10, 20, 30 minutes till the completion of operation ($p > 0.05$).

There was also no statistically significant variation in oxygen saturation at different time intervals in each group when compared to the baseline measurement ($p > 0.05$) (table5).

There was no statistically significant difference between the three studied groups in terms of the incidence and grade of postoperative nausea and vomiting, except for the proportion of no nausea or vomiting, which was statistically higher in the ondansetron group (82.4%) compared to the control group (47.1%) (P0.05) (table 6).

In terms of the incidence of post-dural puncture headache, there was no statistically significant difference between the three examined groups at 6, 12, 24, and 14 days following delivery ($p > 0.05$). While there was a statistically significant difference in the incidence of post-dural puncture headache at 48 hours ($p = 0.014$) and 7 days following birth ($p = 0.031$) across the three examined

groups. Post-dural puncture headache was statistically more common in the control group than in the neostigmine and ondansetron groups (p 0.05). At 48 hours and 7 days following delivery, the incidence of post-dural puncture headache was statistically higher in the neostigmine group compared to the ondansetron group (p 0.05) (table7).

There was no statistically significant difference between the three studied groups in terms of postoperative VAS score at 6, 12 hours, and 14 days after delivery (p > 0.05), but there was a statistically significant difference between the three studied groups in terms of median VAS score at 24, 48 hours, and 7 days after delivery. The VAS score in the control group was statistically greater than in the neostigmine and ondansetron groups. In addition, the VAS score in the neostigmine group was statistically greater than in the ondansetron group (table S1).

In terms of the number of patients who required postoperative analgesia (Paracetamol), the control group (47.1%) was statistically significantly greater than the neostigmine group (29.4%) (p=0.03). Furthermore, the percentage of patients who required analgesia was higher in the control group (11.8%) than in the ondansetron group (p=0.01), with no statistically significant difference between the neostigmine and ondansetron groups (P=0.2). In the three groups studied, no patients required theophylline (table S2).

There was no statistically significant difference between the three studied groups in terms of the incidence of neck rigidity at 6, 12, 24, and 14 days after delivery (p > 0.05), but there was a statistically significant difference between the three studied groups in terms of the incidence of neck rigidity at 48 hours (p = 0.026) and 7 days (p = 0.050) after delivery. The incidence of neck rigidity increased statistically in the control group relative to the ondansetron group at 48 hours and 7 days after delivery (P=0.007 & 0.001, respectively). However, the incidence of neck rigidity increased statistically non-significantly in the control group relative to the neostigmine group, and there was no statistically significant difference between the neostigmine and ondansetron groups (P>0.05) (tableS3).

There was no statistically significant difference between the three investigated groups in terms of postoperative constipation (p = 0.721), weariness (p = 0.891), drowsiness (p = 0.183), or dizziness (p = 0.150) (tableS4).

Table 1: Basic characteristics and clinical data of the parturients among the 3 studied groups.

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance
Age (years): Mean ± SD	28.24 ± 5.73	26.06 ± 4.71	26.41 ± 5.08	F= 0.860 P= 0.429
Gestational age (weeks): Mean ± SD	38.41 ± 0.94	38.88 ± 1.11	38.29 ± 1.16	F= 1.427 p= 0.250
BMI (Kg/m^2): Mean ± SD	29.05 ± 3.26	29.44 ± 2.70	29.26 ± 2.33	F= 0.082 p= 0.921
Gravidity: Median (Range)	3 (1 – 5)	3 (1 – 5)	2 (1 – 5)	KW= 1.145 P= 0.562
Parity: Median (Range)	2 (0 – 3)	2 (0 – 4)	1 (0 – 4)	KW= 1.954 P= 0.376
ASA score: n (%)				
ASA II	14 (82.4%)	14 (82.4%)	15 (88.2%)	MC = 0.297 P= 0.862
ASA III	3 (17.6%)	3 (17.6%)	2 (11.8%)	
Previous CS: n (%)	10 (58.8%)	10 (58.8%)	9 (52.9%)	χ^2 = 0.160 P= 0.923

Quantitative data were expressed as mean ± SD or median (range).

Qualitative data were expressed as number (Percent)
Group C: control group. Group N: neostigmine and atropine group.
Group O: ondansetron group.
SD: standard deviation. F: one-way ANOVA. KW: Kruskal Wallis. $\chi^{2:}$ Chi-square test
MC: Monte-Carlo test BMI: body mass index. n: number of parturient.

Table 2: Surgical data of the parturients in the three studied groups.

Variables	**Group C (n=17)**	**Group N (n=17)**	**Group O (n=17)**	**Test of significance**
Duration of surgery (min): Mean ± SD	65.06±11.01	65.53 ± 9.06	65.71 ± 8.21	F= 0.021 P= 0.979
Volume of blood loss (ml): Mean±SD	462.18 ± 52.35	441.2 ±42.12	448.44 ±58.50	F= 0.731 p= 0.487

Quantitative data were expressed as mean ± SD.
Group C: control group. Group N: neostigmine and atropine group.
Group O: ondansetron group
SD: standard deviation F: one-way ANOVA. n: number of parturients.

Table 3: Intraoperative heart rate changes of the parturients in the 3 studied groups at different times.

Heart rate (B/min)	**Group C (n=17)**	**Group N (n=17)**	**Group O (n=17)**	P-value
Baseline:	93.26±11.42	94.35±11.03	93.27 ± 14.73	0.407
Immediately After spinal anesthesia:	118.69 ± 11.376$^{\#}$	119.18 ± 14.581$^{\#}$	120.08 ± 15.635$^{\#}$	0.279
immediately after delivery	103.38 ± 14.593	105.96 ± 12.930	104.62 ± 13.06	0.505
10 min after drug infusion	99.20 ± 14.564	98.98 ± 17.103	99.07 ± 14.332	0.717
20 min after drug infusion	97.28 ± 13.093	96.33 ± 13.019	96.28 ± 12.87	0.529
30 min after drug infusion	95.47 ± 12.191	95.40 ± 12.133	94.55 ± 14.51	0.805
End of surgery	94.82 ± 12.525	93.47 ± 12.118	93.29 ± 14.09	0.438
F **P**	F= 7.5 P <0.0001	F=8.04 P <0.0001	F=7.8 P <0.0001	

Quantitative data were expressed as mean±SD
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group
F: Fissure's Exact test. $^{\#:}$ statistically significant compared to its baseline reading

Table 4: Intraoperative mean arterial blood pressure (MAP) (mmHg) of the parturients in the three studied groups at different times.

MAP (mmHg)	**Group C (n=17)**	**Group N (n=17)**	**Group O (n=17)**	P-value
Baseline **Mean ± SD**	88.89±9.92	86.44±16.59	89.53± 9.39	0.548

MAP (mmHg)	Group C (n=17)	Group N (n=17)	Group O (n=17)	P-value
Immediately After spinal anesthesia Mean ± SD	78.69 ± 11.376 #	76.18 ±14.581 #	77.08 ±15.635 #	0.326
immediately after delivery Mean ± SD	80.38 ± 14.593	79.96 ± 12.930	79.62 ± 13.06	0.288
10 min after drug infusion Mean ± SD	86.20 ± 14.564	85.98 ± 17.103	85.07 ± 14.332	0.848
20 min after drug infusion Mean ± SD	88.28 ± 13.093	87.33 ± 13.019	89.28 ± 12.87	0.236
30 min after drug infusion Mean ± SD	89.47 ± 12.191	88.40 ± 12.133	90.55 ± 14.51	0.367
End of surgery Mean ± SD	89.82 ± 12.525	90.47 ± 12.118	89.29 ± 14.09	0.956
F P	F= 2.3 P= 0.03	F=2.09 P= 0.05	F= 2.8 P= 0.01	

Quantitative data were expressed as mean ± SD. F= Fissure's Exact test. Statistically significant (p≤ 0.05).Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group

#: statistically significant compared to its baseline reading P: intergroup comparing.

Table (5): Intraoperative Oxygen saturation (%) of the parturients in the three studied groups at different times.

Oxygen saturation (%)	Group C (n=17)	Group N (n=17)	Group O (n=17)	P-value
Baseline:	98.4 ± 1.1	98.4 ± 1.1	98.4 ± 1.1	0.9
Immediately after spinal anesthesia:	98.3 ± 1.0	99.0 ± 1.0	97.7 ± 1.9	0.9
Immediately after delivery	98.4 ± 1.1	98.4 ± 1.1	98.4 ± 1.1	0.9
10 min after drug infusion	98.9 ± 1.0	98.9 ± 1.1	98.9 ± 1.1	0.9
20 min after drug infusion	98.6 ± 1.4	98.6 ± 1.4	99.0 ± 1.0	0.9
30 min after drug infusion	99.0 ± 1.0	99.0 ± 1.0	99.0± 1.0	0.9
End of surgery	98.3 ± 1.0	98.4± 1.1	97.7 ± 1.9	0.7
F P#	F=8.2 P#=0.7	F=3.8 P#=0.8	F=9.5 P#=0.6	

Quantitative data were expressed as mean ± SD.
Group C: control group. Group N: neostigmine and atropine group.
Group O: ondansetron group

Table (6): Postoperative nausea and vomiting (PONV) of the parturients in the 3 studied groups.

Grades of IONV	Group C (n=17)	Group N (n=17)	Group O (n=17)	Fischer exact test
No nausea nor vomiting N (%)	8 (47.1%)	13 (76.5%)	14 (82.4%)*	P1=0.11 P2=0.04 P3=0.67

Grades of IONV	Group C (n=17)	Group N (n=17)	Group O (n=17)	Fischer exact test
Nausea n(%)	5 (29.4%)	3 (17.6%)	2 (11.8%)	P1=0.41 P2=0.2 P3=0.62
Nausea and vomiting n(%)	3 (17.6%)	1 (5.9%)	1 (5.9%)	P1=0.28 P2=0.28 P3=1
Vomiting more than twice in 30 min. n(%)	1 (5.9%)	0 (0%)	0 (0%)	P1=0.31 P2=0.31 P3=1

Qualitative data were expressed as number (Percent)
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group.MC: Monte-Carlo test n: number of parturients.
P1 group C versus N, P2 group C versus O, P3 group N versus O
*: statistically significant compared to control group.

Table 7: Incidence of Post Dural puncture headache of the parturients in the three studied groups at different times.

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance	Fischer exact
After 6 hours	0 (0)	0 (0)	0(0)	-	-
After 12 hours	0 (0)	0(0)	0 (0)	-	-
After 24 hours	7 (41.2%)	4 (23.5%)	3 (17.6%)	MC = 2.560 P= 0.278	P1=0.27 P2=0.13 P3=0.67
After 48 hours	7 (41.2%)*	4 (23.5%)˙	0 (0%)	MC = 8.577 P= 0.014	P1=0.04 P2=0.003 P3=0.03
After 7 days	6 (35.3%)*	4 (23.5%)˙	0 (0%)	MC = 6.966 P= 0.031	P1=0.04 P2=0.007 P3=0.03
After 14 days	2 (11.7%)	1 (5.9%)	0 (0%)	MC = 5.795 P= 0.61	P1=0.14 P2=0.17 P3=0.31

Qualitative data were expressed as number (Percent)
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group
MC: Monte-Carlo test. n: number of parturients. Statistically significant ($p \leq 0.05$).
P1 group C versus N. P2 group C versus O. P3 group N versus O.
*: statistically significant compared to N&O groups ˙: Statistically significant compared to O group

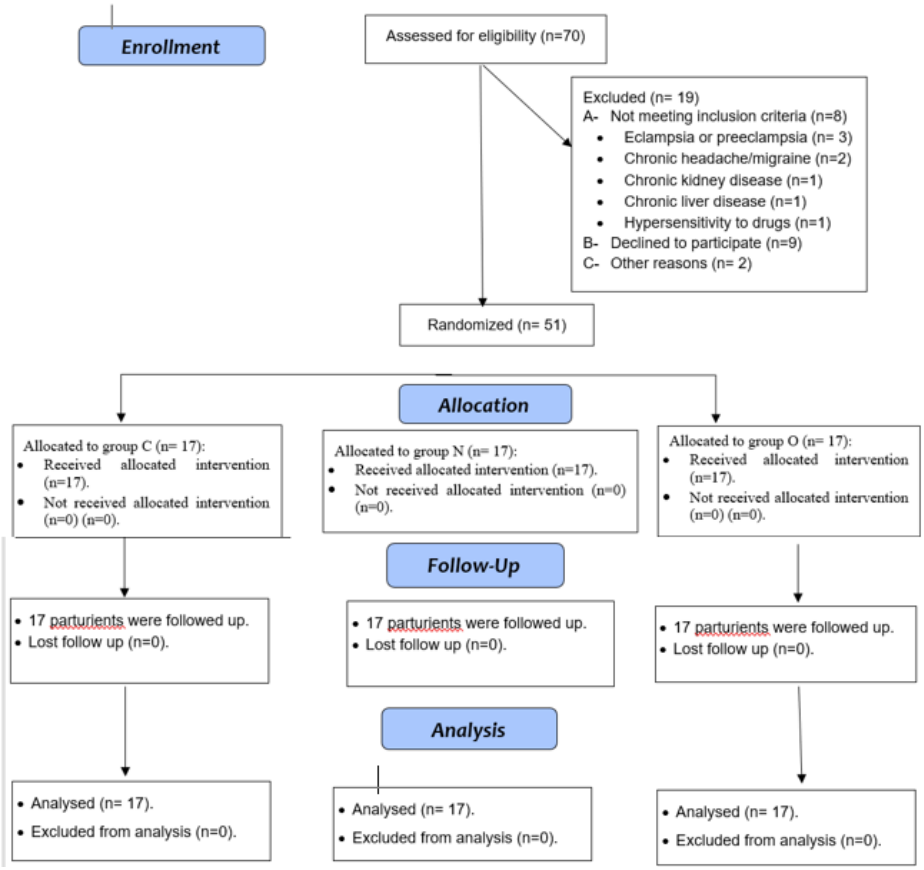

Figure 1: Flow chart of the cases in the study

DISCUSSION

Spinal anesthesia (SA) is frequently used in obstetrics for cesarean sections (CS). It is easy to use, affordable, strengthens the fetomaternal link, and offers analgesia following surgery. Also, the risk of general anesthesia for the mother and fetus is eliminated. Nevertheless, there are a few drawbacks to this type of anesthetic, including hypotension, post-dural puncture headache (PDPH), nausea, vomiting, cardiac arrest, and respiratory arrest[15].

Post dural puncture headache (PDPH) is more common in obstetric patients due to their sex, age and higher rates of exposure to neuroaxial blocks. And despite resolving spontaneously, PDPH pain is very severe, awful unpleasant experience that makes the patient unsatisfied with spinal anesthesia resulting in its refusal in other operations, moreover it interferes with baby care, increases of hospital stay and health care cost [16].

Since a clear pathophysiology for post-stroke headache has not been established, methylxanthines, sumatriptan, and caffeine increase the vasoconstriction of cerebral blood vessels, while adrenocorticotropic hormone (ACTH) increases intravascular volume. As a result, a variety of therapeutic options are used to relieve headaches in clinical practice and clinical trials [17]. The production of CSF is increased by certain postures, such as lying prone, which lowers pressure in the subarachnoid region and facilitates the formation of a seal over the dura; the epidural blood patch (EBP) mechanically stops CSF leakage [18].

It's important to comprehend the process underlying the prevention of headaches following spinal anesthesia in order to make the optimal therapeutic decision. Uncertainty exists regarding the precise process and etiology of the complication [19].

The current study was conducted to compare between the effect of prophylactic I.V injection of neostigmine with atropine versus I.V injection of ondansetron on the prevalence and severity of PDPH in women undergoing

spinal anesthesia for an elective cesarean section. Parturients' and surgical characteristics were comparable among the studied groups.

There was a two-week follow-up period for PDPH features in the analyzed groups in the current study.

In the current study, as regards the heart rate, MAP and saturation of oxygen At baseline, immediately after spinal anesthesia, immediately after delivery, and immediately after medication infusion, there was no statistically significant difference between the three investigated groups at 10, 20, 30 minutes till the end of surgery ($p > 0.05$), while within each group the mean arterial pressure lowered during spinal anesthesia, then increased immediately following delivery and after medication infusion, whereas HR climbed following spinal anesthesia, then decreased immediately following delivery and after drug infusion.

The most frequent side effect following spinal anesthesia is hypotension, particularly in women having cesarean sections. This may be explained by a decrease in the mother's cardiac output, venous return, and systemic vascular resistance brought on by the sympathetic block brought on by spinal anesthetic. Furthermore, progesterone's vasodilator impact might contribute to this issue [20,21].

The auto-transfusion of blood through uterine contractions and the release of aorto-caval compression, which enhanced cardiac output by as much as 60–80%, were linked to the elevated level of MAP shortly following birth [22].

The results of the study conducted by Langesaeter and Dyer [23] showed that the onset of spinal anesthesia was linked to a rapid and profound drop in systemic vascular resistance with a compensatory increase in HR and no discernible changes in stroke volume. The changes in HR observed in the current study were similar to those of their study. Bradycardia with hypotension is a less common reaction to spinal anesthesia. Under the medical term "supine hypotensive syndrome," this condition is thought to be caused by vena-caval blockage or vagal reflex bradycardia linked to an insufficiently full heart, or "Bezold–Jarisch reflex" [24].

Moreover, neither ondansetron had any discernible effects or neostigmine with atropine injection about the hemodynamics of mothers. These outcomes corroborated the research that was done by Shokrpour et al [25] who compared between the preventive effect of dexamethasone and ondansetron in controlling headache caused by spinal anesthesia in parturients receiving spinal anaesthetic for a planned cesarean delivery and found that the mother's hemodynamics was not significantly affected by ondansetron and Saafan et al [26] who investigated the effects of gabapentin, neostigmine, and aminophylline on the avoidance of post-dural puncture headache during cesarean section and revealed that neostigmine had no significant effect on the maternal hemodynamics.

The incidence of PDPH ranged from 0 to 42.6% following spinal anesthesia and 81% following an unintentional dural puncture, according to the evidence [27 - 29].

The same range was reported in the current study, the incidence of PDPH in the control group was 41.2% after 24 hours.

There was no statistically significant difference between the three groups under investigation in the current study with relation to the incidence of headache at 6, 12, 24 hours and at 14 days after delivery ($p > 0.05$). However, there was a statistically significant difference between the three studied groups as regarding the incidence of headache at 48 hours and at 7 days after delivery ($p = 0.014$ and 0.031 respectively). The incidence of headache was higher in the control group as compared to the neostigmine and the ondansetron group. Also, the incidence of headache was higher in the neostigmine group as compared to the ondansetron group.

Regarding the effect of ondansetron, the current results were in accordance with Pazoki et al [14] Participants comprised 195 patients who received spinal anesthesia for elective cesarean sections (C/S). Block randomization was then used to divide the subjects into three equal groups. Five minutes prior to surgery, participants in the first, second, and control groups were given 8 mg,

4 mg, and normal saline, respectively, of ondansetron. Normal saline was added to create a final volume of 5 cc. After surgery, the incidence of post-dural puncture headache was found to be considerably higher in the placebo group (P < 0.010), 48 hours after surgery (P = 0.001), and 4 days after surgery (P = 0.01) compared to the ondansetron 8 mg and 4 mg groups. At all times, the placebo group had a higher incidence of post-dural puncture headache than the other groups; the distributions for the 8 mg ondansetron, 4 mg ondansetron, and placebo groups were 34.92%, 35.94%, and 71.87%, respectively.

Regarding the effect of neostigmine, Elsawy et al [30] who included 180 patients who had spinal anesthesia for an elective cesarean section, and the subjects were assigned into two equal groups. The intervention group received neostigmine 20 µg/kg and atropine 0.01mg/kg diluted in 50 ml of normal saline 0.9%, and the control group received 50 ml of normal saline 0.9% after umbilical cord clamping, the author found that In the neostigmine group, the overall incidence of PDPH was 2.2%, a substantial decrease from the 13.30% in the control group (P=0.003).

As regarding the severity of PDPH, the VAS scores at 6, 12, 24, and 14 days following birth did not show a statistically significant difference between the three groups under study (p > 0.05).

There was a statistically significant difference between the three studied groups as regard the median VAS score at 48 hours and at 7 days after delivery. The VAS score was higher in the control group as compared to the neostigmine and the ondansetron groups. Also, the VAS score was higher in the neostigmine group as compared to the ondansetron group.

Regarding the effect of ondansetron, the current results agreed with Shokrpour et al [25] who showed that the VAS score was significantly higher in the control group compared to the ondansetron group at 12, 24 and 48 hours following the operation.

The present findings similarly corroborated those of Pazoki et al. [14], who demonstrated that the 8 mg ondansetron group had the lowest VAS score at all times, including 24, 48 hours, and 4 days following surgery, while the placebo group had the highest VAS score (P < 0.05).

Regarding the effect of neostigmine, Ibrahim et al [31] a recent Egyptian study that conducted on 60 patients who reported with post-dural puncture headache following an elective cesarean delivery under spinal anesthesia for six months at hospitals affiliated with Ain Shams University. The study participants were distributed into three groups (neostigmine, hydrocortisone and conventional methods). The results of the study showed that at 2, 6, 24, 48, and 72 hours following the initiation of treatment, the mean VAS score in the neostigmine group was considerably lower than that of the other groups (p<0.001).

Along with conservative care of 85 patients with fluids and analgesics, Mahmoud et al. [32] also carried out a randomized, controlled, double-blind research comparing neostigmine and atropine (n = 41) to a saline placebo (n = 44) for treating PDPH. At every point in time following the intervention, the visual analog scale scores obtained from neostigmine/atropine treatment were considerably higher (P<0.001) than those from saline treatment.

On the contrary, in a study conducted by Shetabi, et al [33] who included 62 patients to study the impact of neostigmine and atropine given intravenously to prevent post-dural puncture headaches during cesarean sections. Two groups of patients were randomly assigned (n = 31 each group). While the control group got a 10 ml intravenous infusion of normal saline, the experimental group received 0.5 mg of neostigmine and 0.5 mg of atropine. After a week of follow-up, they compared the two groups' incidence and severity of post-dural puncture headache over the first 48 hours. The results of this study showed that 0.5 mg of neostigmine and 0.5 mg of atropine is linked to a non-significant decrease in post-dural puncture headache incidence (P=0.11) and severity (P=0.18). The difference between this study and ours may be because the author used different dose of neostigmine and atropine, also our study was different as we follow up the patients for two weeks whereas in their study the follow-up period lasted for just one week.

In the current study, there was decrease in the incidence of nausea and vomiting in both the neostigmine group and ondansetron group as compared to the control group, however, this difference didn't reveal a statistically significant difference.

Within the same line, Mahmoud et al [32] reported decrease in the incidence of PONV after treatment with neostigmine and atropine as compared to placebo, but the difference didn't reach a statistically significant value.

Similar findings were reported by Pazoki et al. [14], who found that at 24 hours, the placebo group's PONV incidence was considerably higher than that of the other two groups (those receiving 4 mg and 8 mg of ondansetron) ($P < 0.001$). After surgery, the PONV did not significantly differ between the examined groups 48 hours ($P=0.086$) or 4 days ($P = 0.409$). The 8 mg and 4 mg ondansetron groups had the same incidence of PONV.

Ondansetron preventively attenuates the onset of spinal anesthesia-induced hypotension and reduces the need for vasodilator medications, as demonstrated by Gao et al [34]. Additionally, this lessened problems like N/V and bradycardia.

In an investigation by Yazigi et al [35], the use of 8 mg of ondansetron decreased N/V. The study's goal was to ascertain the impact of prophylactic ondansetron in the treatment of N/V.

The second most frequent complaint during the recovery phase is PONV. Multiple routes involving receptors located both peripherally and centrally can initiate PONV. In the central nervous system, the nucleus tractus solitarius (vomiting center) and area postrema (chemoreceptor trigger zone) contain 20 high concentrations of 5-HT3 receptors [36]. Ondansetron is one 5-HT3 antagonist that has been shown to dramatically lower the incidence of PONV. Furthermore, a number of double-blind, randomized, controlled studies have demonstrated the effectiveness of ondansetron in comparison to other antiemetics [37].

Regarding the number of patients needed post-operative analgesia, it was significantly higher in the control group (47.1%) compared to neostigmine group (29.4%) ($p=0.03$) and ondansetron group (11.8%) ($p=0.01$).

This agreed with Shokrpour et al [25] Who found that the number of patients needed postoperative analgesia was significantly higher in the placebo compared to the ondansetron group ($P=0.01$).

Regarding the number of patients needed post-operative analgesia with neostigmine, it was higher in the control group (47.1%) compared to the neostigmine group (29.4%) but was statistically non-significant ($p>0.05$).

Mofeed et al [38] found that there was increase in the number of patients needed post-operative analgesia in the control group (53.3%) compared to the neostigmine group (23.3%) and it was statistically significant ($P<0.001$).

In the current study, as regards the PDPH associated symptoms, there was no statistically significant difference between the three studied groups as regard constipation, tiredness, drowsiness and dizziness. However, there is a statistically significant difference in the incidence of neck rigidity between the three study groups at 48 hours, 7 days and 14 days following the delivery. No reported neck rigidity was reported in the ondansetron group. The incidence was lower in the neostigmine and atropine group compared to the control group, it didn't achieve a statistically significant difference.

Mahmoud et al [32] reported that the incidence of neck stiffness, was comparable in the 2 groups (neostigmine and atropine versus a saline placebo).

CONCLUSIONS

Intravenous injection of 0.08 mg/kg ondansetron is more effective in lowering the incidence and severity of post-dural puncture headache compared to 20g/kg neostigmine plus 10g/kg atropine intravenous injection in parturients undergoing spinal anesthesia for elective cesarean section.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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Table S1: Postoperative VAS score to determine the post dural puncture headache along the follow up of the parturients in the 3 studied groups.

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance	
After 6 hours Median (range)	0 (0)	0 (0)	0 (0)	KW= 0.96 P= 0.998	P1=0.68 P2=0.99 P3=0.99
After 12 hours Median (range)	0 (0)	0 (0)	0 (0)	KW= 0.961 P= 0.998	P1=0.99 P2=0.4 P3=0.46
After 24 hours Median (range)	4 (2-5) *	4 (2-5) •	2 (1-4)	KW= 13.125 P= 0.001	P1=0.003 P2=0.004 P3=0.006
After 48 hours Median (range)	4 (3-5) *	3 (2-5) •	2 (1-3)	KW= 30.380 P < 0.001	P1=0.0001 P2<0.0001 P3=0.0001
After 7 days Median (range)	3 (2-4) *	3 (2-4) •	2 (0-3)	KW= 22.619 P < 0.001	P1=0.0001 P2=0.0001 P3=0.01
After 14 days Median (range)	2 (0-3)	1 (0-3)	1 (0-3)	KW= 7.681 P= 0.899	P1=0.99 P2=0.05 P3=0.06

Quantitative data were expressed as median (range).
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group
KW: Kruskal Wallis test. n: number of parturients. Statistically significant ($p \leq 0.05$).
P1 group C versus N. P2 group C versus O. P3 group N versus O.
*: statistically significant compared toN&O groups • **:** Statistically significant compared to O group

Table S2: Number of patients needed postoperative analgesia (Paracetamol and theophylline) in the 3 studied groups.

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance
Patients needed Paracetamol	8 (47.1%)*	5 (29.4%)	2 (11.8%)	P1=0.03 P2=0.01 P3=0.2
Patients needed theophylline	0 (0%)	0 (0%)	0 (0%)	-

Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group
P1 group C versus N. P2 group C versus O. P3 group N versus O.
* : statistically significant compared to N&O groups.

Table S3: Neck rigidity in the parturients in the three studied groups at different times.

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance	Fischer exact
After 6 hours	0 (0)	0 (0)	0 (0)	-	
After 12 hours	0 (0)	0 (0)	0 (0)	-	
After 24 hours	6 (35.3%)	4 (23.5%)	2 (11.8%)	MC = 2.615 P= 0.270	P1=0.45 P2=0.1 P3=0.36
After 48 hours	6 (35.3%)*	3 (17.6%)	0 (0%)	MC = 7.286 P= 0.026	P1=0.24 P2=0.007 P3=0.06
After 7 days	5 (29.4%)*	3 (17.6%)	0 (0%)	MC = 5.634 P= 0.050	P1=0.8 P2=0.01 P3=0.06
After 14 days	0 (0%)	0 (0%)	0 (0%)	-	

Qualitative data were expressed as number (Percent)
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group.
MC: Monte-Carlo test. n: number of parturients. *: Statistically significant compared to O group
P1 group C versus N. P2 group C versus O. P3 group N versus O.

Table S4: Associated postoperative side effects of the parturients in the study groups:

Variables	Group C (n=17)	Group N (n=17)	Group O (n=17)	Test of significance	Fischer exact
Constipation n (%)	5(29.4%)	4(23.5%)	3(17.6%)	MC= 0.654 P= 0.721	P1=0.69 P2=0.8 P3= 0.67
Tiredness n (%)	4 (23.5%)	4 (23.5%)	3 (17.6%)	MC= 0.232 P= 0.891	P1=1 P2=0.67 P3=0.67
Drowsiness n (%)	4 (23.5%)	1 (5.9%)	1 (5.9%)	MC = 3.400 P= 0.183	P1=0.14 P2=0.14 P3=1
Dizziness n (%)	3 (17.6%)	0 (0%)	1 (5.9%)	MC = 3.798 P= 0.150	P1=0.06 P2=0.28 P3=0.31

Qualitative data were expressed as number (Percent).
Group C: control group. Group N: neostigmine and atropine group. Group O: ondansetron group.
MC: Monte-Carlo test. n: number of parturients.
P1 group C versus N. P2 group C versus O. P3 group N versus O.