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Original Article

The Prophylactic Effect of Acetaminophen and Caffeine on Post Dural Puncture Headache after Spinal Anesthesia for Cesarean Section: A Randomized Double-Blind Clinical Trial

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Abstract

Background: Post-dural puncture headache (PDPH) is the most common complication following spinal anesthesia among parturients undergoing cesarean section surgery. The purpose of this study was to evaluate the effectiveness of acetaminophen and caffeine in preventing PDPH.

Methods: This double-blind, randomized clinical trial was conducted on 96 obstetric women, who were candidates for elective cesarean section. Following the randomization of participants into two groups, participants in the intervention group received tablets of acetaminophen (500 mg)+caffeine (65 mg), and participants in the control group received placebo tablets orally 2 hours before spinal anesthesia induction and then every 6 hours after surgery up to 24 hours. All parturients were evaluated for frequency and intensity of PDPH every 6 hours until 24 hours after surgery and then 48 and 72 hours after surgery. Overall satisfaction during the first 72 hours of postpartum was evaluated. The data were analyzed using SPSS software. $P<0.05$ was considered statistically significant.

Results: Participants in the intervention group were 70% less likely to experience PDPH after spinal anesthesia (OR=0.31 P=0.01, 95% CI [0.12-0.77]). They also experienced significantly milder headaches 18 hours, 48 hours, and 72 hours later. Participants in the intervention group reported higher levels of satisfaction at the end of the study (P=0.01). No side effects related to the intervention were reported.

Conclusion: Prophylactic administration of acetaminophen+caffeine decreases 70% the risk of PDPH and significantly attenuates pain intensity in obstetric patients who underwent spinal anesthesia for cesarean section.

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Keywords ● Acetaminophen ● Caffeine ● Post-dural puncture headache ● Anesthesia, spinal

What's Known

- The pharmacological approach is an approved strategy for managing postdural puncture headache (PDPH) after spinal anesthesia during cesarean delivery.
- The therapeutic effects of acetaminophen and caffeine have been studied, and their combination was recognized to be a safe means of treating PDPH.

What's New

- The present study investigated the prophylactic effect of this combination among obstetrics. Patients were given acetaminophen and caffeine before receiving spinal anesthesia.
- It was found that women who received prophylactic medication were 70% less likely to develop PDPH. They also had significantly less severe headaches and higher overall satisfaction.

Introduction

Spinal anesthesia is a neuraxial technique in which a local anesthetic agent is injected directly into the intrathecal space. This technique is commonly used in surgical operations involving

the lower abdomen and pelvis.[1] It is also the most commonly used anesthetic technique for cesarean section due to its simplicity, fast effect, and adequate analgesia and muscle relaxation.[2, 3] Spinal anesthesia, the same as other anesthetic techniques, has side effects. Patients frequently report nausea, vomiting, back pain, and a severe postural headache, known as post-dural puncture headache (PDPH).[4]

Considering that female sex, young age, and pregnancy are risk factors for developing PDPH, this condition is one of the most common side effects of spinal anesthesia in obstetric patients.[5] This severe headache disrupts baby care, extends hospital stays, healthcare expenditures, causes discomfort, and dissatisfaction.[6, 7] As the devastating side effect of PDPH following cesarean section under spinal anesthesia has been cleared, the preventive management of this complication seems reasonable.

Several studies have been conducted on different prophylactic and therapeutic techniques to control PDPH, ranging from safer treatments such as saline or blood patches to more experimental ones such as cosyntropin or morphine injection.[8-10] However, when it comes to obstetric patients and their specific postpartum condition, we must proceed cautiously to achieve a satisfactory level of efficacy while also ensuring the safety of the mother and her breastfed newborn.

In this way, this randomized clinical trial was designed to investigate the prophylactic and therapeutic effects of acetaminophen and caffeine on PDPH in obstetric patients undergoing spinal anesthesia for delivery, while also monitoring the side effects and overall patient satisfaction.

Patients and Methods

This single-center randomized, double-blind, parallel clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT2014 1009019470N98) and conducted in the Hafez Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran), in April 2020. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.448) and conformed to the ethical guidelines of the Declaration of Helsinki (1975). Written informed consent was obtained from the participants before their enrollment.

Study Population

All obstetric patients who were eligible for a full-term elective cesarean delivery under spinal anesthesia were included. Patients with a history of migraine headaches, cardiovascular disease, taking anticonvulsants and serotonin reuptake inhibitors, and having contraindications for spinal anesthesia were excluded from the study. A total of 96 eligible patients were randomly assigned to intervention and control groups using the block randomization method. A nurse who was not involved in the study assessment assigned the patients to random groups.

Sample Size

At first, a pilot study with 34 participants and 17 cases in each group was conducted. The proportion in one group was 23.5% (P_1), and the other was 52.9% (P_2). Using the below formula, a sample of 48 patients in each group with a total of 96 provided a power of 80% (β=20%) at a 0.05 level of significance (α=0.05).

$$n=(Z_{1-\alpha/2}+Z_{1-\beta})^2*[P_1(1-P_1)+P_2(1-P_2)]/(P_1-P_2)^2$$

Study Intervention

All participants had overnight fasting and were permitted to drink clear liquid up to 2 hours before the operation. The recruited cases were assigned to each group using block randomization in 16 blocks of size 6. The blocks list was extracted from (www.sealedenvelope.com). Both the enrolled patients and anesthesiologists who provided the intervention and assessed patients' postoperative conditions, were blinded to the group randomization.

All parturients in the intervention group received oral acetaminophen+caffeine tablets (500+65 mg, respectively; Jalinous, Iran) 2 hours before spinal anesthesia and then every 6 hours up to 24 hours post spinal anesthesia. In addition, all parturients in the control group received an oral placebo 2 hours before spinal anesthesia and then every 6 hours up to 24 hours post spinal anesthesia. Then, they were monitored for 72 hours after the procedure.

After randomizing eligible parturients, they lay supine on the operating table with 10 degrees of left uterine displacement and received oxygen 6 L/min using a simple face mask. All cases had intravenous access through peripheral venous catheter 18 G (Vanosafe, India) and received 10 mL/Kg ringer solution (Ghazi 0.5 L INF P-Bottle, Iran) for hydration. Standard ASA monitoring was employed, which included noninvasive automated systolic, diastolic, and mean arterial blood pressure monitoring, heart rate, and pulse oximetry. After recording baseline hemodynamic parameters, the attending physician of obstetric anesthesia administered the spinal anesthesia in a sitting position through interspace L3-L4 or L4-L5 using Quincke spinal needle No: 25 (Dr.

Japan Co., Ltd., Japan). Then, 9 mg of hyperbaric bupivacaine (Bupivacaine Injection 20 mg/4 mL (0.5%), spinal, Mylan S.A.S, France) and 10 µg of fentanyl (Fentanyl Mylan Injection 50 mµg/mL, 2 mL, Mylan S.A.S, France) were injected into the subarachnoid space. The parturients were again laid down, and after confirmation of appropriate sensory and motor block, a cesarean section was conducted.

Study Assessments

The participant's demographic data, including age, weight, height, BMI, preoperative and postoperative nausea and vomiting (N/V), and vital signs, including heart rate, blood pressure, and oxygen saturation, during the surgery were recorded in both groups.

Bradycardia was defined as HR<60. In the case of bradycardia, 0.5 mg intravenous (IV) atropine (0.5 mg/mL Caspian Tamin Pharmaceutical Company, Iran) was administered. Hypotension was defined as a fall of systolic blood pressure (SBP) to ≤90 mmHg or 30% less than the basal SBP. Therefore, in case of hypotension, 5 mg ephedrine (Ephedrine Hydrochloride Injection Parenteral 50 mg/1 mL, Sterop, Belgium) IV was administered.

The primary outcome of this study was the evaluation of the frequency and severity of PDPH. The secondary outcomes included the amount of postoperative analgesic consumed, postoperative N/V, and overall satisfaction. PDPH is defined as a headache in the frontal or occipital area with a throbbing nature and usually accompanied by photophobia, blurred vision, double vision, decreased hearing with tinnitus, dizziness, nausea, and vomiting. PDPH is generally aggravated by an upright position and is relieved by a decumbent posture. Regarding that PDPH typically occurs within 24-72 hours following dural puncture,[11] we recorded the frequency and severity of PDPH (measured by a visual analog scale [VAS]) every 6 hours till 24 hours after surgery, and then 48 and 72 hours thereafter.

After 72 hours, the overall post-surgical satisfaction was evaluated. Participants were asked to rate their satisfaction as follows: Completely unsatisfied (1), Unsatisfied (2), Neutral (3), Satisfied (4), Completely satisfied (5).

Parturients with moderate post-partum pain (4≤VAS≤7) received 1 g Apotel (Acetaminophen 1 gr, 150 mg/mL, Aburaihan Pharmaceutical Co., Iran) intravenously, and patients with severe post-partum pain (VAS>7) received pethidine (Relidin 50 mg ampule, Aburaihan Pharmaceutical Co., Iran) 50 mg intramuscularly (IM).

Statistical Analysis

Continuous data were presented as mean±SD or median (IQR) and compared using the *t* test and Mann-Whitney-U test. Categorical data were expressed as frequencies (percentages) and compared using the Chi square and Fisher's

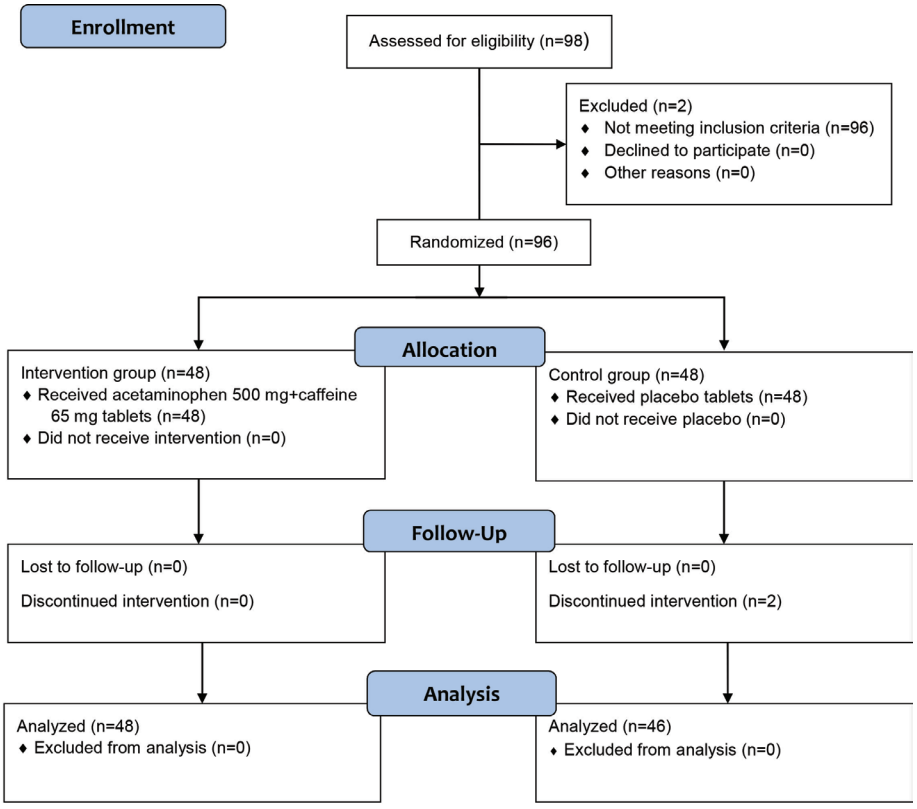

Figure 1: The CONSORT diagram demonstrates the allocation process of the participants throughout the trial.

exact tests. The binary logistic regression test was used to analyze the association between receiving intervention and the frequency of PDPH in 24, 48, and 72 hours after surgery. All the statistical analyses were performed using IBM Statistics SPSS software for Windows (version 26.0, Armonk, NY: IBM Corp). P<0.05 was considered statistically significant.

Results

Data from 48 participants in the case group and 46 in the control group were recorded and analyzed. A flow diagram illustrating parturients recruitment is shown in figure 1.

The demographic characteristics of each group are presented in table 1.

For analysis of the frequency of PDPH among groups, the univariate binary logistic regression test was used which indicated that participants in the intervention group were 70% less likely to PDPH after spinal anesthesia (OR=0.31 P=0.01, 95% CI [0.12-0.77]). After spinal anesthesia, the prophylactic administration of acetaminophen and caffeine decreased the chance of PDPH development by 82%, 68%, and 70% in the first 24, 48, and 72 hours, respectively (table 2).

Aside from frequency, the severity of PDPH was also recorded and analyzed every 6 hours till 24 hours after surgery, and then 48, and 72 hours after surgery. Table 3 shows the result of the PDPH severity analysis.

To assess the complications presented by participants, vital signs were recorded during the procedure. The frequency of bradycardia, hypotension, and preoperative and postoperative N/V were recorded and analyzed.

In the intervention group, 5 (10.4%) cases developed operative bradycardia and received atropine. None of the participants in the placebo

Table 1: Demographic characteristics of participants

Characteristics	Acetaminophen+Caffeine (n=48)	Placebo (n=46)	P value
Age (year)	31.54±4.12	32.83±4.89	0.17
Weight (Kg)	77.83±11.72	79.11±10.32	0.57
Height (cm)	159.23±7.10	158.80±4.93	0.73
BMI (Kg/m^2)	30.74±4.53	31.40±4.00	0.45

BMI: Body mass index; Data are expressed as mean±SD. The *t* test was used to compare means between groups. P<0.05 was considered statistically significant.

Table 2: Univariate analysis of frequency of PDPH in intervention vs. Control group

Variables	PDPH in Acetaminophen+ Caffeine group (n=48)	PDPH in the placebo group (n=46)	Odds ratio (95% CI)	P value
After 24 h	2 (4.2)	9 (19.6)	0.18 (0.04-0.88)	0.03
After 48 h	7 (14.6)	16 (34.8)	0.32 (0.12-0.87)	0.02
After 72 h	10 (20.8)	21 (45.7)	0.31 (0.13-0.78)	0.01

PDPH: Post-dural puncture headache; Frequency is expressed as n (%). A binary logistic test was used to analyze the frequency of PDPH among groups. P<0.05 was considered statistically significant.

Table 3: Severity analysis of PDPH during the study

Pain scale	Acetaminophen+Caffeine (n=48)	Placebo (n=46)	P value
VAS 6 h	0 (0-0)	0 (0-0)	0.99
VAS 12 h	0 (0-0)	0 (0-0)	0.99
VAS 18 h	0 (0-0)	0 (0-10)	0.01
VAS 24 h	0 (0-10)	0 (0-10)	0.07
VAS 48 h	0 (0-10)	0 (0-10)	0.04
VAS 72 h	0 (0-10)	0 (0-10)	0.01

VAS: Visual analogue scale; Data are expressed as median (Q1-Q3). Mann-Whitney test was used to compare medians between groups. P<0.05 was considered statistically significant.

Table 4: Patients' satisfaction 72 hours after cesarean section

Variable	Acetaminophen+Caffeine (n=48)	Placebo (n=46)	P value
Completely unsatisfied	0 (0)	4 (8.7)	0.001
Unsatisfied	3 (6.20)	10 (21.7)	
Neutral	7 (14.6)	9 (19.6)	
Satisfied	30 (62.5)	13 (28.3)	
Completely satisfied	8 (16.7)	10 (21.7)	

Data are expressed as frequency (percentage). The Chi square test was used to compare frequencies between groups. P<0.05 was considered statistically significant.

group developed this complication (P=0.06). Thirty-five participants in the intervention group and 25 in the placebo group developed operative hypotension and received ephedrine (P=0.08).

While none of the cases reported preoperative N/V, there were records of three patients in the intervention group and four in the placebo group that had post-operative N/V, which was not statistically significant (P=0.71).

To control pain, 3 (6.2%) cases in the intervention group received 1 g of apotel IV (P=0.24). None of the cases received pethidine.

At the end of the study, patients were asked about their overall satisfaction. It was observed that participants who received acetaminophen and caffeine reported significantly higher levels of satisfaction than those in the placebo group. The reports of the participants' satisfaction are summarized in table 4.

Discussion

In this randomized clinical trial, the administration of acetaminophen and caffeine as a preventive method was investigated. It was found that parturients who received 500 mg acetaminophen+65 mg caffeine before induction of anesthesia and then every 6 hours were 70% less likely to develop PDPH in the first 72 hours after surgery. Except for the first 24 hours after surgery, parturients in the intervention group experienced significantly milder PDPH from 18 hours after surgery to 72 hours later. The prophylactic administration of acetaminophen and caffeine not only significantly decreased the frequency and intensity of PDPH after spinal anesthesia for cesarean section, but also increased the mothers' overall satisfaction in the postpartum period (P=0.01). PDPH was the most prevalent complication following spinal anesthesia among obstetric patients.[12] It was reported that up to 81-88% of the pregnant women might develop PDPH.[13] Since many mothers could not provide proper care for their newborns as a result of this headache, the preventive methods for PDPH could improve the motherhood experience, increase baby care, and shorten the length of hospital stay.[7, 14, 15]

Several interventional and medical treatments are used to control PDPH in patients. Acetaminophen and nonsteroidal anti-inflammatory drugs are among them.[16] Although acetaminophen is one the most often used medications for PDPH treatment,[17] the results of randomized controlled clinical trials (RCTs) on its effectiveness are inconclusive. Mahoori and colleagues reported that acetaminophen had a less significant effect on PDPH treatment than theophylline, gabapentin, and pregabalin.[18, 19]

Caffeine is also one of the medical treatments for PDPH, and there are reports on the efficacy of both oral and intravenous caffeine administration. Zeger and colleagues found that administering caffeine sodium benzoate was 80% effective in the treatment of PDPH.[20] However, clinical evidence did not appear to support caffeine's efficacy in preventing PDPH.[21]

Several studies investigated the prophylactic effects of acetaminophen and caffeine combination. Esmaoglu and others studied the effect of the administration of 500 mg acetaminophen and 75 mg caffeine an hour before lower extremity surgery and then every 6 hours till 72 hours. They found no significant difference in the frequency of PDPH between placebo and intervention groups (11/70 in the placebo group and 10/70 in acetaminophen+75 mg caffeine group).[22] However, regarding sex-specified classification, a significant difference was observed. 23% of female patients in the placebo group and 7% of female patients in the intervention group developed PDPH. The present study did not provide any sex-specific statistical analysis of the findings.

In another RCT on the prophylactic effect of acetaminophen and caffeine on the frequency and intensity of PDPH, patients undergoing lower extremity surgery received the compound of 500 mg acetaminophen, 65 mg oral caffeine, and 8 mg venous dexamethasone an hour before spinal blocking in the intervention group. In this study, Masoudi and colleagues reported that although taking this prophylactic combination was associated with a decrease in frequency rate, intensity, and length of PDPH, no statistically significant effect was observed.[23]

Although there have been few studies on the prophylactic effect of the acetaminophen and caffeine combination, previous research suggested that the acetaminophen and caffeine combination might be effective in managing and reducing the pain of PDPH after cesarean section.[24] In the present study, it was observed that the prophylactic administration of acetaminophen and caffeine in parturients who underwent spinal anesthesia for cesarean section significantly reduced the chance of PDPH development in 24, 48, and 72 hours after surgery.

The small sample size of this clinical trial, as well as the delicate differentiation of PDPH from other types of headaches among enrolled cases, might lead to bias in this study. Therefore, more research is required to confirm the safety and efficacy of prophylactic administration of acetaminophen and caffeine among obstetrics patients

Conclusion

The findings of the present study indicated that prophylactic administration of 500 mg acetaminophen and 65 mg caffeine compound to parturients undergoing spinal anesthesia for cesarean section decreased the chance of development of PDPH by 70%. Participants who received prophylactic medication also reported milder headaches and higher levels of satisfaction with their postpartum experience 72 hours after the procedure.

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Authors' Contribution

All authors had substantial contributions to the conception and design of the work, acquisition, analysis, and interpretation of data for the work, drafting the work and reviewing it critically for important intellectual content, and final approval of the version to be published. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Mohammad Ali Sahmeddini and Naeimehossadat Asmarian, as the Editorial Board Members, were not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the article without their knowledge.

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