Original Article

Effect of venous dexamethasone, oral caffeine and acetaminophen on relative frequency and intensity of postdural puncture headache after spinal anesthesia

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Abstract

Background: Postdural puncture headache (PDPH) is a relatively common complication after regional anesthesia, especially in younger people, bothersome to patients and needs prophylaxis to prevent this complication. This study was conducted aiming to determine the preventive effect of dexamethasone plus caffeine and acetaminophen on relative frequency and intensity of PDPH after spinal anesthesia.

Materials and Methods: In a clinical trial study, 90 candidates for the lower extremities orthopedic elective operation were divided into two groups of 45 individuals each. Intervention group received the compound of 500 mg acetaminophen +65 mg oral caffeine +8 mg venous dexamethasone an hour before spinal blocking, and the control group received placebo tablets + a dexamethasone equivalent volume of venous normal saline. The level of postoperative headache at the time of entrance to recovery and discharge, 6, 12, 24, 48, and 72 h postoperatively were measured based on Visual Analog Scale criterion in the two groups and then compared with each other.

Results: During the study, 24 patients in the control group and 17 patients in the intervention group were afflicted with headache; however, with no significant difference ($P = 0.14$). Total frequency of headache incidence was 35 times in the control group and 27 times in the intervention group ($P = 0.32$).

Conclusions: Though the taking of acetaminophen + caffeine + dexamethasone is associated with a decrease in headache intensity and duration and decrease in PDPH incidence, compared with placebo, however, no essentially and statistically significant effect was produced.

Key Words: Acetaminophen, caffeine, dexamethasone, headache, postdural puncture

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Received: 07.04.2015, **Accepted:** 31.08.2015

INTRODUCTION

Postdural puncture headache (PDPH) is a relatively common complication after regional anesthesia, with prevalence of 0.5–24%,[1] bothersome to patients and sometimes a prohibiting factor for spinal anesthesia. PDPH risk factors include the female sex, youth, pregnancy, history of headache or previous PDPH, type of operative procedure, technique of spinal

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.180635

How to cite this article: Masoudifar M, Aghadavoudi O, Adib S. Effect of venous dexamethasone, oral caffeine and acetaminophen on relative frequency and intensity of postdural puncture headache after spinal anesthesia. Adv Biomed Res 2016;5:66.

anesthesia, several attempts for dural puncture, and needle tip presentation.[1-12]

Different mechanisms are responsible for PDPH formation. However, its major etiology has not been completely recognized. Distension of intracranial vessels and increase in brain blood flow can play a primary role in PDPH formation.[4] Now-a-days, many surgeries are performable under spinal anesthesia, and because of nonexistence of many complications due to general anesthesia and in cases when general anesthesia is not possible for patients, spinal anesthesia is applied.

Lower extremities orthopedic surgeries are easily performable using spinal blocking. Yet the prevalence of headache, especially in younger people causes the need for prophylaxis to prevent this complication. For this purpose, different studies have so far been conducted on medicines and preventive effect on the incidence of intra- and post-operative complications, including the prevention of headache incidence, with different and sometimes contradicting results.[1,4-7,11,13-16] For example, in their study conducted in 2011 at Kerman University of Medical Sciences, Doroudian *et al*. studied the effect of dexamethasone on the prevention of PDPH incidence after spinal anesthesia in lower extremities orthopedic surgeries and concluded that dexamethasone does not significantly influence the prevention of PDPH incidence; however, decreases its intensity.[5] Yet in the study by Yousefshahi *et al*., conducted at Tehran University of Medical Sciences, application of dexamethasone increased PDPH incidence and intensity after spinal anesthesia for cesarean sections, with no effect on postoperative nausea and vomiting.[1] In their study conducted in Turkey, Esmaoglu *et al*. concluded that acetaminophen-caffeine compound is not effective in the prevention of PDPH.[4] Yet in their study conducted in Boston, Camann *et al*. concluded that application of oral caffeine decreases PDPH intensity in patients under spinal anesthesia.[6] In another study, cosyntropin was used to decrease headache after spinal anesthesia and it was concluded that application of cosyntropin delays the incidence of PDPH.[7] This study was designed taking into consideration the limited research conducted in relation to administration of prophylactic medications and existence of contradiction in the obtained results and also lack of any study in prescribing the combination of dexamethasone, caffeine, and acetaminophen together in the prevention of PDPH. In this study, we aimed to determine the preventive effect of venous dexamethasone, oral caffeine, and acetaminophen medicinal compound on relative frequency and intensity of PDPH after spinal anesthesia and in comparison with the control group.

MATERIALS AND METHODS

This is a double-blind, randomized clinical trial study (registration number: 391198 at Isfahan University of Medical Sciences) conducted in 2014 at Isfahan Ayatollah Kashani Training Treatment Center whose statistical universe were the patients admitted for the lower extremities orthopedic elective operation at the above-mentioned hospital. The study's inclusion criteria were the 8–75 years age group, no addiction to narcotics and tranquilizers, no consumption of alcohol, American Society of Anesthesiologists category 1 and 2, and patients' consent for participation in the study. Exclusion criteria were considered to be technique change in anesthesia during operation to general anesthesia, more than one try at spinal anesthesia, operation lengthening for over 2.5 h, and patients bleeding much leading to the need for blood transfusion.

The sample size required in this study was determined to be 43 patients in either group using the sample size estimation formula to compare the two mean values (mean pain intensity in two intervention and control groups) considering confidence level of 95%, test power of 80%, postoperative pain intensity, standard deviation estimated at the level of 1.33, and the least significant difference between the two groups considered to be at the level of 0.8. For more confidence, 45 patients were studied in each group.

Work method

The proposal was approved and the permit was received from the university's Medical Ethics Committee. The patients of the statistical universe, the candidates for the lower extremities orthopedic elective operation who underwent spinal anesthesia in Kashani Hospital orthopedic operation room, provided their written consents and were selected. All patients were similarly treated with venous liquid therapy using 7 cc/kg of Ringer serum and were divided into two groups using the block random allocation method. In the intervention group, before spinal blocking, Codimal tablets, containing 500 mg of acetaminophen +65 mg of caffeine, were orally administered an hour before operation with 100 cc of water, and half an hour before operation, 8 mg of venous dexamethasone was administered. In the control group, placebo tablets +100 cc of water were orally given an hour before operation and 2 cc of venous normal saline (equivalent to 8 mg of dexamethasone) was administered half an hour before operation. The doses of acetaminophen and caffeine were selected according to the previous studies [4-6] and available compound of Codimal tablets

and considering the additive effect of dexamethasone on PDPH.

Blinding was performed as follows: Dexamethasone and normal saline were prepared by one of the anesthetists and Codimal tablets were administered by him an hour before operation at the inclusion time. Pain intensity and the incidence of nausea and vomiting were studied by the researcher who was unaware of the medicinal compound applied.

Both groups underwent spinal anesthesia using 3.5 cc of 0.5% marcaine +25 mg of fentanyl for spinal anesthesia. The L4–L5 or L5–S1 space and spinal needle number 23[17] were used through the midline. The amount of liquid therapy was the same in both groups, 10 cc/kg/h, based on the intraoperative bleeding level. The block level was assessed and recorded at the beginning of the operation in all patients.

For sedation, 2–3 mg of midazolam was intraoperatively administered to all patients. At the end of the operation, after admission to recovery, before discharge from recovery, and 6, 12, 24, 48, and 72 h after operation, the levels of headache, nausea, and vomiting were measured based on Visual Analog Scale (VAS) criterion and were recorded in each patient's special form.

In each phase, if patients' pain intensity (based on VAS criterion) exceeded 3, 325 mg/4 h of oral acetaminophen tablets would be administered, and in case of no response to this medication, 0.05 mg/kg prn of venous morphine was used.

The results were analyzed using SPSS statistical software, version 22 (IBM Corp., Armonk, NY), statistical *t*-test (for comparison of quantitative data between two groups), Chi-square test (for comparison of qualitative data between the two groups), and repeated measures ANOVA (for analysis of quantitative changes during intervention).

RESULTS

In this study, 90 patients undergoing surgery under spinal anesthesia were randomly divided into two equal groups. The demographic parameters were similar in both the study groups ($P > 0.05$) [Table 1]. The mean volume of liquids received by the two (control and intervention) groups were 1684.4 ± 492.2 ml and 1711.1 ± 457.9 ml, respectively, with no significant difference according to *t*-test ($P = 0.79$) [Table 1].

According to the obtained results, no patient was intraoperatively afflicted with nausea and vomiting. Yet during stay in recovery, one patient (2.2%) in the intervention group and one patient (2.2%) in the control group were affected by nausea, with no case of vomiting incidence in recovery. Table 2 shows the frequency distribution of headache incidence from admission to recovery up to 72 h later in the two groups. According to this table, at the time of the patients' admission to recovery, more patients suffered from headaches in the intervention group. At the time of the patients' hospitalization in the ward, however, less patients had headache in the intervention group than in the control group, with no significant headache incidence (in the two groups) according to Chi-square, Fischer precise, and frequency distribution tests ($P > 0.05$). In general, during the study, 24 patients in the control group and 17 patients in the intervention group suffered from headache (35.3% vs. 37.8%), with no significant difference ($P = 0.14$). Total frequency of headache incidence was 35 times in the control group and 27 times in the intervention group. Based on Chi-square test, however, headache incidence frequency was not significantly different between the two groups ($P = 0.32$). Figure 1 shows headache incidence frequency from the admission to recovery up to 72 h later. According to this figure, 46.7% of control group and 62.6% of intervention group had no headache, at 7 times of this study, also 35.6% of control group and 26.7% of intervention group suffered from

Table 1: Demographic and general variables distribution in the two study groups

Variable	Group		*P*
	Control	Intervention	
Age (year)	37.7±17.4*	36.6±13.8	0.1
Weight (kg)	72.5±9.9	74.6±13.2	0.4
Sex (male/female) (*n* (%))	29/16 (64.4/35.6)	39/6 (86.7/13.3)	0.6
Volume of liquids received (ml)	1684.4±492.2	1711.1±457.9	0.79

*Mean±SD. Intervention group: Received 8 mg IV dexamethasone + 500 mg oral acetaminophen + 60 mg oral caffeine, control group: Received placebo with same volume of normal saline + placebo tablet. SD: Standard deviation, IV: Intravenous

Table 2: Headache incidence distribution during the postoperative period in the two study groups

Time	Group		*P*
	Control	Intervention	
Admission to recovery	1 (2.2)*	4 (8.9)	0.36
Discharge from recovery	2 (4.4)	3 (6.7)	0.99
6 h later	2 (4.4)	3 (6.7)	0.99
12 h later	7 (15.6)	2 (4.4)	0.16
24 h later	12 (26.7)	6 (13.3)	0.11
248 h later	7 (15.6)	5 (11.1)	0.54
72 h later	4 (8.9)	4 (8.9)	1

*Data are shown as *n* (%). Intervention group: Received 8 mg IV dexamethasone + 500 mg oral acetaminophen + 60 mg oral caffeine, control group: Received placebo with same volume of normal saline + placebo tablet. IV: Intravenous

headache at least one time. 13.3% of control group and 4.4% of intervention group twice had headache and 2.2% of control group and 4.4 of intervention group suffered 3 times from headache.

Figure 2 shows headache intensity during the patients' stay in recovery up to 72 h later in the two groups.

The mean headache time in the patients suffering from headache during intervention was 94 ± 19.7 min in the control group and 43.7 ± 10 min in the intervention group, and according to *t*-test, headache time was significantly lower in the intervention group ($P = 0.025$) [Figure 3].

During the study, 18 patients in the control group and 12 patients in the intervention group took excess acetaminophen (40% vs. 26.7%). Yet according to Chi-square test, the difference (between the two groups) was not significant ($P = 0.18$). The mean acetaminophen taken was 173.9 ± 44.8 mg in the control group and 101.7 ± 29.3 mg in the intervention group, and according to *t*-test, no significant difference was observed between the two groups ($P = 0.18$). Three patients in the control group and one patient in the intervention group accordingly used morphine for pain relief (6.7% vs. 2.2%). Yet according to Fisher precise test, the difference (between the two groups) was not significant ($P = 0.62$). The amount of the morphine administered to each patient was 5 mg.

DISCUSSION

This study generally aimed to determine the preventive effect of venous dexamethasone, oral caffeine, and acetaminophen medicinal compound on relative frequency and intensity of postdural puncture headache after spinal anesthesia and comparison with the control group. In this study, two groups of 45 patients each undergoing surgery with spinal anesthesia were studied [Figure 4]. Regarding age, sex, weight distribution, and the amount of the liquids administered, the two groups did not show any significant difference, and no interrupting effect of them was observed upon the study of headache incidence.

From the start of entrance to recovery up to 72 h after operation, the patients were studied for headache incidence and other complications including nausea and vomiting. According to the obtained results no patient suffered from nausea and vomiting during operation. Yet during stay in recovery, one patient of the group receiving placebo and one patient in the group receiving dexamethasone + acetaminophen + caffeine were afflicted with nausea. However, no case of vomiting incidence was observed in recovery. Regarding headache incidence at the start of entrance to recovery, two patients in the control group and three patients in the intervention group suffered from headache. Yet 6 to 72 h after operation, more patients suffered from headache in the control group than in the intervention group, with no significant difference observed between the two groups.

On the other hand, headache incidence frequency and headache duration were not significantly different in the two groups, though headache frequency and duration were higher in the control group.

In our study, intervention group received dexamethasone, acetaminophen, and caffeine; although some studies have shown that preoperative application of dexamethasone has no significant effect on postoperative headache relief (1 and 5).

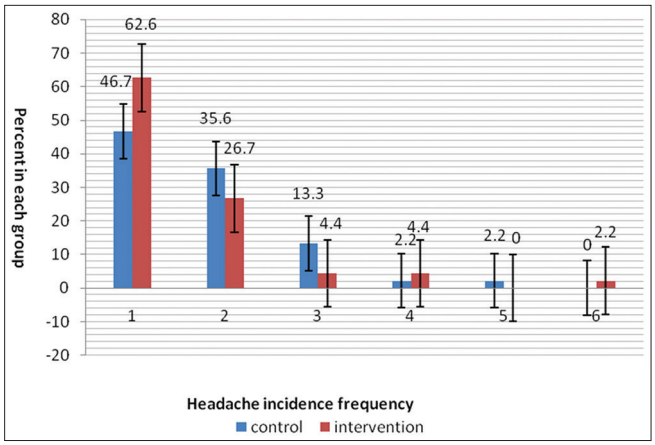

Figure 1: Headache incidence frequency (%) in the two study groups. Intervention group: Received 8 mg intravenous dexamethasone +500 mg oral acetaminophen +60 mg oral caffeine. Control group: Received placebo with same volume of normal saline + placebo tablet

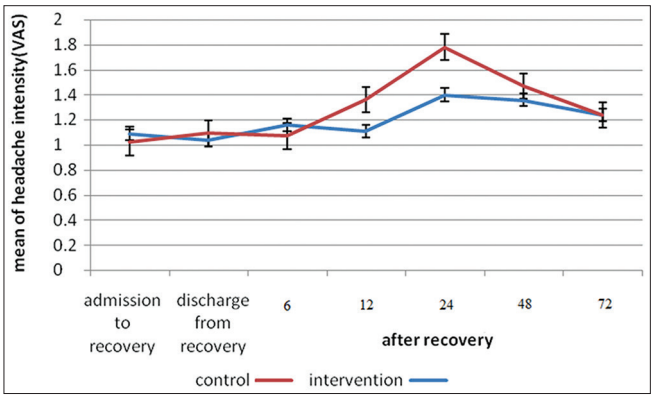

Figure 2: Mean headache intensity from admission to recovery up to 72 h later in the two study groups. Intervention group: Received 8 mg intravenous dexamethasone +500 mg oral acetaminophen +60 mg oral caffeine. Control group: Received placebo with same volume of normal saline + placebo tablet

Yet the study by Hakim has been indicative of dexamethasone's positive effect on postoperative headache relief in spinal anesthesia.[7] On the other hand, the study by Esmaogla *et al*. in Turkey showed that application of acetaminophen + caffeine has no essential and statistically significant effect on postoperative headache incidence under spinal anesthesia.[4] Yet the study by Doroudian *et al*. has shown that application of dexamethasone has been associated with lower intensity of postoperative headache in spinal anesthesia.[5] It should be considered as a limitation in our study that we used spinal needle number 23 for all the patients, and if smaller needles have been used, it may result in significant differences between the two groups.

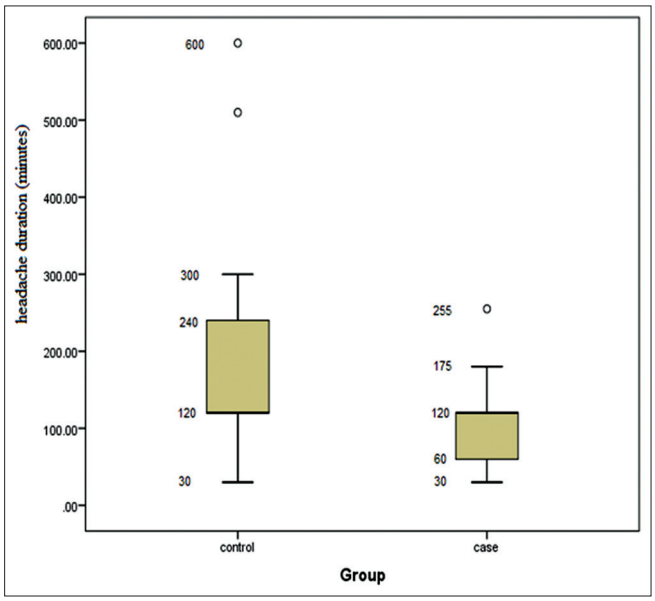

Figure 3: Median, range, 25% and 75% percentiles of headache duration (minutes) in the two study groups. Intervention group: Received 8 mg intravenous dexamethasone +500 mg oral acetaminophen +60 mg oral caffeine. Control group: Received placebo with same volume of normal saline + placebo tablet

During the study, 40% of the control group and 26.7% of the intervention group took excess acetaminophen. Yet the mean amount of the acetaminophen taken was significantly higher in the control group, with no significant difference observed in the two groups; however, 6.7% of the control group and 2.2% of the intervention group accordingly received morphine for pain relief, with no significant difference in the two groups. Regarding the results from this study and comparison with other studies, the general conclusion which can be arrived from this one is that, though associated with headache intensity and duration decrease and also with PDPH incidence decrease, application of acetaminophen + dexamethasone

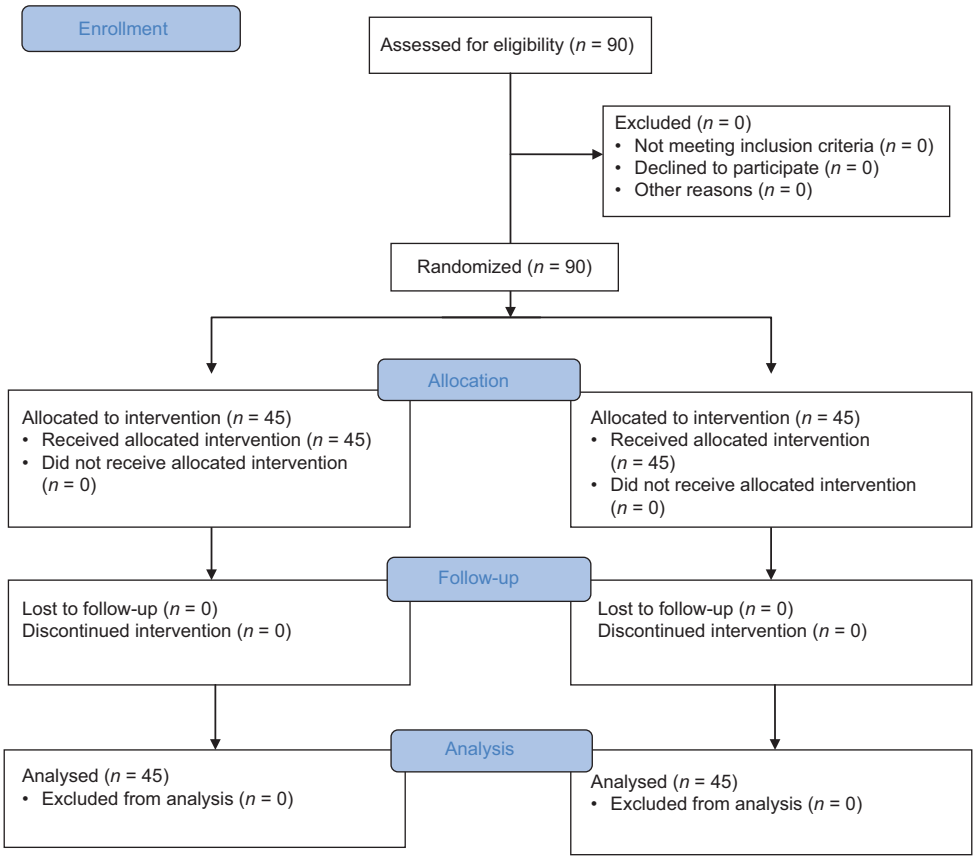

Figure 4: CONSORT flow diagram

displays no essential and statistically significant effect compared with placebo. It is, thus, advised to conduct much research on identifying methods of how to cope with PDPH incidence.

Financial support and sponsorship
Isfahan University of Medical Sciences.

Conflicts of interest
There are no conflicts of interest.

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