



## SHORT COMMUNICATION

### Effects of aminophylline and dexamethasone prophylaxis on headache after spinal anesthesia in cesarean section: a randomized clinical trial



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The term “Post-Dural Puncture Headache” (PDPH) refers to a headache that was confirmed using the third version of the international headache classification. It happens following a Lumbar Puncture (LP), worsens with sitting or standing, and resolves with relaxation and lying down.<sup>1</sup> Many drugs were investigated in a clinical trial design to prevent and treat this kind of headache. The dominant mechanism is a blockage in the CSF leak. The prone position also reduces headaches by decreasing pressure in the subarachnoid space.<sup>2</sup>

However, no study has ever been performed on the effect of aminophylline and dexamethasone prophylaxis on headache after spinal anesthesia in the C-section. Regarding the high incidence of this complication in patients under the C-section with spinal anesthesia and the lack of approval of a definitive drug for the prophylaxis, as well as limited reports on the effect of aminophylline and controversial findings on the effect of dexamethasone, we decided to design this study to compare the effects of dexamethasone and aminophylline on the prevention of headache after spinal anesthesia in the c-section.

The present randomized, double-blind clinical trial was conducted from November 2017 to November 2018 with the IRCT20180429039459N1 code and IR.KAUMS.MEDNT.REC.1396.50 Clinical trial registration number on 180

eligible patients aged 18 to 45 years with American Society of Anesthesiologists (ASA) physical status I–II who underwent elective C-section with spinal anesthesia for the first time in Shahid Beheshti Hospital in Kashan, Iran. According to the results of other studies, which determined the presence of pain in the dexamethasone (15.4%) and placebo (6.2%) groups,<sup>3</sup> and given the frequency of pain in the aminophylline (31.7%) and control (5%) groups was, and of in the other study,<sup>4</sup> the sample size was compared to the pain level in the two groups of dexamethasone and aminophylline, which required the largest sample size. The sample size in each group was calculated to be 60 for an accuracy of 5% and a confidence interval of 95%. Inclusion criteria were all pregnant women between the ages of 18 and 45 who underwent the elective C-section for the first time with spinal anesthesia. The exclusion criteria were history of previous headaches and migraines, presence of psychiatric problems, preeclampsia, coagulation disorders, peripheral neuropathy, spinal cord disorders, history of a prior surgery with spinal anesthesia, history of drug use and medication within 24 hours before C-section, history of peptic ulcer, arrhythmia, and seizures, converted spinal anesthesia to general anesthesia, history of allergy to aminophylline or dexamethasone, and a history of diabetes.

Following patients’ admission, informed consent was obtained, and then they were divided into one of the aminophylline, dexamethasone, or placebo groups using the

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**Table 1** The mean and standard deviation of age and BMI in the studied patients based on the type of intervention, frequency of intervention type in the patients studied based on the incidence of headache, the onset of postoperative pain, the use of analgesics and the frequency of attempts for spinal anesthesia and relationship between headache severity based on intervention groups in regression model.

Variables		Intervention type						p-value	
		Aminophylline		Dexamethasone		Placebo			
Age	Mean	27.43		27.57		28.30		0.571	
	SD	5.08		4.68		4.70			
BMI	Mean	27.40		25.17		25.68		0.367	
	SD	4.07		3.85		3.43			
			<b>Frequency</b>	<b>Percentage</b>	<b>Frequency</b>	<b>Percentage</b>	<b>Frequency</b>	<b>Percentage</b>	
Headache	Yes	7	11.7	11	18.3	13	21.7	0.386	
	No	53	88.3	49	81.7	47	78.3		
Headache severity	3.00	2	28.6	0	0	0	0	<0.001	
	4.00	5	71.4	2	18.2	0	0		
	5.00	0	0	9	81.8	1	7.7		
	6.00	0	0	0	0	12	92.3		
The onset of postoperative headache	4 hours	0	0	0	0	3	23.1	<0.001	
	12 hours	0	0	0	0	5	38.5		
	24 hours	6	85.7	2	18.2	5	38.5		
	48 hours	1	14.3	3	27.3	0	0		
	5 days	0	0	4	36.4	0	0		
	7 days	0	0	2	18.2	0	0		
Use of analgesics	Opium	31	51.7	30	50	30	50	0.978	
	NSAID	29	48.3	30	50	30	50		
Attempts for spinal anaesthesia	1	55	91.7	55	91.7	54	90	0.99	
	2	5	8.3	5	8.3	6	10		
		<b>Model</b>	<b>Coefficients<sup>a</sup></b>			<b>T</b>			
			<b>Unstandardized coefficients</b>	<b>Std. Error</b>	<b>Standardized coefficients</b>				
			<b>B</b>		<b>Beta</b>				
Aminophylline and placebo	Fix		2.610	0.211	–		12.371	<0.001	
	Intervention group		1.104	0.085	0.951		13.035	<0.001	
Dexamethasone and placebo	Fix		2.608	0.362	–		7.207	<0.001	
	Intervention group		1.105	0.140	0.860		7.907	<0.001	
Aminophylline and Dexamethasone	Fix		2.610	0.356	–		7.328	<0.001	
	Intervention group		1.104	0.212	0.794		5.217	<0.001	

SD, Standard Deviation.

<sup>a</sup> Dependent Variable: headache severity.

permuted block randomization method. A Visual Analog Scale (VAS) was taught to the patients. A subjective psychometric response scale was used to measure distinct behavioral or physiological phenomena such as pain based on a linear numerical gradient with 0 to 10 degrees. All patients received 7 mL of Ringer solution as a bolus per kg of body weight. The same person performed spinal anesthesia using a G25 cutting needle through L4–L5 or L3–L4 intervertebral spaces and with 12.5 mg of hyperbaric bupivacaine 0.5% with a median approach for all patients. After the neonate was born and the umbilical cord was clamped, aminophylline at a dose of  $1.5 \text{ mg} \cdot \text{kg}^{-1}$  and dexamethasone at a dose of  $0.1 \text{ mg} \cdot \text{kg}^{-1}$  with a final volume of 5 mL with normal saline was slowly infused intravenously into patients in the respective groups. The third group also received 5 mL of normal saline intravenously as a placebo. The frequency of attempts to perform spinal anesthesia, age, Body Mass Index (BMI), type, and the dose of consumed analgesics in the hospital and at home were recorded. The patients were asked about the presence or absence of headache and, if present, the quality, type, and severity of headache at 6, 12, 24, and 48 hours, 5 and 7 days after surgery, and information was recorded. The patient and the investigator were unaware of the study groups and the received drug type. The necessary treatment was appropriately applied in the presence of headaches in terms of severity. The VAS was used to record headache severity as follows: Score 0 for no pain, 1–3 for mild pain, 4–6 for moderate pain, and 7–10 for severe pain.

All study participants were informed about the research's basics and objectives, the confidentiality of the data, and the lack of mention of the questionnaire's name. Also, they could voluntarily refuse to participate in the study. The findings of the study were analyzed by SPSS 16 using measures of central tendency and dispersion. Based on the distribution, the data was displayed with associated charts and tables.

Differences in variables between three groups, according to the distribution, were measured by Chi-square, ANOVA, or Kruskal-Wallis tests. The Chi-Square test was used for inter-group comparison, and the incidence time between the three groups was compared by survival analysis. The significance level was considered to be 0.05.

The overall mean age of the patients was  $27.43 \pm 5.8$ , and the overall mean BMI was  $24.77 \pm 4.97$ . The detailed results of age and BMI are presented in Table 1. Table 1 shows no significant difference between age ( $p = 0.571$ ) and BMI ( $p = 0.367$ ), depending on the type of intervention in the patients, and the patients are homogeneous and comparable in this regard.

This study measured the frequency of intervention types in the patients studied based on the incidence of headache, the onset of postoperative pain, analgesics, and the frequency of attempts for spinal anesthesia; the results are presented in Table 1. As shown in Table 1, there is no significant relationship between the type of intervention and the incidence of headache, between the kind of intervention and the used medication, and between the kind of intervention and the frequency of attempts for spinal anesthesia. However, there is a significant relationship between the type of intervention and the onset of postoperative headache, whose onset is the fastest in the placebo group and the latest in the dexamethasone group. This study examined the relationship between headache severity and type of intervention in patients whose results are presented in Figure 1. This study's findings showed a significant relationship between headache severity and type of intervention in the studied patients ( $p < 0.001$ ), with the highest headache severity in the placebo group and the lowest headache severity in the aminophylline group.

According to the findings, there was no significant difference between the three groups in the rate of headache

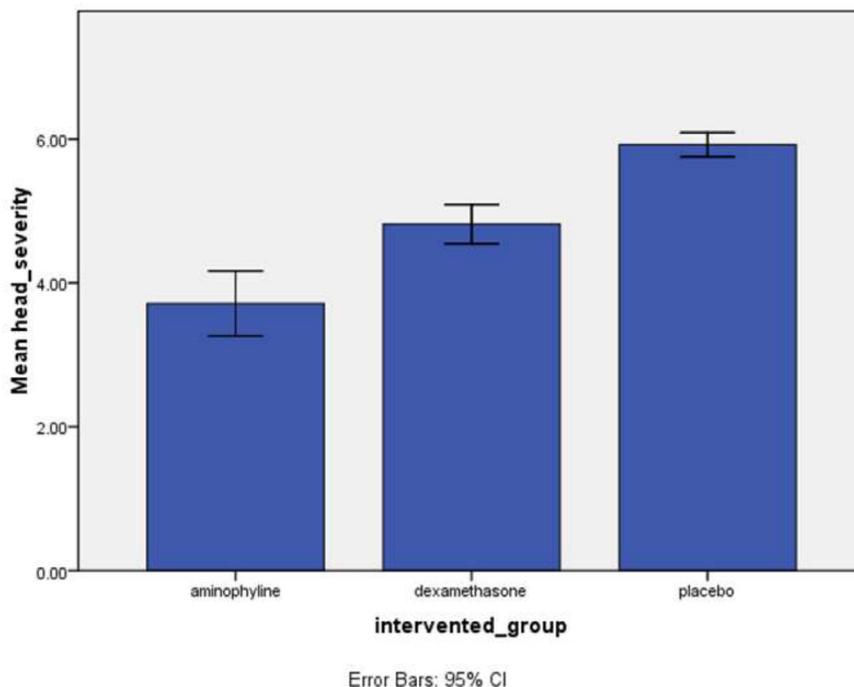


Figure 1 Mean distribution and standard deviation of headache severity in the studied patients based on the type of intervention.

induction in the logistic regression model ( $p = 0.150$ ). By eliminating the effect of age, BMI, frequency of attempts, and type of drug used, there was still no significant difference in headache induction between the three groups ( $p = 0.115$ ). In this study, the relationship between headache severities in different intervention groups was studied by the regression model presented in Table 1. The findings showed that the placebo group had a higher headache of 1.104 units than the aminophylline group, and this difference was significant ( $p < 0.001$ ). The placebo group had a higher pain severity than the dexamethasone group (1.105 units), and this difference was significant ( $p < 0.001$ ). The dexamethasone group also experienced more pain severity than the aminophylline group (1.104), and this difference was significant ( $p < 0.001$ ).

Our study showed that intravenous administration of aminophylline and dexamethasone, compared with placebo, significantly reduced headache after spinal anesthesia in patients undergoing spinal anesthesia. The headache severity was also significantly lower in patients treated with aminophylline than in patients treated with dexamethasone. It is suggested that future studies should compare the effects of dexamethasone and aminophylline on headache after spinal anesthesia in c-section with larger sample sizes, different doses of therapy, in combination and alone. Using a method to increase infusion accuracy into the epidural space, especially in the incidence rate of severe headache, can be a suggestion for future studies.

## Ethics approval

All procedures performed in studies involving human participants followed the institutional and national research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Bioethics Committee approved the study of the Medical University of Kashan (n° IRCT20180429039459N1). Consent to participate: Informed consent was obtained from all individual participants included in the study. Consent for publication: Patients signed informed consent regarding publishing their data. Availability of data and material: The

data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.bjane.2021.11.012](https://doi.org/10.1016/j.bjane.2021.11.012).

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