Original Article

Effect of Intravenous Injection of Aminophylline on Rapid Reduction of Headache Caused by Spinal Anesthesia

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Abstract

Introduction: Post-Dural puncture headache (PDPH) is one of the most common and important complications after spinal anesthesia and lumbar puncture. This study aimed to determine the effect of intravenous injection of aminophylline on rapid relief headache caused by spinal anesthesia.

Materials and Methods: This was a clinical trial conducted on the cesarean section candidates referred to Razi Hospital of Torbat-Heydariyeh and Bohlool Hospital of Gonabad affiliated to Gonabad University of Medical Sciences, Gonabad, Iran between 2018 and 2020. Sixty individuals were selected accessibly and purposefully in terms of the inclination criteria and were then randomly assigned into two groups (using the permutation block method). Group A received 3 mg/kg aminophylline plus 500 cc normal saline, and group B received 500 cc normal saline, infused over two hours. The severity of the headache was examined one to two hours after the infusion using a Visual Analogue Scale. Data were analyzed using SPSS version 21.

Results: The mean score of headache one hour after the infusion in group A (2.04 ± 1.80) was significantly lower than group B (7.1 ± 3.88) ($p < 0.001$). The mean score of headache two hours after the infusion in group A (0.36 ± 0.08) was significantly lower than group B (6.62 ± 2.02) ($p < 0.001$).

Conclusion: This study showed that intravenous injection aminophylline had significant efficacy in PDPH treatment.

Keywords: Cesarean Section, Spinal Anesthesia, Post-Dural Puncture Headache, Aminophylline.

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INTRODUCTION

Cesarean section is one of the most common surgical operations in hospitals and is mainly performed with spinal anesthesia (1). Spinal anesthesia is the selected method for elective cesarean (2, 3), leads to a sympathetic block, motion block, analgesia, and anesthesia. It creates appropriate anesthesia and muscle relaxation with the least amount of medication (4). Spinal anesthesia is widely used because of creating great anesthesia, especially in the lower abdomen part, perineum, and lower organ, as well as reducing postoperative pain (2). Despite the advantages of performing spinal anesthesia, it is accompanied by some complications such as post-dural puncture headache (PDPH), paraplegia, cauda-equina syndrome, epidural hematoma, neural damage, and transient neurological symptoms (3, 5, 6). In this context, headache is one of the most common complications after spinal anesthesia (7). PDPH defines as a pulsatile and diffuse headache and stems from frontal or occipital origins. It gets worse by sitting and standing and gets better by supine position (3, 4). Severe headaches may be accompanied by nausea, vomiting, neck, shoulder, and back pain, dizziness, tinnitus, diplopia, photophobia, hearing loss, cortical blindness, cerebral nerve

palsy, and seizure (3-5, 8). A study conducted at Alzahra hospital in Rasht, Iran, showed that 15.4% of those who underwent cesarean section experienced the PDPH (9).

Epidemiological statistics showed that 10% to 30% of the patients suffer from PDPH after 48 to 72 hours (4). In some cases, spontaneous recovery is within seven days of the surgery, while in 87% of cases, symptoms exist more than six months. PDPH is mostly observed in obese young women, pregnant women, and those who receive the anesthesia with bigger-sized needles and multiple punctures. In this regard, a study mentioned that continuous spinal infusion and time of the patients' movement play no significant role in the incidence rate and intensity score of PDPH (3). Bier et al. mentioned in their study for the first time that cerebrospinal fluid (CSF) leakage was the cause of PDPH (10, 11). To confirming that other studies showed that CSF leakage leads to PDPH by decreasing the CSF pressure and elongating the meningeal membranes. Meanwhile, cerebral vasodilation following the CSF leakage can also create headaches (3).

Accordingly, its common treatments include fluid therapy (oral and intravenous injection, IV), use of sumatriptan, corticotropin, caffeine, NSAIDs (Non Steroid Anti Inflammatory Drugs), opioids (drugs), and finally using blood patch for treatment (4, 12). Physicians use oral or intravenous injection (IV) of sumatriptan, corticotropin, caffeine, non-steroid anti-inflammatory drugs, opioids, or blood patch for PDPH treatment. Although the epidural blood patch has no significant preventative effect, the therapeutic use of blood path (20cc at the appropriate site, 24 hours after dural puncture) can result in early recovery (90% of cases) and permanent improvement of symptoms (61% to 75% of cases). However, blood patch is generally not acceptable to patients because it is invasive (3).

According to the mechanism of PDPH, aminophylline might be a great choice for PDPH treatment. Aminophylline can cause cerebral vasoconstriction and block the purine receptors and injectable form was better than oral forms.

Due to the limited studies on the PDPH treatment, this study aimed to assess the effect of intravenous injection (IV) of aminophylline on the rapid reduction of PDPH.

Materials and Methods

This research was a clinical trial study performed after obtaining ethics authorization from the Regional Ethics-in - Research Council at Gonabad University of Medical Sciences, and after coordination with the research environment as well as obtaining the written informed consent from the patients who met the inclusion criteria of the study. The sample size was estimated as 60 patients and 30 patients for each group. A sample was selected using a simple random sampling method among the patients who were referred to Razi Hospital of Torbat-Heydariyeh and Bohlool Hospital of Gonabad for cesarean section undergoing spinal anesthesia in 1397. Inclusion criteria were as follows: age between 18 and 45 years old, no history of allergy to aminophylline or other methylxanthine derivatives with obtaining a detailed description of them, willingness to participate in the intervention and completing informed consent, no history of heart disease, no pulmonary disease, no thyroid disorders, no drug allergies to the consumed drugs, no Parkinson's disease, no dysautonomia, no Reynold's syndrome, no alcohol abuse, and no vasodilator use. Also, the exclusion criteria of this study included the following: re-spinal anesthesia, unwillingness to continue co-operation in the study, general anesthesia, and consumption of methylxanthine derivatives.

Sampling was made in the form of accessible among all women with headache caused by cesarean section with spinal anesthesia who were selected after having the inclusion criteria by random assignment method using permutation blocks. Therefore, group A received 3 mg/kg aminophylline in 500 cc normal saline and group B received only 500 cc IV injection of normal saline and 4 – blocks (e.g. 2121) that 6 states were recorded in all possible states and with the help of random number table, the number of 29 research samples were placed into 4- blocks in both group A and B.

Then, in the first step, the questionnaires including demographic information were completed by interviewing the patients and referring to their case. Following that, necessary training related to perform intervention was given to sample's individuals. Then, the same fluids volume equal to 5cc / kg normal saline serum was infused to the patients in the operating room and during the operation. After transferring them to the women's ward, the patients received 2 liters (first liter was Ringer and the second liter was dextrose 5% plus 1 g Apotel in first liter of serum) in both groups for pain relief immediately after finishing cesarean section, at the time of hospitalization, and also after discharge (diagnosis of headaches after discharge of the patient to ensure the incidence of headache caused by spinal anesthesia was solely performed by the anesthesiologist). In addition, the patient was controlled in terms of the incidence and intensity of headache by the anesthesiologist and the researcher. also, in case of headache incidence caused by spinal anesthesia after cesarean section, Visual Analogue Scale and Pain Profile Record Form were completed for both groups and 3mg / kg aminophylline with 500 cc normal saline were infused to the patients of group A during two hours, and only 500 cc normal saline was infused to the patients of group B over 2 hours. It is necessary to note that, in the patients who complained from pain rather than headache, one gram of Apotel ampoule with 100 cc normal saline serum and 100 mg diclofenac sodium suppository were used for controlling their pain, if necessary as prescribed by the anesthesiologist and the physician's opinion. Also, the number of suppositories consumed and the time of their application were recorded in the

questionnaire. Finally, data were collected and then analyzed by SPSS software version 21 and statistically chi-square and independent t-tests. P<0.05 values were considered as statistically significant.

RESULTS

The mean age of participants in groups A and B was 29.6 ± 11.27 and 30.6±6.28 years, respectively, and the difference was not statistically significant (p=0.57). The mean weight of participants in groups A and B was 70.16 ± 8.94 and 75.75 ± 8.94 Kg, respectively, and the difference was statistically significant (p= 0.01). The mean BMI of participants in groups A and B was 26.4 ± 02.19 and 29.02 ± 3.20 Kg/M^2, respectively, and the difference was statistically significant (p = 0.006).

The mean severity of PDPH before intervention in group A and B was 7.43 ± 2.17 and 7.1 ± 3.83, respectively which indicated no significant difference (p = 0.34) (Table 1).

Table 1: Comparison of PDPH severity before intervention in group A and B

Group	Mean ± Standard deviation	Independent t-test result
A (N=30)	7.43 ±2.17	T=0. 96 Df=58 P=0.34
B (N=30)	7.1±3.83	

*p-value refers to the difference between two groups.

The mean PDPH severity of group A prior to intervention, one, and two hours after the intervention was 7.43 ± 2.17, 1.80 ± 1.04, and 0.36±0.08, respectively, and the difference was statistically significant. The mean PDPH severity of group A prior to intervention, one, and two hours after the intervention was 7.1 ±3.83, 7.1±3.88, and 6.1±2.02, respectively, and the difference was statistically significant (p>0.05) (Tables 1, 2, and 3).

Table 2: Comparison of PDPH severity one hour later in group A and B

Group	Mean± Standard deviation	Independent t-test result
A (N=30)	1.80 ±1/04	t=10.31 df=58 P*<0.001
B (N=30)	7.1±3.88	

*p-value refers to the difference between two groups.

The mean severity of PDPH one hour after the injection in group A was 4.99 scores lower than group B, and the difference was statistically significant (p <0.001). (Table 2) The mean severity of PDPH two hours after the injection in group A was 5.99 scores lower than group B, and the difference was statistically significant (p <0.001) (Table 3).

Table 3: Comparison of PDPH severity two hours later in group A and B

Group	Mean± Standard deviation	Independent t-test result
A (N=30)	0.36± 0.08	t=10.31 df=58 P*<0.001
B (N=30)	6.2±1.02	

*p-value refers to the difference between two groups.

The results also showed that, over time, the mean PDPH score in group A have had a more reduction, which is statistically significant (p <0.001).

To investigate the effect of IV injection of aminophylline on PDPH in women undergoing cesarean section, regarding the reason that, PDPH in women was measured by passing 1 hour and 2 hours from the intervention, and cannot be ignored from independence between measurements. Also, concerning being quantitative (headache score of the patients) of the response variable to analyze data, the Generalized Estimating Equations method was used in longitudinal studies.

DISCUSSION

This study showed that IV injection of aminophylline had a significant effect on the PDPH treatment and led to rapid reduction of headache in the patients. Consistent with the results of our study, Wu C et al. assessed the efficacy of IV injection of aminophylline (250 mg daily for two days) compared to placebo (serum Sodium Chloride 0.9% 500 cc) in the PDPH treatment and showed that aminophylline was more effective and safer than placebo (13). Besides, Mahoori A et al. compared the theophylline (250 mg, three times a day, orally) with acetaminophen (500 mg, three times daily, orally). The results showed that theophylline was significantly a better choice on the PDPH treatment (14). Sadeghi et al. assessed the effect of aminophylline on 120 participants undergoing cesarean section (1.5 mg/kg, IV, single dose) after umbilical cord clamping, to prevent PDPH. The results showed that aminophylline could be an effective medication in preventing the PDPH (15). Ergün U et al. conducted a study on the effect of IV injection of theophylline on PDPH treatment in Turkey and mentioned that IV injection of theophylline was an effective treatment method, easy, rapid, and with minimum invasion, and can be used as a therapeutic method prior to invasive techniques (16). In the mentioned research, the type of drug used (theophylline) was different from the present study (aminophylline) and similar results were obtained.

In the present study, the intensity of headache in group A was significantly lower compared to group B, which indicated being usefulness of methylxanthine with the aim of rapid reduction of PDPH intensity. Moreover, no side

effects such as nausea, vomiting, arrhythmia, seizures, and allergic reactions were observed in this study, indicating that this dose of aminophylline was safe and effective in treating PDPH.

Aminophylline is one of the methylxanthine drugs. The mechanism of its effect on the treatment of PDPH has remained unclear. Methylxanthine drugs inhibit phosphodiesterase as un-elective and cause bronchodilation and cerebral vasoconstriction. Moreover, they perform serial vasoconstriction via adenosine receptor block. It seems that this is the main mechanism of theophylline and aminophylline in the PDPH treatment. They can also induce CSF production by stimulating the Na-K pump (13). Aminophylline can inhibit adenosine, create cerebral vasoconstriction, and inhibit pain transmission through painful structures. It can inhibit phosphodiesterase and increase intracellular cyclic phosphate adenosine concentration. Also, aminophylline can inhibit calcium uptake by reticulum endoplasmic in endothelial cells, stimulate calcium-potassium pumps, and increase CSF secretion (4, 13).

Conclusion

According to the results of this study, the IV injection of aminophylline (with the aforementioned dosage) is highly recommended in the rapid treatment of PDPH.

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Ethical Approval

This research under code IRCT20180607040003N1 has Ethics permission No.IR.GMU.REC.1396.62 from the Regional Ethics in Research Council of Medical Sciences University of Gonabad.

Conflict of Interests: No case was expressed by the authors**.**

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