Original Article

Prophylactic administration of aminophylline plus dexamethasone reduces post-dural puncture headache better than using either drug alone in patients undergoing lower extremity surgery

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Abstract

Background: Post-dural puncture headache (PDPH) is a known complication of neuroaxial anesthesia and may be associated with significant morbidity. As invasive treatment for PDPH has known complications, pharmacologic management may be preferable. The main objective of the present study was to evaluate the effects of combining administration of intravenous aminophylline and dexamethasone on PDPH in patients who underwent lower extremity surgery in comparison with using either drug alone and also comparing them with placebo.

Materials and Methods: One hundred and forty patients, aged 20-65 years, scheduled for lower extremity surgery in Alzahra University Hospital under spinal anesthesia were enrolled in this randomized, double-blind, placebo-controlled study. Patients were divided into four groups of 35 each and received aminophylline 1.5 mg/kg i.v. (group A), dexamethasone 0.1 mg/kg (group D), aminophylline 1.5 mg/kg plus dexamethasone 0.1 mg/kg i.v. (group AD), and placebo (group P). The incidences of PDPH and complete response were evaluated at 6-48 h after arrival to the ward in the four groups.

Results: Patients in group AD had significantly lower incidence of PDPH (5.88% vs. 20.58% for group A and 17.14% for group D with $P < 0.05$), the highest incidence of complete response, and also, less analgesic requirement compared with groups A, D, and P throughout 6-48 h (1.2 ± 0.4 vs. 2.3 ± 0.75 for group A, 1.8 ± 0.6 for group D, and 3.3 ± 1 for placebo group with $P < 0.05$).

Conclusion: Combine administration of aminophylline 1.5 mg/kg plus dexamethasone 0.1 mg/kg significantly reduced PDPH better than using either drug alone in patients who underwent lower extremity surgery under spinal anesthesia.

Key Words: Aminophylline, dexamethasone, post-dural puncture headache, spinal anesthesia

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Received: 20.01.2013, **Accepted:** 16.06.2013

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.124631

INTRODUCTION

Post-dural puncture headache (PDPH) is a common adverse effect following spinal anesthesia, occurring in 2.5-40% of patients who are candidates for spinal anesthesia, and it typically begins within 2 days but may be delayed for as long as 2 weeks and almost resolves spontaneously within a few days.[1-3] The

How to cite this article: Naghibi K, Hamidi M. Prophylactic administration of aminophylline plus dexamethasone reduces post-dural puncture headache better than using either drug alone in patients undergoing lower extremity surgery. Adv Biomed Res 2014;3:5.

classic symptoms of PDPH consist of photophobia, nausea and vomiting, neck stiffness, tinnitus, diplopia, and dizziness, in addition to the often severe cephalgia.[4] The headache is usually severe and throbbing, frontal in origin, with radiation to occiput and is exacerbated by sitting or standing.[5] The positional nature of the headache and dramatic improvement on assuming the supine position remains the standard diagnostic criterion for this condition.[6,7]

PDPH still remains a disabling complication of spinal anesthesia, and although we have made enormous progress in understanding this clinical entity, including its epidemiology, pathophysiology, clinical symptoms, prevention, and treatment, however, this entity still needs further studies.[8,9]

There is considerable variability in the incidence of PDPH, which is affected by many factors such as age, gender, needle type, size, and also operation type, and the number of attempts for dural puncture.[10]

In general, PDPH is more common in young women, particularly in pregnancy.[11] Pharmacological management and prevention of PDPH is a minimally invasive treatment modality.[4]

Prevention of PDPH is aimed at limiting the cerebrospinal fluid (CSF) leak at the site of lumbar puncture, and treatment of PDPH consists of conservative measures such as analgesics and antiemetics.[12] Current treatment or preventive modalities for PDPH include theophylline, caffeine, sumatriptan, etc., but none have been shown to effective till date.[7] The efficacy of aminophylline and dexamethasone in prevention of PDPH has been proven in some double-blind and placebo-controlled studies.[13,14] Theophylline is thought to have the same mechanism of action as caffeine (i.e. antagonizing adenosine, thereby causing cerebral vasoconstriction) and is used in combination with aminophylline for the treatment of PDPH.[12]

It is not clear if combining aminophylline with dexamethasone would provide superior prophylaxis against PDPH than using either drug alone.[15-16]

We assumed that prophylactic administration of aminophylline plus dexamethasone will cause more reduction in the incidence of PDPH than either drug being used alone or placebo. Therefore, we designed this randomized, double-blind, placebo-controlled study to evaluate the effects of combining administration of intravenous aminophylline with intravenous dexamethasone on PDPH in patients who underwent lower extremity surgery in comparison with using either drug alone.

MATERIALS AND METHODS

One hundred and forty American Society of Anesthesiologists (ASA) physical status I-II patients, aged 20-65 years, scheduled for lower extremity surgery under spinal anesthesia gave written informed consent to participate in this double-blind, randomized, placebo-controlled study, which was approved by our institute ethics committee. The patients with history of migraine or other type of headache, previous intolerance to the aminophylline or dexamethasone administration, or who had received any analgesic within 24 h before surgery were not included in this study. The patients with any unpredictable condition in surgery or any complication such as severe hypotension [whenever systolic blood pressure (SBP) was reduced more than 25% of baseline] or with more intraoperative vasopressor drug requirement were excluded.

No premedication was given to the patients. Before surgery, the patients were informed about using visual analog scale (VAS), ranging from 0 (none) to 10 (worst possible pain), for evaluation of their headache. By using a computer-generated random number table, patients were randomly allocated to one of four groups (n = 35 for each group) as follows: group A received aminophylline 1.5 mg/kg i.v.; group D received dexamethasone 0.1 mg/kg i.v.; group AD received aminophylline 1.5 mg/kg i.v. plus dexamethasone 0.1 mg/kg i.v.; and group P received saline (placebo) i.v. 15 min before the end of the surgery. A nurse anesthetist prepared identical syringes containing either normal saline or the study medications for each subject. All medications were 5 ml in volume and were given i.v. 15 min before the end of the surgery. The patients and the investigator who collected all data were blinded to the group randomization.

After the patients arrived to the operating room, noninvasive arterial blood pressure [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial blood pressure (MAP)], heart rate (HR), respiratory rate (RR), and Pulse Oximeter Oxygen Saturation (SpO2) level were monitored.

Prior to spinal anesthesia, all patients received 20 ml/kg Ringer's lactate as preloading fluid.

Spinal anesthesia was performed with 3 ml of hyperbaric bupivacaine 0.5% (15 mg) at L3-L4 interspace with a 23-gauge Quincke spinal needle after

local infiltration of 3 ml of 2% xylocaine.

[Several factors have been shown to be important contributors to the risk for PDPH, including needle size and type. Small-bore (high-gauge) needles have been shown to reduce the risk of PDPH [17]. Smaller needle sizes increase the failure rate of the lumbar puncture because they are more difficult to use.[7] So, for avoiding of multi puncture, we used 23-gauge needle]. Positive aspiration of clear CSF before and after the injection confirmed correct needle placement. All patients received IV infusion of midazolam 0.05 mg/kg for light sedation during spinal anesthesia.

Demographic data of patients (age, gender, weight), ASA physical status, types of operation, duration of surgery (the time from beginning of surgery till the closure of the last suture), duration of anesthesia (the time from spinal anesthesia till two segment regression of sense), and post-anesthesia care unit (PACU) stay time (the time from arrival of patients to the PACU till discharge from it) were recorded.

The incidences of PDPH, complete response, and the severity of PDPH were evaluated at 6-48 h after arrival to the ward in the four groups. If patients had intolerable headache, acetaminophen 15 mg i.v. was administered.

If the headache did not respond to the routine measures, invasive procedures such as epidural blood patch or epidural saline injection may be used,[13] but fortunately, none of our patients needed these invasive procedures.

If patients had no PDPH throughout the 48 h, it was considered as a complete response.

By using VAS score, PDPH was evaluated at 6-48 h after arrival to the ward. Acetaminophen 15 mg/kg i.v. was administered if the patients had VAS score of >5 cm and the total dose of rescue analgesic was recorded.

The sample size was estimated based on a power calculation, which showed that 35 patients per group was necessary to achieve 80% power with $\alpha = 0.05$. Data are presented as mean (SD), numbers, or median.

Differences among groups' mean were compared using one-way analysis of variance (ANOVA), and *post-hoc* comparisons at various points in time were made by using Bonferroni's type I error rate correction for multiple tests of significance. Repeated measure analysis of variance was used for analysis of continuous variables. Categorical variables were analyzed by Pearson chi-square test, and by Fisher's exact test when the anticipated number was <5. Mann — Whitney U-test was used as appropriate. The difference in median sedation level among the four groups was analyzed by the Kruskal — Wallis test. $P < 0.05$ was set as statistically significant. All statistical analyses were performed using SPSS 20 for Windows statistical package.

RESULTS

One hundred and forty patients were enrolled in the study. Two patients were excluded from the study due to profound hypotension ($n = 1$) and need for more sedation ($n = 1$), but other drug or spinal complications such as tachycardia, bradycardia, restlessness, and shivering did not happen in our patients. There was no difference in patient characteristics such as sex, ASA, age, weight, types of operation performed, duration of PACU stay, duration of surgery, and duration of spinal anesthesia among the four groups [Table 1].

When compared with groups A, D, and P, the AD group had a lower incidence of PDPH (6-48 h) and the highest incidence of complete response ($P < 00.5$).

The time to the first analgesic demand was significantly more in groups A, D, and P compared with group AD ($P < 0.05$). Postoperative analgesic requirement was significantly less in groups A, D, and AD compared with group P ($P < 0.05$) .

Table 1: Patients' characteristics, duration of surgery, duration of hospital stay

Variable	Group A ($n = 35$)	Group D ($n = 35$)	Group AD ($n = 35$)	Group P ($n = 35$)	*P*
Sex (M/F)	25/10	30/5	26/9	28/7	>0.05
Age (years)	45.7±7.4	47.4±8.4	42.3±6.7	49.4±5.3	>0.05
ASA (I/II)	21/14	19/16	20/15	22/13	>0.05
Weight (kg)	68±5.2	70.2±12.2	72±13	66±7.2	>0.05
Height (cm)	165±11	170±8	163±12	161±5.5	>0.05
Duration of surgery (min)	76±25	90±35	106±11	98±22	>0.05
Duration of hospital stay (days)	1.4±0.6	2.1±0.8	1.6±0.6	1.8±0.3	>0.05

Values are presented as mean ± SD or the number of patients. No significant differences were noted between the four groups; Group A = intravenous aminophylline group; group D = intravenous dexamethasone group; group AD = intravenous aminophylline plus dexamethasone group; group P = intravenous saline (placebo) group; ASA = American Society of Anesthesiologists; PDPH = post-dural puncture headache

The results of our study did not show any significant adverse effect such as tachycardia or restlessness due to study drug administration.

There were significant differences in the VAS scores and postoperative analgesic demand among the four groups. Median sedation level was not significantly different among the four groups [Table 2].

DISCUSSION

A great number of patients who underwent surgery under spinal anesthesia are at high risk for PDPH and warrant using analgesics.[16] The aim of this study was to evaluate the prophylactic effect of combined use of intravenous aminophylline and dexamethasone on PDPH in patients who underwent lower extremity surgery under spinal anesthesia. Our study showed that aminophylline 1.5 mg/kg i.v. plus dexamethasone 0.1 mg/kg i.v. produced a greater reduction in the incidence of PDPH till 48 h after orthopedic surgery compared with using aminophylline or dexamethasone alone, while it had no important side effects.

Also, administration of aminophylline plus dexamethasone significantly decreased postoperative analgesic requirement in comparison with using aminophylline or dexamethasone alone.

Spinal anesthesia is accompanied with high incidence of PDPH.[1-5] Previous studies showed that the incidence of PDPH was between 2.5% and 70%.[4,6-11] Our results showed that there was high incidence of PDPH (42.85%) 6-48 h after lower extremity surgery under spinal anesthesia. Risk factors of PDPH are age, female sex, pregnancy, history of headache or previous PDPH, type of operative procedure, technique of spinal anesthesia, and several attempts for dural puncture.[4,7,12,13]

In our study, all these factors were matched well among the four groups. Consequently, the differences in the incidence of PDPH between groups can be due to the study drug used.

There are many previous studies regarding use of dexamethasone or aminophylline for prophylaxis and treatment of PDPH.[13-18] Zajac *et al*. showed that aminophylline 250 mg once daily, when administered i.v., was not effective in decreasing the incidence of PDPH in comparison to caffeine or magnesium premedication.[14]

In a study performed by Yousefshahi *et al.*, it was shown that administration of dexamethasone 8 mg/kg after spinal anesthesia significantly increased the incidence and severity of PDPH in women who underwent cesarean section under spinal anesthesia.[15] In another research, Doroudian and colleagues showed that dexamethasone 8 mg i.v., when administered preoperatively, effectively reduced the severity of PDPH while it increased patients' satisfaction.[15]

The mechanism by which aminophylline exerts its anti-cephalgic effect has not been completely elucidated.[19-20]

Sadeghi *et al*.[28] showed that aminophylline administered after spinal anesthesia was effective for reducing PDPH and an arguable phenomenon is probably vasodilatation caused by aminophylline.

It was shown that aminophylline and dexamethasone were tolerated well when given prophylactically[20-24] or therapeutically[25] in the postoperative period. In our study, aminophylline and dexamethasone decreased the incidence of PDPH 6-48 h after surgery, although it remained relatively frequent (5-20%).

The side effects of aminophylline and dexamethasone are infrequent in small dose.[26,27] It was presumed that combination of aminophylline or dexamethasone with the other drugs with analgesic effect will reduce the incidence of PDPH further.

As our results showed, using aminophylline in combination with dexamethasone decreased the incidence of PDPH at 6-48 h from 42.85 to 5.88%. It is possible that when we use two anti-cephalgics with different mechanisms of action, only their anti-cephalgic effects are increased.

Methylxanthines, such as caffeine and theophylline, have been shown to resolve the symptoms of PDPH. The exact mechanism of action of caffeine in PDPH is unknown. PDPH is believed to be caused by adenosine-

Table 2: Patients' VAS, calculated risks for PDPH, and postoperative analgesic demand

Variable	Group A (*n* = 34)	Group D (*n* = 35)	Group AD (*n* = 34)	Group P (*n* = 35)	*P*
Calculated risk for PDPH (%)	20.58	17.14	5.88	42.85	<0.05
VAS	4.1±0.3	3.1±0.8	2.3±0.6	6±1.2	<0.05
Acetaminophen i.v. (mg)	2.3±0.75	1.8±0.6	1.2±0.4	3.3±1	<0.05

Values are presented as mean ± SD or the number of patients. Significant differences were noted between the four groups. There was no significant difference between the four groups in the incidence and severity of adverse effect (>0.05)

induced cerebral vasodilatation, and caffeine may act by antagonizing adenosine, thus leading to cerebral vasoconstriction.[29] Theophylline is thought to have the same mechanism of action as caffeine (i.e. antagonizing adenosine, thereby causing cerebral vasoconstriction) and is used in combination with aminophylline for the treatment of PDPH; it is more commonly available as compared with caffeine.

The adverse effects that were observed in our study were not serious, and there was no significant difference among the four groups. A limitation of our study was the difficulty of using VAS and also the validity of that.

There are still many questions regarding the use of small dose of aminophylline in combination with dexamethasone for PDPH prophylaxis that must be answered. For example, the proper dose of this combination has not been investigated. Also, the optimum timing of administration of combined use of two drugs has not been clearly explained.

CONCLUSION

Our study showed that intravenous administration of 1.5 mg/kg aminophylline plus 0.1 mg/kg dexamethasone significantly reduced PDPH better than using either drug alone in patients who underwent lower extremity surgery under spinal anesthesia. It is necessary to perform additional studies to determine the timing and safety of using combination therapy with different dosing schedules before final conclusion can be elicited.

ACKNOWLEDGMENTS

We would like to express our gratitude to all those who made it possible to complete this research. Furthermore, our special thanks are extended to the staff of the surgery ward for their assistance with the collection of our data.

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Source of Support: Isfahan University of Medical Sciences, Isfahan, Iran,
Conflict of Interest: None declared.