

THEOPHYLLINE VERSUS ACETAMINOPHEN IN THE TREATMENT OF POST-DURAL PUNCTURE HEADACHE (PDPH)

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Abstract

Background: Post-dural puncture headache (PDPH) is the most frequent complication of procedures associated with dural puncture for spinal anesthesia or following accidental dural puncture during epidural anesthesia. Since invasive treatments have known complications, pharmacologic management may be preferable. The aim of this study was to evaluate and compare the efficacy of theophylline and Acetaminophen in treatment of PDPH.

Methods: In this single-blind randomized clinical trial, 60 patients with Class I physical status according to ASA classification system, who suffered from PDPH were enrolled. Patients in Theophylline group were received theophylline tablet 250 mg three times per day, and in the other group acetaminophen 500 mg three times per day was administered. Pain intensity was assessed 2, 6, and 12 hour after drug administration using 0-10 cm Visual Analog Scale.

Results: The main VAS values is significantly lower in theophylline group in comparison with the acetaminophen group at 2 (5 ± 1.57 vs. 5.97 ± 1.27), 6 (3.43 ± 1.73 vs. 4.33 ± 1.49), and 12 (2.67 ± 2.35 vs. 4.24 ± 1.97) hours after drug administration ($p < 0.05$). No adverse effects were reported.

Discussion: Theophylline is a safe and effective treatment for PDPH. It may be tried in PDPH patients before using any invasive technique. Further investigations studying other Methylxanthines are recommended as well.

Key words: Theophylline; Lumbar puncture; Headache; Acetaminophen

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Introduction

Neuroaxial blocking has numerous advantages over general anesthesia. Being safe, low required dose of drugs, lower cost for patients, no risk of pulmonary aspirations, no age limits are some benefits of neuroaxial blocking. However, some complications have been reported for spinal anesthesia. Post-dural puncture headache (PDPH) is the most frequent complication of these procedures, which is attributed mostly to the excessive leak of cerebrospinal fluid (CSF) from the puncture point leading to intracranial hypotension, associated with a resultant cerebral vasodilatation¹⁻³. The incidence of PDPH was reported to be 1-30%^{4,5}, with 0%-14.5% incidence rate when small needles are used⁶.

Several invasive and non-invasive treatments were suggested for management of PDPH, including medical therapy with non-steroidal analgesics, morphine, casyntropin^{7,8} or invasive procedures such as blood patch or caudal normal saline injection^{9,10}.

A medical therapy with theophylline has been suggested¹¹, but the recommendations mostly were not evidence-based. Feuerstein et al conducted a preliminary study in 1986 on 11 patients with post-dural puncture headache and compared per oral treatment with theophylline versus placebo¹². They found theophylline to be effective in treating PDPH, however because of the small sample size; the findings were not completely reliable. In 2008, Ergun et al compared the efficacy of intravenous theophylline treatment for PDPH, versus placebo and claimed that intravenous theophylline infusion is effective for decreasing the painfulness of PDPH¹³.

Although more than a quarter of a century has passed since the introduction of theophylline as a treatment for PDPH, surprisingly few studies have focused on this treatment and its efficacy up until now. In this randomized controlled trial, we aimed to investigate and compare the efficacy of oral theophylline therapy versus acetaminophen for the treatment of PDPH.

Methods

This study was implemented with the approval of Scientific & Ethical Review Boards of Urmia

University of Medical Sciences (UMSU), Urmia, Iran. In this single-blind randomized clinical trial, sixty patients with ages between 30-50 years who were candidate of various surgical procedures under spinal anesthesia were enrolled. The patients had a Class I physical status according to the classification system of American Society of Anesthesiology (ASA). All the subjects have experienced PDPH according to the definition of International classification of headache disorders (ICDH-II) prior to recruiting or randomization within groups¹⁴. Participants were randomly recruited into two Intervention and control groups each consisted of 30 patients. According to the power analysis, 54 patients were enough to have a 90% chance of detecting, as significant at the 5% level, an increase in the PDPH remission rate from 20% in the acetaminophen group to 60% success rate in the theophylline group. A total of 60 were entered to this two-treatment parallel-design study. The power of study for detecting the 0.9 difference in means of VAS scores between groups at a two-sided 0.05 significance level will be 92%. All the patients signed an informed consent form prior to participation in the study. For randomized recruitment computer software was used. The patients with central nervous disorders, hypertension, ischemic heart disease, cardiac arrhythmias, hyperthyroidism, age higher than 60 years old and past history of migraine headaches were excluded from the study.

The patients in the intervention group received a tablet of 250 mg Theophylline (the therapeutic dose of theophylline which usually associates with no complication), every eight hours, whilst the cases in the control group were treated with Acetaminophen tablets (500mg) every eight hours (TDS administration to ascertain the blindness of subjects in both study groups). The definition of international classification of headache disorders (ICDH-II) was used to identify post-dural puncture headache (PDPH) cases. For measuring the severity of headache, we applied visual analog scale (VAS), which is a psychometric response scale for measuring subjective characteristics.

The pain scale consisted of a 10 cm horizontal line marked from 0 (denoting no pain) to 10 (denoting worst possible imaginable pain). If headache exists, its intensity was recorded within the continuous spectrum

of this scale. In the 2nd, 6th and 12th hours after the administration of drug, the intensity of headache was evaluated and registered again. Except the anti-headache treatment, other therapies (including fluids and drugs) were similar in patient of both groups. Data were analyzed by independent t-test and chi-square test among two groups using SPSS statistical software ver16 (Chicago, IL). P-value <0.05 was considered statistically significant.

Results

Sixty consecutive patients who met the inclusion criteria were included in the study. Demographic characteristics such as age, gender, and baseline headache intensity were similar between the groups (Table 1).

Table 1
Baseline patients' characteristics

Characteristics	Theophylline group (N = 30)	Acetaminophen group (N = 30)	P-value
Age (Mean ± SD)	40.06 ± 5.95	40.00 ± 6.43	0.6
Sex (Male/Female)	19/11	22/8	0.4
Baseline pain	5.46 ± 1.33	5.96 ± 1.20	0.13

The visual analogue scale scores on 2nd, 6th, 12th hours after treatment were significantly lower ($P < 0.05$) in the Theophylline group compared to the Acetaminophen group (Table 2).

Table 2
The VAS at 2, 6, and 12 hrs after treatment in the two groups

Headache intensity	Theophylline group (N = 30)	Acetaminophen group (N=30)	P-value
2 hrs after treatment	5.00 ± 1.57	5.97 ± 1.27	0.01
6 hrs after treatment	3.43 ± 1.73	4.33 ± 1.49	0.03
12 hrs after treatment	2.67 ± 2.35	4.24 ± 1.97	0.005

Both theophylline and acetaminophen were well tolerated and no adverse events (such as nausea, diarrhea, dizziness, lightheadedness or tachycardia) were reported in both groups. Also no patient requested to be withdrawn from the study.

Discussion

Several studies proposed the potential role of theophylline in treating PDPH, but only two trials were investigated its efficacy until now. In this study the intensity of pain was significantly lower in the group treated with oral theophylline compared to the group treated with Acetaminophen 2 hours, 6 hours and 12 hours after receiving medical treatment. The patients have not reported any adverse effect due to treatment with theophylline (no nausea, diarrhea, dizziness, lightheadedness or tachycardia).

Similar to our findings, both of the studies which are implemented by Feuerstein et al and Ergun et al, have reported the theophylline to have beneficial effect in treating PDPH in comparison with the placebo. However because of the limited sample size in the study of Feuerstein et al, we can only consider it as a pilot study¹². The study protocol was different in study of Ergun et al compared to ours¹³. In Ergun's study, theophylline was administered intravenous, but we have studied the efficacy of oral theophylline therapy in treatment of PDPH. The other difference is related to the use of Acetaminophen, as a simple analgesic in our study instead of using placebo. The findings of this study are in favor of the superiority of theophylline therapy over Acetaminophen in treating PDPH.

Intravenous aminophylline reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention in patients undergoing elective caesarean section⁸. However based on the results of Zajac et al, prophylactic administration of aminophylline did not influence the incidence of PDPH¹⁵.

Methylated xanthines and their derivatives are from the pharmacologic group of nonselective phosphodiesterase inhibitors, which leading to the relaxation of bronchial smooth muscles (bronchodilatation) as well as cerebral vasoconstriction. It seems that the vasoconstriction through blocking adenosine receptors is the main mechanism of theophylline or aminophylline in treating the PDPH. Also it supposed to induce CSF production by stimulating Na-K pumps¹⁶.

A limitation for this study was the limited number of patients who were compatible with our

inclusion (PDPH & ASA grade I) and exclusion criteria (especially the exclusion of patients with any history of hypertension, ischemic heart disease or migraine headache). The difference among the half life of acetaminophen with theophylline, at least theoretically, could be a limitation for the findings of this study.

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lightheadedness or tachycardia).

Since we have enrolled only patients with class I physical status according to ASA classification system to our trial, implementation of further studies on the use of theophylline or aminophylline in the treatment of PDPH in other patient groups is suggested.

Conclusion

According to the findings of this study, the authors recommend the use of theophylline in treating the post-dural puncture headache. Theophylline revealed to be a safe and effective medical therapy in the cases that invasive therapy is not necessarily indicated.

There was no conflict of interests in this study.

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