JARSS 2020;28(4):247-54
doi: 10.5222/jarss.2020.74436

Özgün Araştırma / *Original Article*

Evaluation of Theophylline Efficiency in Post-Dural Puncture Headache

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Postdural Delinme Baş Ağrısında Teofilin Etkinliğinin Değerlendirilmesi

ABSTRACT

Objective: *In clinical studies, intravenous theophylline has been reported to be effective in the treatment of postdural puncture headache (PDPH), but its efficacy is not clear to some clinicians due to the small number of patients in these studies. This treatment can be used as an intermediate step in the treatment of PDPH, if the efficacy and safety of theophylline is proven. We aimed to evaluate the efficacy and safety of an intravenous (IV) injection of theophylline on PDPH.*
Methods: *Sixty-five PDPH patients who were injected with IV theophylline according to our "Postdural Puncture Headache Algorithm" were evaluated retrospectively. The primary and secondary endpoints were the degree of headache and the patient's overall response to the treatment, respectively. Treatment safety was evaluated based on the occurrence of adverse reactions.*
Results: *Before the initial theophylline administration, the visual analog scale (VAS) score was 6.0±1.6 points. The VAS scores at one hour post-treatment were 1.8±1.4 points. The mean VAS scores of the patients after theophylline infusion decreased significantly compared to before (p=0.001). Hemodynamic changes due to theophylline were not statistically significant (p>0.05). There were no reports of theophylline-related adverse events in the patient records.*
Conclusion: *An iv injection of theophylline is an effective and safe treatment for PDPH. Intravenous theophylline treatment may find a place between the conservative treatment and invasive interventional therapy in step therapy of PDPH.*

Keywords: *Post-dural puncture headache, theophylline, algorithm, orthostatic headache*

ÖZ

Amaç: *Klinik çalışmalarda, intravenöz teofilinin post-dural delinme baş ağrısı (PDBA) tedavisinde etkili olduğu bildirilmiştir, fakat bazı klinisyenlere göre çalışmalardaki hasta sayılarının az olması nedeniyle bu durum net değildir. Teofilinin etkinliği ve güvenliği kanıtlandığında, bu tedavi PDBA tedavisinde bir ara adım olarak kullanılabilir. Çalışmamızda, intravenöz (iv) teofilin uygulamasının PDBA üzerine etkinliğini ve güvenilirliğini değerlendirmeyi amaçladık.*
Yöntem: *"Post-Dural Delinme Baş Ağrısı Algoritması" na göre intravenöz teofilin uygulanan 65 PDBA hastası retrospektif olarak değerlendirildi. Birincil ve ikincil sonlanım noktaları sırasıyla baş ağrısının derecesi ve hastanın tedaviye yanıtıydı. Tedavi güvenilirliği yan etki oluşumuna göre değerlendirildi.*
Bulgular: *İlk teofilin uygulanması öncesi Görsel Analog Skala (VAS) skoru 6.0±1.6 idi. Tedaviden bir saat sonra VAS skorları 1.8±1.4 idi. Teofilin infüzyonu sonrası hastaların ortalama VAS skorları öncekine göre anlamlı olarak azaldı (p=0.001). Teofilin nedeniyle hemodinamik değişiklikler istatistiksel olarak anlamlı değildi (p>0.05). Hasta kayıtlarında teofilinle ilişkili yan etki bildirimi yoktu.*
Sonuç: *İntravenöz teofilin uygulaması PDBA tedavisinde etkili ve güvenli bir yöntemdir. İntravenöz teofilin tedavisi, PDBA'nın basamak tedavisinde konservatif tedavi ve invaziv girişimsel tedavi arasında bir yer bulabilir.*

Anahtar kelimeler: *Post-dural delinme baş ağrısı, teofilin, algoritma, ortostatik baş ağrısı*

Received/Geliş: 15 May 2020
Accepted/Kabul: 25 June 2020
Publication date: 27 October 2020

Cite as: Yıldırım HU, Bakır M, Rumeli Atıcı S. Evaluation of the theophylline efficiency in post-dural puncture headache. JARSS 2020;28(4):247-54.

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INTRODUCTION

Lumbar puncture (LP) is a technique used for sampling of cerebrospinal fluid (CSF) as well as in the application of drugs (anesthesia, chemotherapy, radiology, etc.). Post-dural puncture headache (PDPH) is a common complication (30-40%) of LP [1-3]. PDPH may occur depending on the patient with underlying conditions (dehydration, intracranial hypotension, physical and physiological causes) or intervention-related causes (needle diameter, number of retries, needle type) [4]. According to the diagnostic criteria of "3rd Edition of International Classification of Headache Disorders" (ICHD-3 beta); dural puncture headache onsets within 5 days after the incident of dural puncture, CSF leakage in imaging, and a CSF pressure of less than 60 mmH_20 are observed, and it can not be characterized better by another ICHD-3 diagnosis [1].

Hydration, mobilization and restriction of oral caffeine are the first steps of treatment. Other treatment modalities for PDPH are administration of theophylline, corticotrophin, subcutaneous sumatriptan, gabapentin, pregabalin, intramuscular adrenocorticotropic hormone, intravenous hydrocortisone, epidural saline injection and application of epidural blood patches (EBPs) [2,5]. Caffeine, gabapentin, pregabalin and hydrocortisone have yielded controversial results in the treatment of PDPH. These drugs are not recommended for use during lactation [6]. Theophylline is a methylxanthine derivative and is thought to treat PDPH by decreasing intracranial blood flow and venous enlargement, and increasing CSF production [7]. Among the treatment options, before the epidural blood patch application or saline injection, theophylline administration is frequently reported in case reports [8,9].

In our algology clinic, PDPH treatment is performed according to an algorithm including theophylline infusion. The aim of this study was to evaluate the efficacy of theophylline by retrospective analysis of patients presenting with PDPH.

MATERIAL and METHODS

From February 2006 to April 2018, patients who admitted to Algology Department and fulfilled the diagnostic criteria of PDPH were enrolled. This retrospective study was approved by the ethics committee of the Mersin University. Seventy-eight patients with PDPH were included in the study. Thirteen patients who were not treated with IV theophylline were excluded from the study. The information related to the age and sex of the patients, concomitant diseases, neuro-axial anesthesia method used, and its indication, the level of the epidural anesthesia applied and diameter of the needle were recorded. The physical examination findings of the patients with headache, time to the onset of headache after LP and to theophylline application, number of theophylline injections, visual analogue scale (VAS) scores before and after the treatment, blood pressure and heart rate values were examined.

Assessment and Treatment Algorithm:
According to the algorithm; oral hydration, oral caffeine and paracetamol 500 mg + caffeine 30 mg + codeine 10 mg drug combinations three times a day are recommended for patients with visual analogue scale (VAS) scores less than 4 points (Figure 1). When considered necessary by the physician, the neurological examination is repeated at the 24th and/or 48th hours. Theophylline 200 mg/45 min/IV infusion is administered under hemodynamic monitoring in patients who had VAS scores of ≥4 points at the time of follow-up examinations or at the time of their first admissions. After theophylline administration, VAS scores were recorded. Forty-five minutes after infusion, standing VAS scores were reassessed. Patients whose symptoms regressed were discharged with control visits recommended at 24th and 48th hours. Patients for whom theophylline treatment were planned on the control visits were hospitalized and followed up. Cranial and/or spinal Magnetic Resonance Imaging (MRI) were/was performed in patients with headaches of variable characteristics, or increasing severity, relevant pathological findings in neurological examination (cranial nerve pathology, motor-sensory deficit, visual disturbances), previous history of cerebrovascular event and intracranial surgery. Application of epidural blood patches is planned for patients who had VAS scores of >4 points after 48 hours and evidence of CSF leakage on imaging. The administration of theophylline at the expected time for blood patch application could be reapplied if the severity of symptoms had decreased.

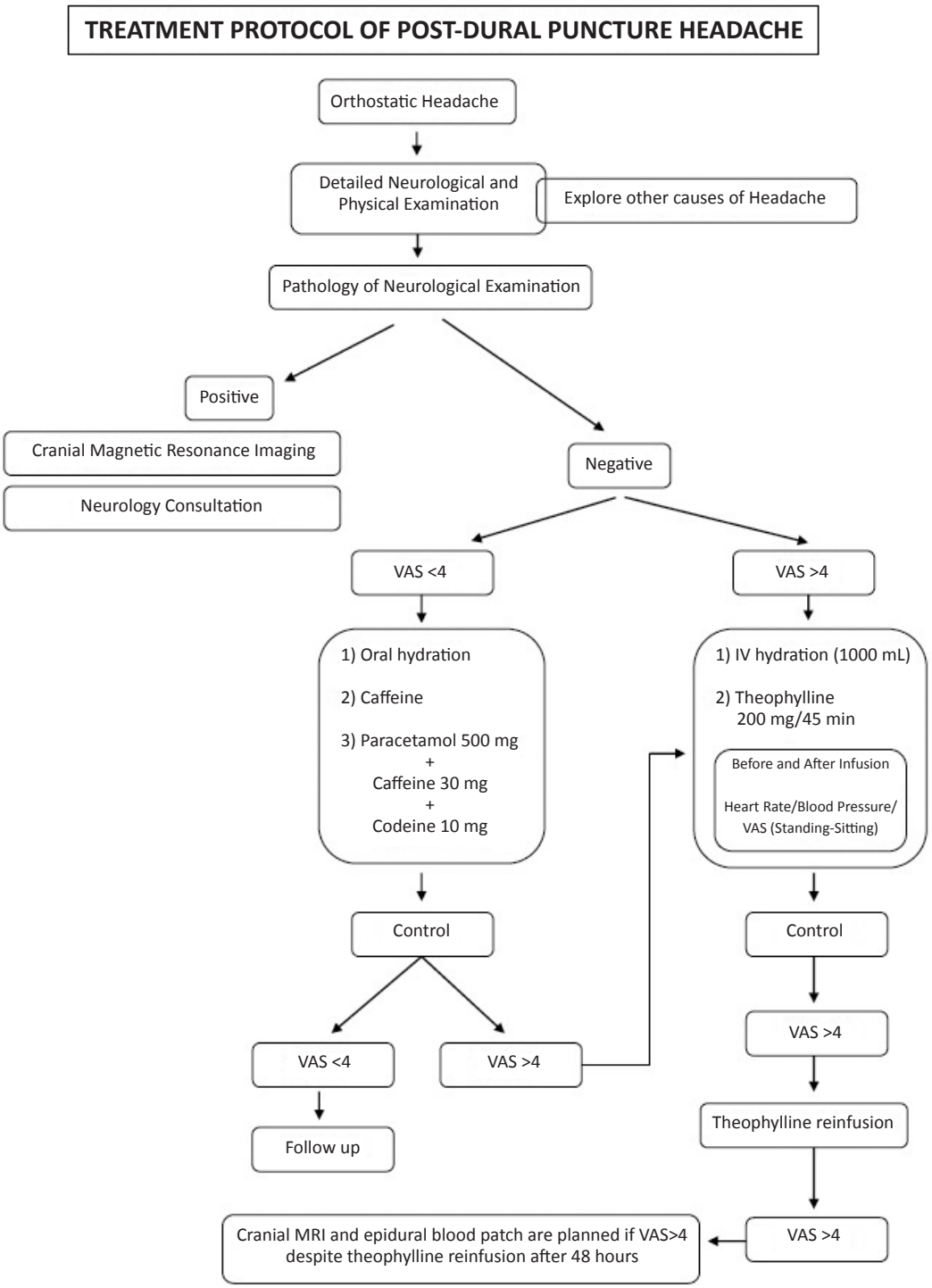

Figure 1. Treatment protocol of PHDH. Treatment protocol developed by the Algology Department of Mersin University

Statistical analysis:

Data for statistical evaluation were entered in the Statistical Package for Social Sciences version 24 (SPSS v.24) program. E-PICOS program was used in calculations based on "MedicRes Good Biostatistics Practice" Descriptive statistics were used for categorical variables frequency calculations were expressed in percentages. "Chi-square" test was applied for cross comparison tables. Independent group t-test and dependent group t-test were used for comparison of mean values. $p<0.05$ was set as the value for statistical significance.

RESULTS

Of the 65 patients who received theophylline, 39 were female (60%) and 26 were male (40%). The mean age of the patients was 34.1±10.9 years. There was no difference between male and female patients in terms of age average (p>0.05).

Headache was caused by spinal anesthesia in 58 (89.2%), diagnostic lumbar puncture in 5 (7.7%), epidural catheter insertion in 1 (1.55%) and epidural steroid administration in 1 patient (1.55%). Fifty eight patients had undergone surgery (33% orthopedic, 45% gynecologic and 22% other surgical procedures) (Table I).

Table I. Causes of headaches in PDPH

Causes of headaches	Number	Percent (%)
Cesarean Section	26	40
Lower extremity surgery	19	29
Diagnostic lumbar puncture	5	8
Genitourinary surgery	5	8
Gastrointestinal surgery	4	6
Lung surgery (for analgesia)	4	6
Epidural steroid injection	1	1.5
Epidural catheter placement	1	1.5

The lumbar puncture level was L3-L4 in 20 (48.7%) and L4-L5 in 21 patients (51.3%).

The records on lumbar puncture levels of 24 patients could not be reached.

Needle diameters used in lumbar puncture were 22 G in 44 (67.9%) and 18 G in 2 (3.1%) patients. The data on needle diameters of 19 (29%) patients were missing.

Table II. Patients with orthostatic headache and other complaints

Complaints	Number	Percentage (%)
Nausea	19	28.3
Tinnitus	11	16.4
Dizziness	10	15
Vomiting	8	12
Diplopia	5	7.4
Photophobia	5	7.4
Phonophobia	3	4.5
Numbness of left arm	3	4.5
Pain of left arm	2	3.0
Numbness of face	1	1.5

The number of patients with orthostatic headaches was 37 (56.9%). Seven of the patients (10.8%) had an additional complaint and 21 (32.3%) had multiple complaints (Table II). No complaints of fever or neck stiffness were detected.

Headache started 47.3 h (median: 24 h, min: 1 h, max 412 h) after lumbar puncture. Headache started in 6 patients (9.2%) within <23 hrs, while within 24-120 hrs in 53 (81.5%) and >121 hrs (6.2%) in 4 patients after lumbar puncture. The onset of headache records of 2 (3.1%) patients could not be reached.

The average time interval to theophylline administration was 139.7 hrs (median: 96 h, min 24 h, max 912 h). In 46 patients, theophylline infusion was started after 24-120/hrs in 46, and after >121 hrs in 17 patients.

The mean VAS scores of the patients after theophylline infusion decreased significantly compared to baseline (p=0.001) (Figure 2).

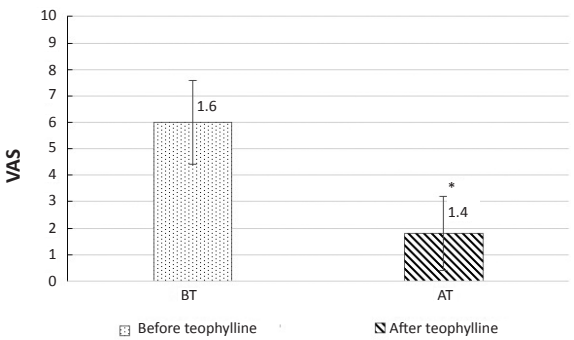

Figure 2. VAS values (mean(SD)) of patients before (BT) and after theophylline (AT). *p=0.001

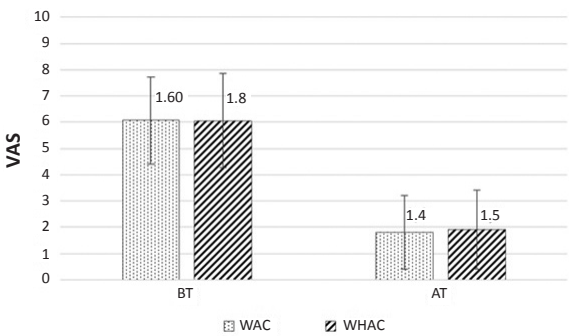

Figure 3. VAS values (mean(SD)) of patients before (BT) and after theophylline (AT) with (WAC) or without additional complaint (WHAC). Before; p>0.05, After; p>0.05

The mean VAS averages of the patients with any additional complaints compared with patients who had only orthostatic headache were similar (p>0.05, p>0.05, respectively) (Figure 3).

The mean heart rates were 75.63±10.5 bpm before and 77.76±10.1 bpm after theophylline infusion (p>0.05). The mean systolic blood pressures were 116.63±12.6 mmHg before and 119.05±12.5 mmHg after infusion (p>0.05). Mean values of diastolic blood pressures were 69.27±9.3 mmHg and 71.24±7.6 mmHg before, and after theophylline infusion, respectively (p>0.05).

There were no reports of theophylline-related adverse events in the patient records.

Theophylline infusion was administered once in 44 (67.7%), twice in 17 (26.1%) and thrice in 4 (6.15%) patients (Table III). The third theophylline infusion was performed for symptomatic treatment in the period of epidural blood patching. No other treatment was needed in 11 (64.7%) of the patients who were administered theophylline infusion twice. An epidural blood patch was applied in 10 patients (Table III). Epidural blood patch was applied in four patients with inadequate theophylline treatment and six patients with relevant imaging findings. Repeated applications were made to reduce the severity of the symptoms until the patch was made. In 8 (80%) of the patients for whom the blood patch, was applied, and 14 (25.5%) of the patients who did not receive the patch had a concomitant disease (p=0.001).

Table III. PDPH treatment

Treatment	n	%
The number of theophylline administration		
1	44	67.7
2	17	26.1
3	4	6.1
Patients treated only with theophylline	55	84.6
Epidural blood patch applied patients	10	15.4
Inadequate response to theophylline	4	6.2
Radiological finding of leakage	6	9.2

DISCUSSION

Our study was a retrospective evaluation based on the efficacy of theophylline in PDPH treatment. Fifty-five patients (84.6%) were treated successfully with theophylline. In addition to cases with headache, theophylline was an effective treatment for our patients with neurological symptoms. We showed that theophylline treatment was effective in patients for whom epidural blood patch application was planned. Hemodynamic changes and drug-related side effects were not detected in the patients.

According to the "3rd edition of the International Classification of Headache Disorders (ICHD-3 beta)", orthostatic headache begins within 5 days after dural puncture [1]. In some case reports, orthostatic headache has been reported even 5 days after dural puncture. In our study, in 81.5% of patients, headache started within 5 days following dural puncture and was in similar with ICHD-3 beta [10].

The theory of venous dilatation, one of the theories explaining the development of dural puncture- related headache, also appears to explain the efficacy of vasoconstrictor drugs such as theophylline [11]. Methylxanthines are associated with phosphodiesterase inhibition, adenosine antagonisation and calcium re-uptake from the sarcoplasmic reticulum [12,13]. Adenosine is a potent vasodilator in the brain [14,15]. Adenosine receptor blockers such as theophylline have been shown to reduce adenosine regulated vasodilation [16]. Ibayashi et al. [7] showed that the rat pial vessel diameter decreased with theophylline infusion. Case reports using theophylline except in patients with PDPH also support this result. For example, in one study, it was reported that headache regressed, and pathologic imaging findings disappeared in patient with Arnold Chiari Type 1 malformation who received theophylline therapy [17]. Hungs et al. [18] reported that theophylline treatment reduced the severity of orthostatic headache in a 58-year-old woman with spontaneus intracranial hypotension headache with a history of 1.5 years. The rapid decline in these complaints in patients who had severe neurological findings in PDPH may be considered as the finding that theophylline is a highly effective drug in the treatment of intracranial pressure.

The relationship between needle diameter and development of PDPH has been shown in many studies. It is stated that the use of large diameter needles causes greater lesions in the dura and more frequent

CSF leakage [19]. Also the type of needle used has been associated with development of PDPH. The American Academy of Neurology has suggested using a small-scale atraumatic needle to reduce the risk of PDPH, and placing the stylet into the needle in retries [20,21]. In their study Turnbull et al. [22] showed that the incidence rates of PDPH development after spinal anesthesia were 40% for 22 G, 25% for 25 G, 2-12% for 26 G, and <2% for 29 G. We determined that 22 G spinal needle was used in 67.9% of our patients. Theophylline treatment reduces VAS value and symptoms even related to large holes created by using large bore needles. This condition can be evaluated as an additional indication of the effectiveness of the drug.

There were 6 studies evaluating theophylline activity in PDPH in our literature search [12,13,23,24]. Theophylline was administered intravenously in 4 of these studies and orally in 2 of them. Ergun et al. [12] showed that 35 patients with PDPH who had lumbar puncture at diagnosis or during neuro-axial anesthesia had a mean VAS score of 7.05±1.47 points before the treatment in the 200 mg intravenous treatment group and 2.88±2.31 4 hours after the treatment. There was no statistically significant difference in VAS values compared to the placebo group. In another study, it was reported that 31 patient with PDPH after diagnostic lumbar puncture who had treated with aminophylline, the pre-treatment mean VAS score was 7.72±1.65 points and the mean VAS scores at 30. min, 1. hrs, 8. hrs, 1, and 2. days after treatment were 4.84±2.53, 3.53±2.06, 2.38±1.96, 1.44±1.87, 0.81±1.79 points, respectively. In addition, satisfaction of the patients were evaluated with the "patient global impression of change" (PGIC) scale and more than 50% of the patients described themselves as being healed or very healed [13]. In another study, Akdere et al. [23] compared theophylline with combination of paracetamol-caffeine and placebo in the treatment of PDPH. They stated that other medication group did not detect a significant change and in theophylline group, pre-, and post-treatment mean VAS scores were 7±2.15 and 2.2±2.04 points, respectively [23]. We observed that while standing VAS scores were 6.0±1.6 and 1.8±1.4 points before, and after the infusion, respectively, and we think that theophylline has an important role in the treatment of PDPH.

Despite the publications on the effectiveness of theophylline treatment, we think that clinicians are approaching this treatment with suspicion because of its side effects. When theophylline plasma concentration is above 20 μg mL^{-1}, it causes nausea, vomiting, diarrhea, insomnia, irritability and headache, while over 30 μg mL^{-1} concentration, it causes cardiac arrhythmia, hypotension, hypoglycemia and hypokalemia. When theophylline exceeds a concentration of 40 μg mL^{-1} it can cause epilepsy, brain damage and death. These side effects often occur with high plasma concentrations due to rapid intravenous infusions [25]. Carrier et al. [26] who had infused 500 mg aminophylline in 500 cc % 5 dextrose solution in 20-30 minutes in acute asthma, measured mean peak plasma concentration as 15.1 μg mL^{-1} in the first hour after infusion. In addition, Andreas et al. [27] reported that intravenous theophylline infusion increased systolic blood pressure and heart rate in patients with congestive heart failure, but this was not statistically significant. In previous studies, theophylline was used orally 500 mg 3 times per day for the treatment of PDPH. No advers effects were reported [28]. In our study, there was no significant change in haemodynamic parameters after theophylline infusion.

It has been reported that the use of theophylline for PDPH should be repeated in different studies. In one study, it was reported that 6 patients (35.3%) with a VAS value of <50% needed a second theophylline infusion and in the other study, 5 (25%) of 20 patients required second theophylline infusion [12,23]. In our study, 22 (33.8%) patients received more than one infusion. Half of the patients (50%) improved with second infusion. We believe that repeated infusions can be applied in patients whose symptoms do not show adequate regression in the first application, but patients should be kept under observation and evaluated without delay for epidural blood patch application.

The most important limitation of our study was its retrospective design. Although this study had a retrospective design, patients were treated under a standard treatment protocol. Furthermore, although this study had the largest sample size among current studies on treating PDPH with theophylline drugs, the sample size was still relatively small. Additionally,

the method employed was not compared with a placebo or other current clinical treatments for PDPH. The data on the number of repeated lumbar punctures were not available.

We believe that invasive options in the appropriate patients as a step after theophylline treatment are important in terms of both eliminating the risk of invasive complications and providing the comfort of daily life of the patient. We think that the theophylline infusions can be used as an effective method in PDPH treatment algorithm. However, we believe that prospective randomized controlled trials with large-scale participation are needed to make more accurate interpretations.

Ethics Committee Approval: University of Mersin (11.05.2018)
Conflict of Interest: None
Funding: None
Informed Consent: The patients' consent were obtained

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