Post-dural puncture headache (PDPH) is the most common complication of lumbar puncture. Its clinical manifestations are pain in the forehead and the occipital region, or diffuse headache. The pain is dull or fluctuating, becoming worse when standing and better when lying down, and is often accompanied by symptoms including a stiff neck, tinnitus, hearing loss, photophobia, and...
nausea, which cause great suffering to the patients (1). According to epidemiological data, approximately 10% to 30% of the patients who undergo lumbar puncture suffer from PDPH within 48 hours of the procedure (2,3). Interestingly, the prevalence of PDPH is higher in obese young women and pregnant women (4). Currently, commonly used treatments for PDPH include rehydration, the administration of corticotropin, caffeine, or sumatriptan, and the application of an epidural blood patch (EBP). The efficacy of theophylline has been proven in a placebo-controlled study in which 17 PDPH patients received an intravenous (IV) injection of 200 mg theophylline. The visual analogic scale (VAS) scores 4 hours after treatment were significantly different compared with those of the placebo group (5). At present, the clinical application of theophylline has been replaced by aminophylline and doxofylline because it is difficult to purchase theophylline in most hospitals in China and other countries. In this multicenter study, we assessed the effectiveness and safety of an IV injection of aminophylline on PDPH.

**Methods**

**Study Design**

The study was a multicenter, open-label study to assess the effectiveness and safety of aminophylline on PDPH. The study protocol was approved by a center medical ethics committee and the research board of each participating center. The goal, procedure, and safety aspects of the study were explained to each patient. All patients provided written informed consent to participate in the study.

**Study Participants**

Patients were enrolled at 3 centers in China (the First Affiliated Hospital of Zhengzhou University, the Fifth Affiliated Hospital of Zhengzhou University, and Henan Province Hospital of Traditional Chinese Medicine). Criteria for entry into the study were dural puncture (the puncture was performed at the L3-L4 or L4-L5 level with a 22-gauge needle in each center) performed for diagnosis; headache has developed after the dural puncture; PDPH was defined according to the International Classification of Headache Disorders III (ICHD-3) criteria (2); VAS score of the headache was 5 or more than 5; and an age between 18 and 70 years old.

Exclusion criteria included a previous history of headache that could interfere with PDPH diagnosis in this study; a history of central nervous system diseases including intracranial hemorrhage, seizures, intracranial hypertension, and hydrocephalus; a history of cardiovascular system diseases including coronary heart disease, arrhythmias, and hypertension; and a history of peptic ulcer. Women of childbearing potential should have had a negative pregnancy test result prior to injection. Furthermore, women who were pregnant, nursing, or planning a pregnancy were excluded.

**Aminophylline Treatment**

To insure the time between the onset of headache and the initial treatment was within one hour, all patients who satisfied the inclusion and exclusion criteria were treated with aminophylline with 30 minutes after the PDPH was diagnosed. Aminophylline (250 mg; Shanghai Modern Hasen Pharmaceutical Co., Ltd, Shangqiu, China) was dissolved in 100 mL saline for IV injection and was administered over at least 30 minutes, once daily for 2 consecutive days. During the aminophylline treatment, no other treatment medication or method for PDPH was applied.

**Effectiveness and Safety Measures**

All the follow-up measurements were taken in each site and all the patients were hospitalized during the follow-up period. The primary endpoints of the study were the degree of headache when patients were in a standing position. The degree of headache was evaluated using the VAS (an 11 point scale from 0 – 10 with 0 being no headache). VAS scores were determined with the patient’s standing position (lies flat for more than 10 minutes and then stands for 5 minutes) before the first aminophylline treatment and at 30 minutes, one hour, 8 hours, one day, and 2 days after treatment. The secondary endpoints were the overall response to treatment as assessed on the basis of the Patient Global Impression of Change (PGIC) scale. PGIC is a score evaluated by the patients. In this study, patients gave scores according to their overall condition before and after treatment: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse.

The safety of the IV aminophylline treatment for PDPH was evaluated based on the occurrence of adverse reactions.

**Statistical Analysis**

The IBM SPSS Statistics 19.0 (SPSS Inc., IBM Company, New York, United States) was used for statistical evaluation of the data. Quantitative data are present-
ed as average ± standard deviation. A non-parametric test of multiple related samples (the Friedman test) was used to analyze VAS score data at different time points before and after treatment. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**Patient Characteristics**

Patients were recruited between June 2014 and September 2014. A total of 39 patients were screened, and 32 patients participated (8 in the First Affiliated Hospital of Zhengzhou University, 10 in the Fifth Affiliated Hospital of Zhengzhou University, and 14 in the Henan Province Hospital of Traditional Chinese Medicine). The indication for lumbar puncture in these patients were possible central nervous system infection (16 patients) or demyelinating disease (12 patients) or central nervous system tumors (4 patients). In the end, 31 patients completed the study, one patient dropped out of the study because of the adverse drug reaction. From these 32 patients, 22 were women (68.8%) and 10 were men. The age range was 21 – 66 years, with an average of 49.3 ± 10.4 years.

**Effectiveness Results**

The VAS score of the 32 patients before the first treatment was 7.72 ± 1.65. Thirty minutes after treatment, the headaches of all but 2 patients were relieved to different extents, and the VAS score was decreased to 4.84 ± 2.53. The headaches in 2 patients completely disappeared after the first treatment, resulting in VAS scores of 0. The degree of headache further declined over time; one hour after aminophylline administration the VAS score was decreased to 3.53 ± 2.06. Two days after treatment, the VAS score was 0.81 ± 1.79 and headaches in 24 patients (75.0%) completely disappeared. The VAS scores at different time points after treatment were all statistically significantly different compared with those before treatment \( (P < 0.05) \) (Fig. 1). More than 50% of the patients reported that they were “very much improved” or “much improved” 30 minutes after the initial treatment, increasing to 93.8% 2 days after treatment (Table 1).

**Safety**

During follow-up, one patient experienced an allergic reaction about 30 minutes after the first treatment. The clinical manifestation of the allergic reaction was red rash with moderate itch in the trunk and limbs. The patient discontinued the study and received antihistamine drugs. The red rash disappeared 3 days after the treatment. No other treatment-related adverse reactions were observed in this study.

**DISCUSSION**

Of the 32 PDPH patients enrolled in this study, 22 were women, accounting for a 68.8% participation of women. This is similar to previous studies showing that the prevalence of PDPH is higher in women (1).

So far, few studies have assessed the effectiveness and safety of drugs for the prophylaxis of PDPH (6). Morphone (7), cosyntropin (8), and aminophylline (9,10)
decreased the number of patients affected by PDPH of any severity after a lumbar puncture. But when a PDPH occurs, how should we treat it? In this study, we used a common clinical drug, aminophylline, that was injected intravenously to treat PDPH in 32 patients, and showed statistically significant effectiveness half an hour after administration. An EBP is considered as one of the most effective treatments for PDPH (11), with a success rate above 70% after the initial treatment (12). However, an EBP is an invasive treatment and has the potential to cause radiating pain around the nerve roots at the injection site and around the subarachnoid adhesions. Previous research showed that the rate of nerve root radiating pain when using 15 mL autologous blood in an EBP treatment was as high as 56.3% (14). Caffeine is the most widely accepted pharmacologic treatment for PDPH, it has been proven to be effective in decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions (15). But caffeine belongs to a class of state control of psychotropic substances in a number of countries and prescribing caffeine needs complex procedures and special permission. Traditional therapies such as bed rest and rehydration are usually ineffective when the headache is severe (16). A tight abdominal binder raises the intra-abdominal pressure. The elevated intra-abdominal pressure is transmitted to the epidural space and may relieve the headache (17). Unfortunately, tight binders are uncomfortable and are seldom used in current practice (18). In this study, we administered an IV injection of aminophylline to treat PDPH and achieved an effectiveness similar to that of an EBP or caffeine. The treatment was also relatively straightforward and non-invasive. Therefore, we believe that an IV injection of aminophylline could be the preferred method for the clinical treatment of PDPH.

In addition to assessing the long-term effectiveness of an IV injection of aminophylline, we evaluated its effectiveness as an early-stage treatment for PDPH. We found that the VAS scores were substantially and statistically significantly decreased already half an hour after treatment. PDPH is often accompanied by tinnitus, hearing loss, photophobia, and nausea. Therefore, we used PGIC to evaluate the changes in the overall patient condition half an hour after treatment: 53.1% of the patients described their condition as “very much improved” and “much improved.” In other countries, studies on theophylline for treating PDPH have not evaluated the efficacy of theophylline at the early stage after treatment. Only one study showed that the VAS score decreased from 7.07 ± 1.47 to 2.88 ± 1.47 4 hours after theophylline treatment (5). Relief of headaches following treatments such as an EBP mostly appears several hours after the treatment. Thus, we believe that, compared with theophylline and other treatments, an IV injection of aminophylline could have better early-stage effectiveness in the treatment of PDPH. Nevertheless, this needs to be confirmed by further research.

Although there have been studies with small population sample sizes that showed that theophylline could treat PDPH (5) and mountain sickness (19), there has been no report on treating PDPH with aminophylline. Aminophylline is the double salt of theophylline and ethylenediamine, the latter increasing the water solubility of theophylline. It is generally believed that aminophylline is metabolized in the body to theophylline and then becomes pharmacologically active. However, drugs of the same family, or even different formulae of the same drug, could have different pharmacological effects in the human body (20). In addition, aminophylline has replaced theophylline in many countries due to theophylline’s lack of availability. We obtained a positive treatment outcome and improved early-stage effectiveness. These results have important practical significance.

Clinical pharmacological studies showed that adverse reactions of aminophylline mainly appear at plasma aminophylline concentrations higher than 15 µg/mL. The manifestations include nausea, vomiting, arrhythmia, and convulsions. The dose of aminophylline used in this study was lower than that used for regular clinical treatments and would, hence, not have caused an excessive plasma concentration, explaining the absence of adverse reactions related to the drug treatment except for one patient who experienced an allergic reaction in all 32 treated patients. Therefore, the study results show that an IV injection of 250 mg aminophylline can be regarded a safe treatment for PDPH.

Aminophylline is one of the methylxanthine drugs. Its mechanism underlying the treatment effects in PDPH remains unclear. It is currently believed that the mechanism could be related to specific factors. Firstly, aminophylline could block adenosine, contract intracranial blood vessels, and block the transmission of pain through nociceptive structures. Secondly, aminophylline could inhibit phosphodiesterase and raise the intracellular cyclic adenosine monophosphate (cAMP) concentration. Thirdly, aminophylline could suppress the calcium uptake by the endoplasmic reticulum in endothelial cells, stimulate calcium-potassium pumps, and
increase the secretion of cerebro-spinal fluid (CSF).

Although this study had the largest sample size among current studies on treating PDPH with theophylline drugs and it for the first time evaluated the effectiveness of an IV injection of aminophylline in treating PDPH, the sample size was still relatively small. Furthermore, the method employed was not compared with a placebo or other current clinical treatments for PDPH. It is true that PDPH is a self-limited disease in most patients and most PDPH could disappear with 5 – 15 days under the effect treatment (4). In our study, we found that the VAS scores were statistically significantly decreased already half an hour after the first treatment, although the headache in all patients was moderate to severe (VAS scores ≥ 5) before the treatment. In studies that have a placebo-controlled group, by contrast, there were no statistical differences of the VAS score before and 4 hours after the placebo treatment (5). So, we believe that the improvement we observed in this study is not due to the natural history of PDPH.

**CONCLUSION**

In summary, this study primarily demonstrated that the IV injection of aminophylline may be a straightforward, safe, and effective treatment for PDPH, and has improved early-stage effectiveness. Further double-blind, controlled multi-center studies using an adequate number of patients are required to validate our findings and to explore efficacy comparisons between an intravenous injection of aminophylline and other treatments.

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**REFERENCES**
