

Comparing the effect of pregabalin, gabapentin, and acetaminophen on post-dural puncture headache

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ABSTRACT

Introduction: Post-dural puncture headache (PDPH) is a common complication of lumbar puncture for any purpose. To avoid the need for invasive methods of treating PDPH such as blood patch, the search for novel pharmacological agents to manage PDPH continues. The aim of this study was to compare the effects of acetaminophen, gabapentin and pregabalin in controlling PDPH in patients who underwent surgery under spinal anesthesia. **Materials and Methods:** A total of 90 patients who underwent elective orthopedic surgery under spinal anesthesia and suffered from PDPH consequently were enrolled in this randomized trial. Patients were categorized randomly into three groups. Group A, B and C have received Acetaminophen, Gabapentin and Pregabalin (3 times a day for 3 days), respectively. The effect of medications on the severity of PDPH was evaluated and compared using visual analog scale (VAS). **Results:** The mean VAS score was significantly lower in pregabalin group compared with others 24, 48 and 72 h after the onset of headache ($P = 0.001$ for all of them) and lower in Gabapentin group compared with Acetaminophen group 24, 48 and 72 h after the onset of headache ($P = 0.001$ for all analyses). No adverse outcome was reported in groups. **Conclusion:** Pregabalin and gabapentin are both useful and safe in management of PDPH, but pregabalin is more effective in this regard.

Key words: Acetaminophen, gabapentin, post-dural puncture headache, pregabalin

INTRODUCTION

Post-dural puncture headache (PDPH), since its first description by August Bier in 1898, remains a common complication for surgical patients.^[1-3] It can cause post-operative morbidity for patients who undergo lumbar puncture for diagnostic or therapeutic purposes (administration of drugs or spinal anesthesia).^[2,4] According to the definition of International Headache Society (IHS), PDPH is a headache that develops following a lumbar puncture, occurs or worsens <15 min after assuming the upright position and improves in the recumbent position in <30 min with at least one of the following symptoms: Neck stiffness, tinnitus, hypacusia, photophobia and nausea.^[5] In general, it begins within 2 days and usually

resolves spontaneously in a few days, but it can be severe and disabling and may last for up to 6 weeks.^[4,6] Younger age, female gender, pregnancy and labor, large needle size, direction of the cutting needle bevel when puncturing the dura, multiple dural punctures and previous history of PDPH are among risk factors for occurring PDPH.^[6,7]

Supportive treatments (such as hydration and bed rest), Acetaminophen and non-steroidal anti-inflammatory drugs, opioids and caffeine are now used for the management of PDPH but sometimes these methods are insufficient in controlling PDPH. Thus, to avoid the need for invasive methods such as epidural blood patch (EBP), the search for new pharmacological agents to manage PDPH continues.^[2,8] Gabapentin and pregabalin have been suggested in several studies to be efficient. Gabapentin is an antiepileptic drug and a structural analogue of gamma-Aminobutyric acid (GABA) but it does not act through GABA receptors. It has binding affinity for alpha2-delta type voltage-dependant calcium channels. Gabapentin was approved as an effective agent in management of neuropathic pains by Food and Drug Administration in 2002. Pregabalin, is also an antiepileptic agent and a ligand of the alpha2-delta type voltage-dependent calcium channels.^[8,9] The aim of this study was to compare the

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effects of acetaminophen, gabapentin and pregabalin in controlling PDPH in patients who underwent surgery under spinal anesthesia.

MATERIALS AND METHODS

This double-blinded clinical trial was conducted with the approval of the Scientific and Ethical Review Boards of Urmia University of Medical Sciences and during an 18 month period (between January 2012 and July 2013). After obtaining written informed consent, 90 patients between the age of 20 and 40 years who underwent elective orthopedic surgery under spinal anesthesia and were diagnosed with PDPH according to the criteria of IHS,^[5] were enrolled randomly in this study. All participants were American Society of Anesthesiologist's (ASA) physical status I according to the classification system ASA. The exclusion criteria were: History of chronic headache, hepatic disease, known allergy to gabapentin, pregabalin or acetaminophen, physical status of ASA II or above, multiple lumbar punctures, severe bleeding (> 20% of blood volume), treatment with Vasopressors, signs of meningismus, history of pancreatitis, galactosemia, migraine, or asthma.

All patients were premedicated with 1 mg intravenous Midazolam administration and hydrated with 5 cc/kg Ringer solutions and then underwent spinal anesthesia using 25-gauge quincke needle through the space between 4th and 5th lumbar vertebra in a sitting position and within one try. After observing cerebrospinal fluid (CSF) flow through the needle, 12 mg Bupivacaine 0.5% was injected to reach the sensorial block up to the level of T10. During the lumbar punctures, the bevel direction was ensured to be parallel to the dural fibers. All patients were followed-up for headache during the post-operative period in hospital and after discharge. The patients suffering from PDPH were randomly divided into three groups (A, B and C) using packages with different colors with the same number of drug tablets inside (each 9) so that investigators were not aware of the group's identity. All patients were instructed on how to take the medications (3 times a day). Immediately after diagnosis, treatment was started in all patients suffering from PDPH. Oral fluid therapy as much as tolerable and relative bed rest protocol was identical among three groups, whilst Group A received 500 mg oral Acetaminophen tablets, Group B received 300 mg oral Gabapentin tablets and Group C treated with 100 mg oral pregabalin tablet, each 3 times a day (every 8 h). Headache was evaluated using visual analog scale (VAS), at the time which PDPH symptoms began and was followed 24, 48 and 72 h after it. The pain scale consisted of a 10 cm horizontal line marked from 0 (denoting no pain) to 10 (denoting

worst possible imaginable pain). Data were analyzed via Chi-square and ANOVA test where needed, using SPSS statistical software version 16 (Chicago, IL).

RESULTS

A total of 90 patients, who underwent elective orthopedic surgery under spinal anesthesia and experienced PDPH, were enrolled randomly in our study. The main patients' characteristics in three groups were demonstrated in Table 1 and no significant difference was seen among the age and sex of three groups [Table 1].

The mean VAS score at the onset of headache (time 0), was 7.50 ± 1.35 in Group A, 8.03 ± 1.60 in Group B and 8.87 ± 1.19 in Group C. Significant difference was observed between three groups ($P = 0.001$). The mean pain score was 5.07 ± 1.40 in Group A, 4.87 ± 1.16 in Group B and 3.67 ± 0.71 in Group C, 24 h after headache's onset. VAS scores was significantly lower in Group C compared with B and in Group B compared with Group A ($P = 0.001$). The mean pain score, 48 h after the onset of headache was 3.07 ± 1.37 in Group A, 2.47 ± 1.13 in Group B and 0.87 ± 0.73 in Group C ($P = 0.001$). The mean pain score, 72 h after headache's onset was 1.57 ± 1.04 in Group A, 1.03 ± 0.18 in Group B and 0.13 ± 0.30 in Group C ($P = 0.001$) [Table 2 and Figure 1].

DISCUSSION

PDPH is a common and unpleasant complication of spinal anesthesia.^[7,10] The incidence of PDPH in spinal anesthesia ranges from 0.3% to 20% in different studies.^[10] More than a century passed since its first description, but the PDPH remains a challenge both for patients and anesthesiologists. It is accompanied by post-operative

Table 1: Patient's characteristics among three study groups

Characteristics	Acetaminophen	Gabapentin	Pregabalin	P value
Age (mean±SD)	29.73±5.56	27.50±6.22	29.06±8.78	0.45
Sex (M/F)	15/15	9/21	15/15	0.16

SD: Standard deviation, M: Male, F: Female

Table 2: Pain according to visual analog scale scores in pain's onset and after 24, 48 and 72 h

Variable	Acetaminophen	Gabapentin	Pregabalin	P value
Pain's onset	7.50±1.35	8.03±1.60	8.87±1.19	0.001
After 24 h	5.07±1.48	4.87±1.16	3.67±0.71	0.001
After 48 h	3.07±1.37	2.47±1.13	0.87±0.73	0.001
After 72 h	1.57±1.04	1.03±0.18	0.13±0.30	0.001

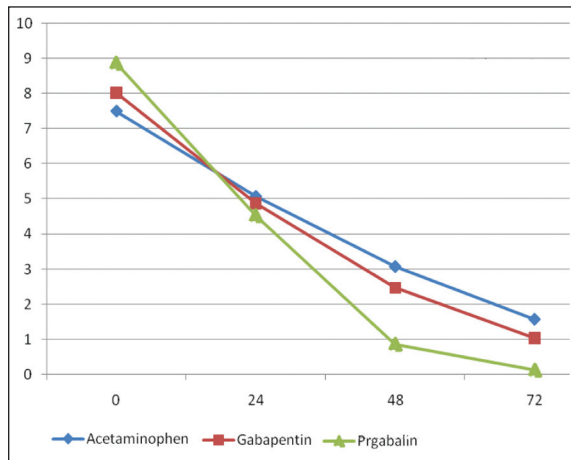


Figure 1: Post-operative pain according to visual analog scale scores in study groups

morbidity, although it is not usually life-threatening.^[2,7,11] Despite the above mentioned probable mechanisms, the exact pathophysiology of PDPH is not fully understood yet.^[3,4] It is presumed that CSF leakage and CSF depletion leads to traction of some pain-sensitive intracranial structures and so, causes PDPH, but dilation of cerebral veins and venous sinuses was also suggested as a reason for this complication.

Since PDPH is naturally self-limited, most authors have suggested 24 h of conservative and supportive therapy (bed rest and hydration) once the diagnosis of PDPH is made.^[12] Several pharmacological agents have been suggested for PDPH management including acetaminophen, caffeine, non-steroidal anti-inflammatory agents, corticosteroids, theophylline and sumatriptan. EBP is a very effective, but invasive method in controlling PDPH and It can be associated with serious complications such as seizure or infection, so less invasive pharmacologic treatments are preferred among patients and anesthesiologists.^[4] It has been indicated in some studies that alpha2-delta type voltage-dependent calcium channels are effective in this pain phenomenon. Both gabapentin and pregabalin have binding affinity for this type of calcium channels. In this regard, it has been claimed in a number of studies that gabapentin and pregabalin can reduce PDPH via affecting this type of calcium channels.^[8]

In the study of Erol, Gabapentin could significantly reduce the pain score, nausea and vomiting in patients with PDPH,^[2] and also the review of Basurto Ona *et al.* demonstrated that gabapentin can decrease the severity of PDPH.^[13] The study of Lin *et al.* also showed that the administration of 400 mg gabapentin 3 times a day, could relieve PDPH remarkably in 24 h.^[14] Wagner *et al.* also reported similar findings in favor of gabapentin in

their study.^[15] Some studies have evaluated the effects of pregabalin in management of PDPH as well. In the study by Huseyinoglu *et al.*, 5 days administration of pregabalin significantly lowered VAS scores after 2nd day of treatment.^[8] Furthermore in the case study of Zencirci, pregabalin was demonstrated to be able to significantly decrease PDPH in patients who had not responded to conventional treatments.^[7] Beside studies which were mentioned above, very few studies have compared the efficacy of gabapentin and pregabalin in reducing PDPH. Moghaddam *et al.* reported that both pregabalin and gabapentin effectively reduced the severity of pain according to the numerical rating scale in PDPH and pregabalin seemed to be more efficient compared to Gabapentin.^[9] In this study, we compared the efficacy of gabapentin and pregabalin with one of the most commonly used analgesics, acetaminophen. All of the three agents (acetaminophen, gabapentin and pregabalin) were effective in lowering VAS scores at 24, 48 and 72 h after headache's onset but pregabalin alleviated the pain more effectively. On the other hand, the PDPH was more severe in the pregabalin group compared with others at the onset of headache and this baseline situation in association with a higher capability of pregabalin reduce the pain in comparison with others, magnifies significantly the effectiveness of pregabalin in alleviating PDPH in our study. As mentioned above, female gender is among risk factors for PDPH.^[16,17] In our study, there was no gender difference among groups; however the frequency of women was higher in gabapentin group. In general, this may support the analgesic effect of gabapentin in this specific patient population (women). Pregabalin and gabapentin have a similar mechanism of action, but differ in pharmacokinetic and pharmacodynamic characteristics.^[18] The results of our study and previous studies, suggest that gabapentin and pregabalin both can successfully reduce the PDPH in patients undergoing elective surgeries under spinal anesthesia. The effect of pre-operative administration of pregabalin on PDPH was also evaluated in the study of Rahmawy *et al.* In this study, pre-operative administration of 150 mg Pregabalin reduced the incidence and the severity of PDPH.^[10]

Some studies have demonstrated that a clinically useful effective dose of oral pregabalin inhibits central sensitization of electrical hyperalgesia in human volunteers. It seems that pregabalin, which has been effective in reducing hyperalgesia, may play an important role in acute post-operative pain control.^[19]

On the other hand pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, norepinephrine, substance P and calcitonin gene-related peptide. It leads to inhibitory modulation of "overexcited" neurons and returning them to a "normal" state. Finally,

pregabalin has a more appropriate pharmacokinetic profile than gabapentin, including dose-independent absorption and far more potent than gabapentin while producing fewer adverse effects.^[20] In our study, no complication was reported due to the administration of gabapentin or pregabalin which supports the safety of short term administration of these two drugs especially pregabalin which was revealed to be more effective in management of PDPH in comparison with others. Ultimately, the authors recommend further studies, assessing the efficacy of pre-operative administration of gabapentin or pregabalin in preventing PDPH.

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