Review Article

The Effect of Sumatriptan, Theophylline, Pregabalin and Caffeine on Prevention of Headache Caused By Spinal Anaesthesia (PDPH): A Systematic Review

Abstract

Spinal anaesthesia (SA) is a common method during surgery due to easy administration, rapid effects, relaxes muscles and controls pain. But, post-dural puncture headache (PDPH) is a common problem after SA that occurs in 6%–36% of SA. We assessed the effect of four common treatment drugs sumatriptan, theophylline, pregabalin and oral caffeine on prevention of PDPH. In this systematic review, all randomized clinical trials (RCTs) during January 2015 and December 2021 were searched from PubMed, Google Scholar, Web of Science, Cochrane review and Clinical Key with a specific search strategy. The article qualities were assessed by two independent authors and were screened for relevant sources based on inclusion and exclusion criteria. Moreover, the included articles data were extracted and checked for regular basis. A total of 421 articles were identified and 193 articles were removed following a preliminary review and finally, 14 articles were included in review. Overall, we identified five RCTs on the effect of caffeine, two RCTs on the effect of sumatriptan, three RCTs on theophylline, three RCTs on pregabalin and one RCT on theophylline and sumatriptan in PDPH prevention. This review supports the effects of theophylline, pregabalin and sumatriptan in the prevention of PDPH incidence and treatment of PDPH intensity, but we cannot draw the same conclusions about caffeine due to some negative results about the caffeine effect. Nevertheless, this extracted conclusion should be considered and interpreted with caution and limited generalizations due to the small number of studies, the variety of evaluated drugs and measures, the low sample size and the bias presented.

Keywords: *Caffeine, headache, pregabalin, review, spinal anaesthesia, sumatriptan, theophylline*

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Introduction

Spinal anaesthesia (SA) for analgesia has more advantages than general anaesthesia during surgery.[1-3] In addition to being easy to administer, SA has rapid effects, relaxes muscles, and controls pain while performing surgery.[4,5] SA is recommended for caesarean delivery[6] due to low risk of maternal pulmonary aspiration and foetal distress.[7] Nevertheless, SA has side effects such as neurological impairment, hypotension, decreased heart rate, nausea and vomiting, urinary retention, back pain, decreased ventilation and post-dural puncture headache (PDPH).[8-12]

PDPH is a common problem after SA and an unpleasant emotional experience.[8,9,13] A prevalence of 6 to 36% has been reported for PDPH following SA.[14,15] Symptoms of PDPH appear a few hours after dura puncture and last up to 7 days (4–6 days).[4] PDPH can be associated with nausea, vomiting, neck stiffness, visual and auditory impairment, seizures, subdural haemorrhage, and rarely cerebral palsy[14,16] The most common risk factors for PDPH include female gender, young age, pregnancy, previous headache history, low CSF pressure, and low body mass index.[14,17-20]

Many treatment protocol are available to prevent and reduce the PDPH[14,21-24] including cosintropin, aminophylline, dexamethasone,[13,25,26] fluid therapy and bed rest,[22,27] epidural saline injection, intrathecal catheter insertion, epidural prophylactic blood patch,[28] performing special anaesthesia techniques[29] and the use of caffeine.[30,31] However, the results of the studies are contradictory. Despite various treatments, PDPH is still an unwanted and annoying complication of SA.[21] Among

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the treatments, caffeine is a safe and effective option in the management of PDPH.[23,31-34] Oral and intravenous theophylline can be effectively treated PDPH, which inhibit the enzyme phosphodiesterase and increase the concentrations of cellular CAMP and antagonistic effects of adenosine receptors.[13] Pregabalin, is a anticonvulsant drug that prevents calcium from entering the body, therefore preventing headaches.[35] Sumatriptan, as a serotonin receptor agonist, effectively relieves migraines and cluster-type headaches.[36] However, different methods for PDPH prevention and treatment are suggested with conflicting results. The effectiveness of drugs used for PDPH was reviewed in 2015, but since then no systematic review or meta-analysis has been conducted, but several clinical trials on theophylline, pregabalin, sumatriptan and caffeine have been conducted. A systematic review of the clinical efficacy of these four drugs is needed in order to inspire future guidelines. Therefore, we aimed to evaluated the results of different treatment interventions of sumatriptan, theophylline, pregabalin, and oral caffeine on prevention of PDPH in a systematic review.

Materials and Methods

In this systematic review, all randomized clinical trials (RCTs) during January 2015 and December 2021 in English-language. The inclusion criteria for RCTs were studies which considered the CONSORT form, human studies that the patients undergone lumbar puncture for SA, studies which the main outcome was headache after spinal, intervention included one or more of sumatriptan, pregabalin, theophylline, caffeine drugs and placebo or any other drug compared with the effect of the main interventions. In addition, study subjects were those who reported headaches following SA, either in the hospital or 5 days after surgery.[37] The exclusion criteria of the study were migraine history, other types of headaches, and other diseases.

The search was conducted in PubMed, Google Scholar, Web of Science, Cochrane review and Clinical Key with a specific search strategy related to sumatriptan, theophylline, pregabalin, caffeine, dural puncture, and spinal headache. Two authors (NA and HM) independently conducted the search in different databases and all sources were entered to EndNote software and duplicated sources removed. As a first step, unrelated and repetitive articles were screened among the found articles based on inclusion and exclusion criteria. To find other articles that may be related, reference lists of articles were manually searched. The titles and abstracts of the articles were reviewed independently by three researchers (two from anaesthesiology and one from the epidemiology department) and the full texts of the articles found to be relevant were then reviewed. Data were extracted by anaesthesiologists (NA and HM) who are the authors of this paper. A data collection form was used to extract clinical trial data for review on a regular basis. The article title, author names, years of publication, country of conducted study, sample size, age and sex of patients, types of study, and findings related to the variables under study.

The primary outcome in this review was headache after SA, myelogram, or diagnostic lumbar puncture that is a common complication caused by the puncture of the dura membrane.[38] In this study, a headache resulting from intentional tearing of the dura membrane in SA, occurring at the forehead or behind the head, aggravated by sitting or standing, and relieved partially or completely by sleeping, was considered. This headache is usually described as ambiguous or pulsating. associated symptoms are nausea and vomiting, anorexia, lethargy, neck pain, dizziness, tinnitus, hearing loss, vision problems such as double vision, blurred vision, photophobia, and paralysis of cranial nerves and seizures. Pain score and the severity of headache pain was measured in all included study by the visual analogue scale (VAS) scale. The VAS is commonly a 10-point scale was used with a score of 0 representing no pain and a score of 10 representing intolerable pain.[35,39,40] In addition, the patient, classification of headache severity was done as: No headache=0, mild headache<3, moderate headache 4–6 and severe headache >6.[41] Nevertheless, in some studies, a 5-point visual analogue pain scale was used to describe the intensity of pain. This scale varied from 0 = no pain, 1 = mild pain (pain which did not affect the everyday activity of patient), 2 = moderate pain (pain which was present on standing but relieved somewhat on lying down, confining them to bed), 3 = severe pain (pain which did not even relieve on lying down) and 4 = very severe pain (severe pain along with associated symptom, i.e., nausea, tinnitus, neck stiffness, etc.).[36,42]

Quality of extracted articles (risk off bias of individual stories)

Cochrane checklist was used to evaluate the quality of the articles. Two anaesthesiologists and an epidemiologist assessed the quality of the articles. The risk of bias in the quality of articles has been evaluated and reported. Reporting was also conducted based on the Prisma checklist. A random sequence generation and allocation concealment evaluation was used to evaluate selection bias in the articles included in this regular review. To evaluate performance bias, blinding performed on participants in each study was investigated and reported. Each of the final articles was evaluated for blinding the outcome in order to find detection bias. To determine reporting bias in each study, incomplete or selective outcome reporting was examined. Figure 1 shows the risk assessment of bias in the included studies.

Four common treatment interventions were assessed in this review for controlling the headache after SA. **Caffeine** is a methylxanthin that prevents sleepiness by blocking adenosine receptors, stimulating certain parts of the autonomic nervous system, and constricting cerebral

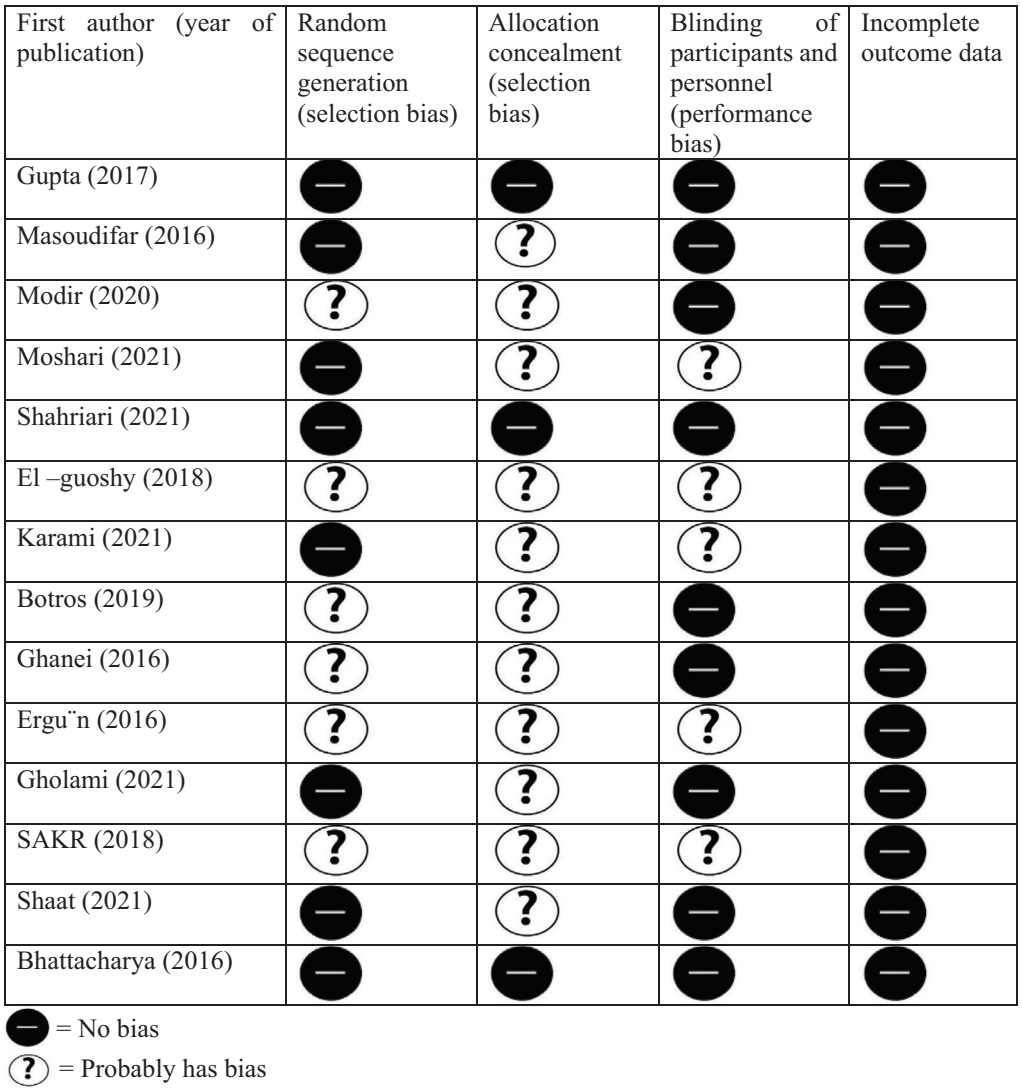

Figure 1: Assessment of risk of bias in included studies

vessels.[14] **Theophylline** tablet is one of the methylxanthines used in the treatment of asthma. It works by inhibiting the phosphodiesterase enzyme, increasing cell CAMP levels, and blocking the effects of adenosine receptors. This ultimately causes cerebrovascular contraction and can be effective in treating PDPH.[43] **Pregabalin** is one of the anticonvulsants that prevents calcium from entering the brain, thereby preventing headaches. It has also been used in patients with epilepsy, chronic pain, and anxiety disorders.[35] **Sumatriptan** is effective in relieving migraines and cluster headaches as a serotonin receptor agonist type 1. Among the most effective anti-migraine drugs, triptans have also been shown to be effective in managing PDPH. This drug is well tolerated and effective especially when combined with analgesics.[36]

Results

A total of 421 articles were identified by searching PubMed, science direct, Google Scholar databases, and manual search references of article sources. As shown in Figure 2, from all searched sources, 193 articles were removed following a preliminary review of their titles and abstracts. Among the remaining articles, 14 met the inclusion criteria and were included in this review.

Study specifications

Table 1 shows the characteristics of included studies including the randomization, blinding, age group of participants, the method of PDPH diagnosis, intervention group treatment, control group treatment and the way of measuring of headache intensity as well as inclusion and exclusion criteria. In addition, descriptive statistics of patients and the pain score based on the VAS is presented in Table 2.

For each intervention group, the number of samples ranged from 20 to 102. Each article reported 0 to 3 dropped patients, with the Modir *et al.*'s[44] study reporting the most (n = 3, 6%) rate of dropout. In this study, participants

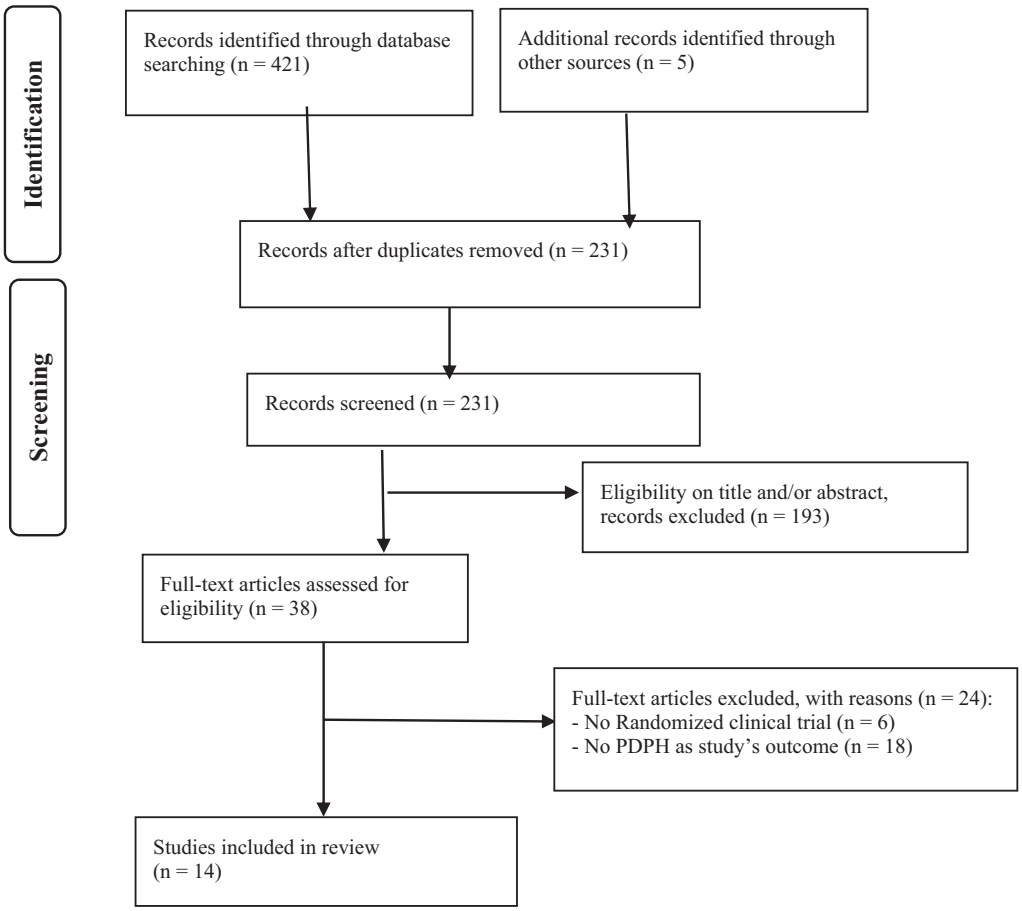

Figure 2: Process of selected articles for the study

ranged in age from 18 to 75 years with an average age of 30.98 years, and the majority of studies involved (female, *n* = 1232 and male, *n* = 337).

As shown in Table 1, seven studies were conducted in Iran, four studies in Egypt, two studies in India, and one study in Turkey. This review identified 5 clinical trials on the effect of caffeine, 2 clinical trials on the effect of sumatriptan, 3 clinical trials on theophylline, 3 clinical trials on pregabalin, and 1 clinical trial on theophylline and sumatriptan in PDPH prevention. Several studies included patients who have been defined as first and second classification by the American Society of Anesthesiologists.[34-36,40,41,44-46]

Treatment interventions

Caffeine effect

Seven different studies assessed the caffeine effect on PDPH. Modir *et al.* found that caffeine usage up to 3 days after surgery and melatonin usage up to 5 and 7 days after surgery significantly reduced postoperative headache scores.[44] In addition, in the Moshari *et al.* study, PDPH decreased in the group that consumed caffeine along with exercise compared to the control group.[41] Nevertheless, in Masoudifar *et al.* study no significant difference observed in pain reduction between caffeine users and placebo users.[34] moreover, the caffeine consumption combined with acetaminophen have less effect on PDPH treatment than mannitol in Shahriari *et al.* study.[45] In other studies, a comparison of caffeine with placebo has been used and showed that Caffeine (CAF) is associated with lower headache intensity and duration and decrease in PDPH incidence after SA.[34,41,44] Nevertheless, superior results of caffeine were not observed in one study.[45] In Shahriari *et al.* study[45] showed that IV mannitol infusion had faster and earlier effect for the treatment of PDPH than acetaminophen-caffeine capsule and is more effective for treatment of PDPH.

Pregabalin effect

According to Bhattacharya *et al.*, pregabalin combined with paracetamol was a better treatment for PDPH than each of the drugs alone.[47] In EL-ghuoshy *et al.* study, pregabalin significantly reduced the incidence of PDPH in pregnant women.[46] In addition, pregabalin significantly reduced the mean score of pain in people undergoing elective caesarean sections.[35] In another study, pregabalin was compared with control group and showed that preoperative oral pregabalin before caesarean section reduced the incidence of PDPH.[46]

Sumatriptan effect

Botros *et al.* study found that sumatriptan intervention reduced pain in comparison control group (multivitamin).[36] The Ghenei *et al.* study showed that prophylactic Sumatriptan

Table 1: Characteristics of included studies

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Sunana Gupta (2017)	India	double	18–65	Exclusion criteria include patients having a history of migraine or other type of headache, cerebrovascular accident, previous neurological disease, any systemic infection and diabetes mellitus	Any patient who reported headache following spinal anaesthesia in hospital or reported within maximum up to 5 days after the procedure was included in the study.	The diagnosis of PDPH was according to the guidelines of the internationalheadache society. All patients had received spinal anaesthesia in the sitting position through midline approach with 25-gauge Quincke needle, and 0.5% hyperbaric bupivacaine was used.	computer-generated random number table	The patient Group C received conventional treatment in the form of recumbent positioning, good hydration, stool softener, a combination of paracetamol and caffeine tablet thrice daily, and a placebo tablet once daily.	Group P received tablet prednisolone 20 mg once daily in addition to the conventional treatment.	VAS
	Mehrdad Masoudifar (2016)	Iran	double	8-75	Exclusion criteria were considered to be technique change in anaesthesia during operation to general anaesthesia, more than one try at spinal anaesthesia, operation lengthening for over 2.5 h, and patients bleeding much leading to the need for blood transfusion	The study's inclusion criteria were the 8–75 years' age group, no addiction to narcotics and tranquilizers, no consumption of alcohol, American Society of Anesthesiologists category 1 and 2, and patients' consent for participation in the study.	level of postoperative headache.	block random allocation	In the intervention group, before spinal blocking, Codimal tablets, containing 500 mg of acetaminophen +65 mg of **caffeine (CAF)**, were orally administered an hour before operation with 100 cc of water, and half an hour before operation, 8 mg of venous dexamethasone was administered.	In the control group, placebo tablets +100 cc of water were orally given an hour before operation and 2 cc of venous normal saline (equivalent to 8 mg of dexamethasone) was administered half an hour before operation.	VAS
	Hesameddin Modir (2020)	Iran	double	19-51	exclusion criteria were more than once spinal anaesthesia attempts, failure of the spinal anaesthetic and the use of other anaesthesia methods, having complete bed rest more than 8 h after surgery, a history of CAF-containing medications, headache before and during the first 8 h after surgery, patient's uncontrolled asthma, reluctance to continue cooperation, and surgery duration >120 min	The inclusion criteria were patients >18 years of age, willingness to participate in the study, lack of sensitivity to CAF and Melatonin (MEL), absence of background diseases such as chronic migraine headache, high BP, diabetes, coagulation disorders, pregnancy poisoning, seizure, and lack of consumption of tobacco and drugs	The headache intensity. The VAS score higher than 2 was defined as PDPH in patients, and the incidence of PDPH was noted in each patient.	-	The **CAF** group received a capsule containing 300 mg CAF (Supernatural company, Canada), whereas the MEL, a MEL 3 mg tablet (Natrol, Canada) 1 h before the spinal anaesthesia given by an anaesthesiologist resident. Each MEL pill was powdered and spilled into empty capsules similar to CAF capsules and given to the patients, for matching and blinding intravenous drugs.	flour was spilled into empty capsules and similarly given to the PBO (placebo) group	VAS

Table 1: Continued

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Mohammadreza Moshari (2021)	Iran	Double.	20-60	Patients were not entered to the study if they had a psychiatric or neurological disorder, allergy to caffeine, hypertension, or intolerance to caffeine, or had consumed caffeinated beverages within the previous 4 h	Inclusion criteria were: The American society of anaesthesiologists (ASA) physical status I–II, aged 20–60 years, candidate for elective inguinal hernia or varicocele surgery.	The severity of headache was scored and assessed by 10-poi (VAS) with 0=no headache and 10=worst headache imaginable, and according to the degree of pain given by the patient, classification of headache severity was done as follows: No headache=0, mild headache<3, moderate headache 4–6 and severe headache >6.	a computer-generated randomization chart	Patients receive oral tablet **caffeine** 0.2 g, as a caffeine group (group 1, n =40), as an exercise group (group 2, n =40), as a Caffeine combine exercise group (group 3, n =40),	controlled group (group 4, n = 40) received placebo tablet	VAS
	Ali Shahriari (2021)	Iran	single-blind	18-35	The exclusion criteria were increased ICP, haemodynamically unstable or markedly hypovolemia, infection, sensitivity to caffeine, and the use of caffeine-containing medications, tobacco, and opioid drugs.	The inclusion criteria were patients within 18-35 years old, American Society of Anesthesiologists (ASA) physical status I and II, and absence of underlying diseases such as chronic headache, hypertension (HTN), tachycardia, diabetes, coagulopathy, preeclampsia, and epilepsy.	The severity of pain of the patients was recorded with VAS (a 10-point scale was used with a score of 0 representing no pain and a score of 10 representing intolerable pain) before the treatment. In addition, pain scores were interviewed by the telephone on the 1, 2, 3, 4, 6, 12, 18, 24, and 48 h after the treatment. Adverse effects were assessed through 48 h after intervention	The block randomization method	In the caffeine group, who received a capsule containing 500 mg acetaminophen and 65 mg caffeine (Dr. Abidi Pharmaceutical Co., Iran) every 6 to 48 h.	Mannitol group received 100 ml IV 20% mannitol serum (manufactured by Shahid Ghazi, Tabriz Pharmaceutical Co., Iran) over 30 min (single dose). In the mannitol group, if a moderate and severe pain persisted for 12 h later, a sodium diclofenac suppository 100 mg was administered and recorded.	VAS
	Mohsen Mohamed El – guoshy (2018)	**Egypt**	A prospective randomized study	-	**Exclusion Criteria:** ASA III, IV and V class patients. Patients who had history of convulsion. Patients with known allergy to local anaesthetic or to the study drug. Patients who had any contraindications to regional anaesthesia (e.g., patient refusal, local infection, coagulation abnormality and tight mitral stenosis). Patients with chronic headache. Patients undergoing urgent caesarean section	**Inclusion Criteria:** Pregnant female. ASA class I or II patients. Patients undergoing elective caesarean section	In our study, we evaluated the effectiveness of preoperative pregabalin at many parameters including: Incidence of postdural puncture headache during 72 h postoperatively, (VAS score > 3) and onset time to modified Bromage scale grade 3 (min).	-	Group II: Dural puncture that was performed by Quincke spinal needle with giving pregabalin 150 mg 2–4 h preoperatively Group IV: Dural puncture that was performed by pencil point spinal needle with giving pregabalin 150 mg 2–4 h preoperatively .	Group I (control group 1): Dural puncture that was performed by Quincke spinal needle **without giving pregabalin** preoperatively. Group III (control group 2): Dural puncture that was performed by pencil point spinal needle **without giving pregabalin** preoperatively.	

Table 1: Continued

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Tohid Karami (2021)	**Iran**	double	-	Exclusion criteria also included the history of migraine, patients with ASA III ASA IV, patients with a history of dural puncture more than once, patients with an indication for emergency C-section, previous history of PDPH, contraindications of spinal anaesthesia, block failure, or patients who need adjuvant injection due to incomplete block, patients with surgical complications such as atony and heavy bleeding or hysterectomy, patients who do not complete the 3-day follow-up period for any reason.	Inclusion criteria included patient consent to participate in the study.	VAS was used to assess the pain severity. In this scale, visual scoring was explained to the patients so that no pain and the worst pain ever experience were represented by 0 and 10, respectively. On the scale, scores 0, 1–3, 4–6, and 7–10 indicate no pain, mild pain, moderate pain, and severe pain, respectively	simple random number table	Patients of the intervention group received pregabalin at a dose of 150 mg the night before spinal anaesthesia	Patients of the placebo group also received a placebo the night before spinal anaesthesia	VAS
	Joseph Botros (2019)	Egypt	double	18-35	Patients with a history of ischemic heart disease, pregnancy-induced hypertension, chronic hypertension, cardiac, vascular, liver and renal impairment, or any other severe or disabling medical condition were excluded from the study. Individuals with a history of migraine, known hypersensitivity to study drugs, previous inadequate response to at least two triptans, currently using ergotamine, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors were excluded as well.	Parturient who had caesarean section under spinal anaesthesia American Society of Anesthesiologists (ASA) physical status Classes I and II and aged between 18 and 35 years and complained from moderate-to-severe PDPH after 25G spinal needle puncture on the 2nd or 3rd postoperative day were included in this study.	A 5-point visual analogue pain scale was used to describe the intensity of pain that was first described by Hakim. [19] 0 = No pain 1 = Mild 2 = Moderate 3 = Severe 4 = Very severe	-	Patients of the sumatriptan (S) group were given oral sumatriptan (Imigran®) 50 mg tablet twice in the first day and then 50 mg once daily for the next 2 days. While those of the naratriptan (N) group were given naratriptan (Naredrix®) 2.5 mg tablet twice daily in the first day then 2.5 mg tablet once daily in the next 2 days	Patients of the control (C) group were given multivitamin tablets in the same dosage regimen.	VAS

Table 1: Continued

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Masoud GHanei (2016)	Iran	double	20-30	Exclusion criteria included a history of migraine headache, sensitivity to sumatriptan, symptoms of ischemic heart disease (angina), cerebrovascular disease (stroke, TIA; Transient Ischemic Attack), a history of peripheral vascular disease (ischemic colitis), uncontrolled hypertension, use of derivatives of ergotamine in the past 24 h, mono amino oxide inhibitors (MAOIs) in the last 2 weeks, severe liver disease, tried more than once for lumbar puncture for spinal anaesthesia, non-cooperative patients, pregnant patient's Caesarean surgery, patients with headache prior to anaesthesia and patients with headache criteria IHS (International Headache Society) are to recognize PDPH.	patients 20 to 30 years of age	Measurement of pain assessment every 8 h for 2 days (Hakim 2010) with 5- point verbal rating scale was down (0: No headache, 1: mild headache, 2: moderate headache, 3: severe headache, 4: unbearable headaches).	-	In the case of sumatriptan 25 mg to 4 doses every 8 h orally to patients were given the first dose of 2 h before anaesthesia (a dose every 8 h is 25 mg prophylactic sumatriptan	The control group was given a placebo at the same intervals. Placebo pharmaceutical company model was prepared containing all the ingredients, except the active ingredient of the drug sumatriptan tablets.	5- point verbal rating scale
	Ufuk Ergu¨n (2016)	Turkey	not	18-61	Patients who had intracranial disorders (central nervous system infections and malignancies, intracranial haemorrhage, hydrocephalus, stroke, cerebral venous thrombosis, intracranial hypertension, convulsions) or systemic disorders (hypertension, hyperthyroidism, cardiac arrhythmia) and those older than 65 years were excluded.	Patients who developed PLPHs after LP in both neurology clinics and other inpatients who had been referred to neurology.	according to The International Classification of Headache Disorders (ICHD), 3rd edition (beta version)	not	200 mg intravenous theophylline (200 mg theophylline in 100 mL 5 % dextrose) was infused over a period of 30 min. Visual analogue scales (VAS) were assessed at 0, 30 and 60 min after the initiation of infusions, while in the sitting position.	not	VAS
	Hamideh Gholami (2021)	Iran	double	17-42	Patients with a history of chronic headache or migraine, hypertension, cerebral infection, asthma, hepatic disease, known allergy to gabapentin or theophylline, previous or current history of preeclampsia, stroke, sub-arachnoid haemorrhage, sinusitis, meningitis, eye problems, prior exposure to spinal anaesthesia, neurological symptoms, visual analogous scale (VAS) (no pain (score of 0) and pain as bad as it could be "or" worst imaginable pain (score of 10) more than eight and patients with no response to the treatments were excluded from the study.	Patients with headache due to spinal anaesthesia and with caesarean delivery, whose body mass index (BMI) was in the range of 20-24.9 Kg/m2 in the first trimester of pregnancy, were included in the study.	We used a researcher-developed checklist designed by three obstetrics and gynaecology specialists affiliated to the department of obstetrics and gynaecology of Zanjan University of Medical Sciences. This checklist included: Pain score at 0, 8, 16 and 24 h after the onset of pain, as well as intervention	balance block randomization	Group B: Theophylline 200 mg, each 8 h. Patients were taught how to use the VAS scale. Medications were given every 8 h and the maximum dose was three doses.	Group A: Gabapentin 400 mg, each 8 h patients were taught how to use the VAS scale. Medications were given every 8 h and the maximum dose was three doses.	VAS

Table 1: Continued

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Salama (2018)	Egypt	-	18-40	Patients with history of migraine or other type of headache, patients with history of previous intolerance to ergotamine or theophylline admin-istration, 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 base line) or with intraoperative vasopressor drug require-ment, hypertensive or diabetic patients, smoker patients, patients with liver and renal disease, patients with coronary artery disease	ASA physical status, both sexes, age from 18 to 40 years old, patients with low tension PDPH diagnosed by post spinal frontal and or occipital discomfort worsened by upright posture and re-lieved by lying supine.	Patients will be asked for headache evaluation in sitting position using 10cm Numerical rating scale (NRS) with anchors of 0=no headache and 5=moderate and 10=worst headache imag-inable in the following times: Before medication, after 1 h of medication then every 6 h till complete resolution of headache.	-	*Group 2:* Theophylline group (GpT): (n=30 patients): Patients received treatment in the form of (theophylline 250mg orally/8 h + paracet-maol 500mg/8 h orally).	*Group 1:* Ergotamine group (GpE): (n=30 pa-tients): Patients received treatment in the form of (erogotamine 1mg/8 h orally + paracetamol 500mg/8 h orally). *Group 3:* Control group (Gp C): (n=30 patients): Patients received treatment in the form of paraceta-mol 500mg/8 h orally.	NRS
	Ahmed Mohamed Shaat (2021)	Egypt	double	21-50	Exclusion criteria included patients with NPRS score <5, ASA physical status >II, age <21 years or >50 years, pregnant women, history of; chronic headache, cluster headache, migraine, convulsions, cerebrovascular accident, previous neurological diseases, signs of meningismus, dysrhythmia, hypertension, ischemic heart disease, hyperthyroidism, peripheral vascular disease (ischemic colitis), liver or renal impairment, use of other methyl xanthine derivatives, use of selective serotonin reuptake inhibitors, use of ergotamine derivatives in the past 24 h, use of monoamine oxidase inhibitors in the last 2 weeks, use of any kind of opiates, allergy to the study medications and any contraindication of oral intake.	Inclusion criteria were; patients with an NPRS score of ≥5, American Society of Anesthesiologists (ASA) physical status ≤ II, age from 21 to 50 years, and first attempt spinal anaesthesia.	Participants were asked to report the severity of their headache after sitting upright for 15 min, using a Numeric Pain Rating Scale (NPRS), which is a psychometric response scale for measuring subjective characteristics; baseline, before drug treatment (T0), 2 h (T2), 6 h (T6), 12 h (T12), 18 h (T18), 24 h (T24), then every 12 h till 48 h (T48) after drug treatment, where 0 = no pain, and 10 = worst possible pain	Randomization was performed by the online application (https://www.randomizer.org/) and concealed using sealed, opaque envelopes	In group T; oral 150 mg theophylline anhydrous tablet (Quibron- T/SR, 300 mg dividose tablet, SmithKline Beecham Egypt L.L.C) every 12 h. All patients in both groups received conservative management for 48 h, after hospital admission, which consisted of nursing in the supine position, hydration with continuous infusion of 30 mL/kg/day Ringer's acetate solution, 1 g paracetamol (Perfalgan, Bristol-Myers Squibb Pharmaceuticals) IV every 6 h. 75 mg diclofenac sodium (Voltaren, Novartis) IM every 12 h. The intervention was continued until achieving an NPRS score ≤3 or for a maximum of 48 h after treatment.	in group S; oral 25 mg sumatriptan succinate tablet (Sumigran 25, 25 mg tablet, Sigma pharmaceutical industries, Egypt) every 12 h. All patients in both groups received conservative management for 48 h, after hospital admission, which consisted of nursing in the supine position, hydration with continuous infusion of 30 mL/kg/day Ringer's acetate solution, 1 g paracetamol (Perfalgan, Bristol-Myers Squibb Pharmaceuticals) IV every 6 h. 75 mg diclofenac sodium (Voltaren, Novartis) IM every 12 h. The intervention was continued until achieving an NPRS score ≤3 or for a maximum of 48 h after treatment.	

Table 1: Continued

ID	First author (year)	Country	Blinding	Age group	Exclusion criteria	Inclusion criteria	The diagnosis of PDPH	Randomization	Group intervention	Control group	Measuring of Headache intensity
	Dipasri Bhattacharya (2016)	India	double	18–55	Patients of American Society of Anesthesiologists III or more with a history of cardiovascular or respiratory disease, dizziness or frequent headache or drug usage, impaired renal and/or hepatic function, and pregnant patients.	patients who developed PDPH subsequently after undergoing elective major gynaecological surgeries, patients aged 18–55 years, weighing between 45 and 70 kg, and belonging to the American Society of Anesthesiologists physical status I and II	A patient's headache was scored using the visual analogue scale (VAS) where the pain intensity of headache ranged from 0 to 100 mm (0 = no pain, 100 = worst possible pain).	block randomization method	the patients were allocated into three equal groups (n = 50, each group) to receive orally either a single dose 150 mg of pregabalin (group 1) or 1000 mg paracetamol (group 2) or a combined dose of paracetamol 1000 mg and pregabalin 150 mg (group 3). All the patients received the same drug that they originally received, if required, and were followed up for 4 days	paracetamol	VAS

significantly decrease the incidence of postdural puncture headache during 48 h after induction of SA.[42]

Theophylline effect

Shaat *et al.*[40] compared theophylline with sumatriptan and showed Oral theophylline is more effective and safer than oral sumatriptan in control of PDPH.[40] Moreover, Mahoori *et al.* study showed that the pain score was significantly lower in theophylline group in comparison with the acetaminophen group and Theophylline is a safe and effective treatment for PDPH.[43] Based on Gholami *et al.* study, theophylline showed a greater reduction in VAS scores in PDPH than gabapentin.[24] In a study by Ergün *et al.* the mean of VAS after theophylline infusion was significantly lower than the control.[48] In the study of Salama *et al.*, theophylline was compared with ergotamine and showed that adding either ergotamine or theophylline to paracetamol were more effective in decreasing intensity of PDPH pain than using paracetamol alone. Therefore, in comparing to ergotamine and paracetamol, theophylline is more effective due to lower pain score and better patient satisfaction.[39] Moreover, in Gholami *et al.* study, theophylline is compared with gabapentin and showed that both gabapentin and theophylline are effective against PDPH, but theophylline was more effective for pain relief than gabapentin.[24] In another study, a significant pain reduction was observed in patients who received theophylline, but the study lacked a control group, therefore, the results could not be considered correctly based on the methodological structure of the study.[48]

Bias resources

Based on inclusion criteria, the studies included in this systematic review are highly heterogeneous and have several sources of bias. As can be seen in Table 1, there are differences between studies in terms of age distribution and inclusion and exclusion criteria. Moreover, the placebo was varied in different studies. In addition, the onset of treatment, drug doses, and prescription times were varied in a large number of studies. The majority of studies have been conducted on women,[35,36,45-47] so selection bias may limit generalization to men. Moreover, the range of outcome assessment time has varied greatly from zero time to 168 h. In two studies, numerical rating scale (NRS)[39] and 5-point verbal rating scale[42] was used, while the VAS was used to measure headache severity in other studies. In a number of studies[35,39,41,46,48] the validity of double blinding is uncertain or ambiguous, and one study[45] used single blinding. Therefore, a risk of bias can be considered in terms of quality of bias. In some studies, the randomization method is not explained in detail, and in a large number of studies[36,39,42,44,46,48] the randomization method was unknown. In most studies, attrition was high. Although, in the most studies the risk of bias was low and had minimal reporting bias.

Table 2: Descriptive statistics and the pain score (VAS) in different time after operation in included studies

ID	First author (year of publication)	Study group	Sample size	Sex (n Male/n Female)	Age (mean)	Zero	30 min	1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	7 hrs	8 hrs	12 hrs	13 hrs	16 hrs	18 hrs	19 hrs	24 hrs	25 hrs	31 hrs	32 hrs	36 hrs	37 hrs	40 hrs	43 hrs	48 hrs	49 hrs	55 hrs	61 hrs	67 hrs	72 hrs	96 hrs	120 hrs	144 hrs	168 hrs
	Sunana Gupta (2017)	Intervention group	30	16/14	42.80	7.73									6.76					6.16								5.36					4.56	3.733			
		Control group	30	17/13	44.33	7.93									6.46					5.53								3.03					1.2	0.36			
	Mehrdad Masoudifar (2016)	Intervention group	45	29/16	36.6	1.50						1.05			1.1					1.4								1.35					1.25				
		Control group	45	39/6	37.7	1.02						1.1			1.35					1.80								1.50					1.25				
	Hesameddin Modir (2020)	caffeine	50	27/23	34.30										1.06					1.12								1.14					1.16		1.06		0.22
		placebo	50	30/20	34.50										1.48					2.02								2.20					2.32		2.20		1.42
		caffeine													1.06					1.12								1.14					1.16		1.06		0.22
		melatonin	50	28/22	33.89										1.40					1.44								1.46					1.46		0.922		0.120
	Mohammadreza Moshari (2021)	Caffeine	40	-																5								4					1	0	0		
		exercise	40																	3								2					0	0	0		
		Caffeine																		5								4					1	0	0		
		placebo	40																	10								10					5	0	0		
		combine	40																	0								0					0	0	0		
		placebo																		10								10					5	0	0		
		combine																		0								0					0	0	0		
		exercise																		3								2					0	0	0		
	Ali Shahriari (2021)	Intervention group	40	0/40	31.10	6.17		5.00	4.71	4.38	4.03	2.96			2.50			1.70		0.73								0.26									
		Control group	40	0/40	29.80	6.72		3.70	3.35	1.65	1.00	0.60			0.26			0.13		0.06								0.06									
	Mohsen Mohamed El –guoshy (2018)	Intervention (Group 2)	100	0/100																0								3					12				
		Control (Group 1)	100	0/100																0								19					16				
		Intervention (group 4)	100	0/100																0								1					6				
		Control (group 3)	100	0/100																0								7					5				
	TOHID KARAMI (2021)	intervention	68	0/68	28.50																																
		control	68	0/68	27.15																																
	Botros (2019)	Intervention (sumatriptan)	63	0/63	25.3	3						1			1					0								0					0				
		Control (naratriptan)	63	0/63	24.5	3						2			2					1								0					0				
		Intervention (sumatriptan)				3						1			1					0								0					0				
		Control (multivitamin)	63	0/63	25.4	3						3			2					2								2					1				
	MASOUD GHANEI (2016)	intervention	102	51/51	25.6	0.26								0.27			0.34			0.34			0.34			0.34		1.91									
		control	102	51/51	25.7	0.37								0.37			0.44			0.46			0.47			0.38		2.5									
	ERGUN (2016)	intervention	20	9/11	33.8	7.10	3.75	2.70																													
		control	NOT	NOT	NOT	NOT	NOT	not																													
	SALLY E. SAKR (2018)	Theophylline (group 2)	30	not	26.23	4.8		2.63					1.56			1			0.2		0	0			0		0		0	0	0	0					
		Ergotamine (group 1)	30	not	26.43	5.2		3.5					2.93			2.3			1.85		1.58	1.4			1.1		0.7		0	0	0	0					
		Theophylline (group 2)				4.8		2.63					1.56			1			0.2		0	0			0		0		0	0	0	0					
		Control (group 3)	30	not	26.25	5.66		4.8					4.03			3.77			2.99		2.34	2			1.6		1.06		0.8	1	1	0					

Table 2: Continued

ID	First author (year of publication)	Study group	Sample size	Sex (n Male/n Female)	Age (mean)	Zero	30 min	1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	7 hrs	8 hrs	12 hrs	13 hrs	16 hrs	18 hrs	19 hrs	24 hrs	25 hrs	31 hrs	32 hrs	36 hrs	37 hrs	40 hrs	43 hrs	48 hrs	49 hrs	55 hrs	61 hrs	67 hrs	72 hrs	96 hrs	120 hrs	144 hrs	168 hrs
	Hamideh Gholami (2021)	Intervention (theophylline)	60	0/60	29	6.20								3.06			1.5			0.7																	
		Control (gabapentin)	60	0/60	28.3	6.03								3.36			2.56			2.23																	
	Ahmed Mohamed Shaat (2021)	Intervention (Theo)	30	9/21	29.33	7.27			5.90			4.03			2.60			1.20		0				0				0								
		Control (suma)	30	11/19	30.50	7.10			6.17			5.37			5.20			4.40		3.47				1.53				0								
		Intervention (suma)	30	11/19	30.50	7.10			6.17			5.37			5.20			4.40		3.47				1.53				0								
		Control (Theo)	30	9/21	29.33	7.27			5.90			4.03			2.60			1.20		0				0				0								
	Dipasri Bhattacharya (2016)*	pregabalin	50		39.52																															
		paracetamol	50		39.52																															
		combined paracetamol and pregabalin	50		39.52																															

*Pain score is not reported in this article

Discussion

This systematic review investigated the effects of oral caffeine, sumatriptan, theophylline, and pregabalin on preventing post-SA headaches. We assessed the effect of four common treatment drugs and concluded on their effect on PDPH incidence, intensity and duration. According to the studies, two mechanisms have been suggested as the causes of PDPH. One of the mechanisms is rupture of the dura mater membrane and loss of cerebrospinal fluid and stretching of pain-sensitive structures inside the skull. Another mechanism is the reduction of intracranial pressure and dilation of cerebral arteries.[38] Although, there is evidence that dilation of arterial blood vessels in the cerebral circulation greatly contributes to headaches as PDPH. Activation of serotonin in cerebral arteries leads to vasoconstriction and may neutralize this effect.[49,50] Caffeine reduces cerebral blood flow by blocking adenosine receptors, which increases contractility of cerebral arteries. In addition, caffeine increases CSF production by activating the sodium potassium pump.[14,51]

Some studies have recommended caffeine as a treatment option for PDPH since caffeine was first used as a therapeutic agent in 1949.[51,52] In Masoudifar *et al.*[34] and Modir et al[44] studies, the combination of acetaminophen plus caffeine and dexamethasone reduced pain intensity, pain duration, and PDPH incidence.[34,44] Nevertheless, negative results[45] regarding caffeine effect has been reported. The Gupta study, showed that pain scores decreased less in patients receiving the combination of paracetamol and caffeine in comparison to prednisolone.[37] Matthews and Wilson demonstrated that benzoate caffeine decreases cerebral blood flow after intravenous administration for the treatment of PDPH by blocking adenosine receptors.[8] In another study, the incidence of PDPH in the caffeine and combined exercise groups was lower than in the group receiving a placebo, the headache was more severe in the control group and the need to receive analgesics in the control group was reported to be higher than caffeine group.[41] In another study, intravenous mannitol had a greater reduction in pain scores than the group receiving acetaminophen-caffeine capsules and was more effective than that.[45] A recent review examined 13 low-volume RCTs with 479 participants to examine whether caffeine, sumatriptan, gabapentin, pregabalin, theophylline, hydrocortisone, Cosintropin, and intramuscular adrenocorticotropic hormone (ACTH) could reduce the incidence of PDPH within 1–2 h when compared to a placebo. In this review, it was shown that caffeine can reduce the incidence of PDPH within 1–2 h when compared with a placebo.[21,23] Caffeine therapy also reduced the need for conservative supplemental treatment options, whereas in our review caffeine was able to lower pain scores and reduce the incidence of PDPH in only two studies compared to the placebo group.

The serotonin receptor antagonist sumatriptan, used to treat migraines, has been linked to PDPH relief in limited

cases.[53] A study showed that sumatriptan was more effective in PDPH treatment than the group receiving naratriptan 6 and 12 h after SA, but for the rest of the time, this effect was not noticeable.[36] In the study by Ghanei *et al.* Sumatriptan prophylaxis was significantly more effective in reducing the incidence of PDPH than the placebo receiving group.[13] In a review[21] Sumatriptan showed no effect in reducing the incidence of PDPH, whereas in our study sumatriptan prophylaxis was significantly effective for this purpose.

Theophylline is a methyl xanthine that contracts cerebral vessels and improves pain intensity compared to placebo in randomized studies.[53] In the study by Ergun *et al.* Theophylline infusion had a rapid and significant effect on reducing pain score.[48] In the study by Gholami *et al.* within 24 h after the intervention, the group receiving theophylline reported lower pain scores than gabapentin, but there was no significant difference between the pain scores of the two groups before the intervention and 8 and 16 h after the intervention.[24] Compared to ergotamine and paracetamol, theophylline significantly decreased NRS, the duration of pain relief was shorter and patient satisfaction was higher.[39] In the study by Shaat *et al.* Theophylline was safer and more effective than sumatriptan in the treatment of PDPH, demonstrated lower NRS scores, shorter PDPH duration, and fewer side effects.[40] In a review,[21] treatment with theophylline showed lower VAS scores compared to acetaminophen in 2, 6 and 12 h. It also showed lower VAS scores compared to conservative treatment at 8, 16, and 24 h later. There was also a reduction in pain with theophylline compared to placebo. Theophylline improved pain in a significantly higher proportion of participants than conservative therapy. In all studies, theophylline decreased pain levels significantly. Also, when compared with sumatriptan, theophylline was safer and more effective in the treatment of PDPH.

Pregabalin is an anticonvulsant drug that prevents calcium from entering the brain. This drug is effective in preventing headaches and has been used for treating epilepsy and chronic pain. Pregabalin also improves anxiety disorders. Few studies have examined the effect of pregabalin on PDPH.[26] Pregabalin significantly reduced pain scores in the study by El-Gusoshy *et al.*[46] A combination of pregabalin and paracetamol was studied by Bhattacharya et al, the combination significantly reduced pain scores compared to either drug alone.[47] According to the study, PDPH severity and incidence may be reduced by using pregabalin the night before SA compared to a placebo.[35] In one review, pregabalin did not show a significant effect,[21] whereas in our review pregabalin showed a significant reduction in pain scores compared to placebo.

Limitations of our study:

In some studies, included in this review, in addition to the main intervention, other interventions including the use of diclofenac[40] and exercise,[41] and caffeine combined with acetaminophen may affect the evaluation of the main intervention.[41] Therefore, there was a possibility of bias in our results and we cannot do meta-analysis due to heterogeneity included studies. In addition, a limited number of studies (RCTs), small sample size, low variety of evaluated drugs, limited generalization of findings due to the low number of included studies. Therefore, future studies suggesting among trials with larger samples and long-term follow-up periods.

Conclusion

This review supports the effects of theophylline, pregabalin, and sumatriptan in the prevention of PDPH incidence and treatment of PDPH intensity, but we can't draw the same conclusions about caffeine due to no superior results about the caffeine effect. Nevertheless, this extracted conclusion should be considered and interpreted with caution and limited generalizations due to the small number of studies, the variety of evaluated drugs and measures, the low sample size and the bias presented.

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Conflicts of interest

There are no conflicts of interest.

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