**Review Article**

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



be assoc ated with nausea, vomiting, neck

[14,16]

cerebral palsy The most common risk

factors for PDPH include female gender,

**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*

**Introduction** and last up to 7 days (4–6 days).[4] PDPH can Spinal anaesthesia (SA) for analgesia has stiffness,i visual and auditory impairment, during surgery.[1-3] In addition to being seizures, subdural haemorrhage, and rarely easy to administer, SA has rapid effects,

more advantages than general anaesthesia

relaxes muscles, and controls pain while young age, pregnancy, previous headache for caesarean delivery[6] due to low risk history, low1 CSF pressure, and low body of maternal pulmonary aspiration and

[4,5]

performing surgery. SA is recommended

mass index.

[ 4,17-20]

foetal distress.[7] Nevertheless, SA has side Many treatment protocol are available effects such as neurological impairment, to prevent and reduce the PDPH[14,21-24] hypotension, decreased heart rate, nausea including cosintropin, aminophylline, and vomiting, urinary retention, back dexamethasone,[13,25,26] fluid therapy and pain, decreased ventilation and post-dural bed rest,[22,27] epidural saline injection, puncture headache (PDPH).[8-12] intrathecal catheter insertion, epidural prophylactic blood patch,[28] performing

PDPH is a common problem after SA and

an unpleasant emotional experience.

[8,9,13]

special anaesthesia techniques[29] and the use A prevalence of 6 to 36% has been reported studies are [ contradictory.t Despitet various PDPH appear a few hours after dura puncture treatments, PDPH isi still an unwanted and

30,31]

of caffeine. However, he resul s of the

[14,15]

for PDPH following SA. Symptoms of

[21]

annoying complicat on of SA. 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]

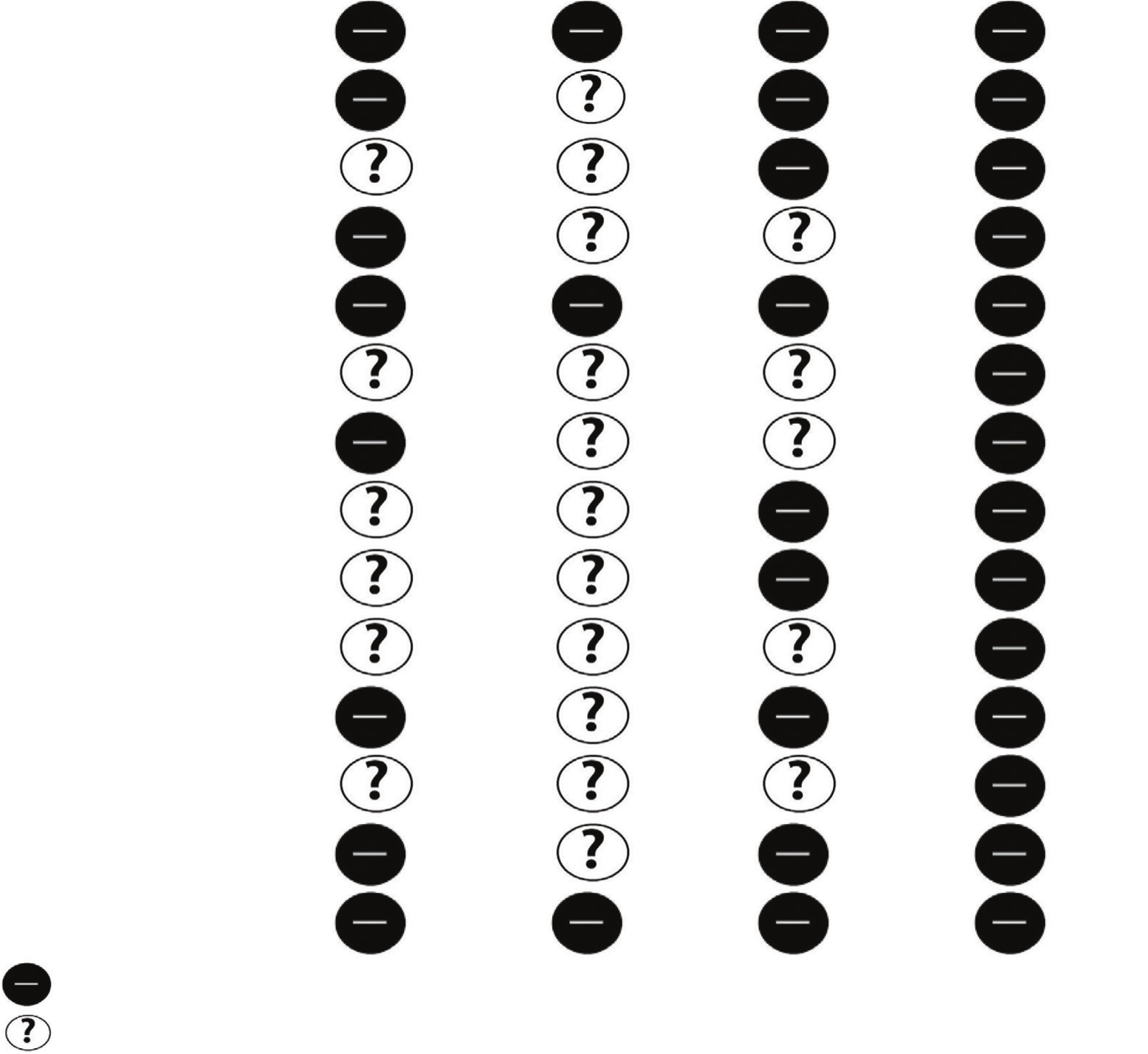
**Quality of extracted articles (risk off bias of individual stories)**

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

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First author (year of publication)

Gupta (2017)

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Incomplete outcome data

Masoudifar (2016)

Modir (2020)

Moshari (2021)

Shahriari (2021)

El –guoshy (2018)

Karami (2021)

Botros (2019)

Ghanei (2016)

Ergu¨n (2016)

Gholami (2021)

SAKR (2018)

Shaat (2021)

Bhattacharya (2016)

= No bias

= Probably has bias

**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

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**Identification**

Records identified through database searching (n = 421)

Additional records identified through other sources (n = 5)

Records after duplicates removed (n = 231)

Records screened (n = 231)

**Screening**

Eligibility on title and/or abstract, records excluded (n = 193)

Full-text articles assessed for eligibility (n = 38)

Full-text articles excluded, with reasons (n = 24): - No Randomized clinical trial (n = 6)

- No PDPH as study’s outcome (n = 18)

Studies included in review (n = 14)

**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

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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.

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 8h after surgery,

a history of CAF-containing

medications, headache before and

during the first 8h after surgery,

patient’s uncontrolled asthma,

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

reluctance to continue cooperation, 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 300mg CAF

(Supernatural company,

Canada), whereas the

MEL, a MEL 3mg

tablet (Natrol, Canada)

1h 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.

**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 20mg 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 2.5h, and

patients bleeding much leading to

the need for blood transfusion

level of postoperative

headache.

block random

allocation

In the intervention

group, before

spinal blocking,

Codimal tablets,

containing 500mg of

acetaminophen +65mg

of **caffeine (CAF)**, were

orally administered an

hour before operation

with 100 cc of water,

and half an hour before

operation, 8mg 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 8mg of

dexamethasone) was

administered half an

hour before operation.

VAS

Hesameddin

Modir (2020)

Iran

double

19-51

-

flour was spilled into

empty capsules and

similarly given to the

PBO (placebo) group

VAS

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were patients within

18-35 years old,

American Society

of Anesthesiologists

(ASA) physical

status I and II, and

diseases such as

chronic headache,

hypertension (HTN),

coagulopathy,

preeclampsia, and

epilepsy.

The inclusion criteria The severity of pain of

with VAS (a 10-point

scale was used with a

score of 0 representing

no pain and a score

of 10 representing

absence of underlying intolerable pain) before

the treatment. In

addition, pain scores

were interviewed by the

tachycardia, diabetes, telephone on the 1, 2,

3, 4, 6, 12, 18, 24, and

48h after the treatment.

Adverse effects were

assessed through 48h

after intervention

The block

the patients was recorded randomization

method

**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**

**Table 1: Continued**

V class patients. Patients who had

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

**Exclusion Criteria:** ASA III, IV and **Inclusion Criteria:**

Pregnant female.

history of convulsion. Patients with 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 72h

postoperatively, (VAS

score > 3) and onset time

to modified Bromage

scale grade 3 (min).

Group II: Dural

puncture that was

performed by Quincke

pregabalin 150mg 2–4h

preoperatively Group

IV: Dural puncture that

point spinal needle with

2–4h preoperatively .

Group I (control group

1): Dural puncture

that was performed by

spinal needle with giving Quincke spinal needle

**without giving pregabalin**

preoperatively. Group

III (control group 2):

was performed by pencil Dural puncture that

was performed by pencil

giving pregabalin 150mg point spinal needle

**without giving pregabalin**

preoperatively.

Moshari (2021)

Mohammadreza 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.

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.

The severity of headache a computer-

generated

randomization

chart

Patients receive oral

tablet **caffeine** 0.2g, 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.

In the caffeine group,

who received a capsule

containing 500mg

acetaminophen and

Pharmaceutical Co.,

Iran) every 6 to 48h.

Mannitol group received

100ml IV 20% mannitol

serum (manufactured

by Shahid Ghazi, Tabriz

65mg caffeine (Dr. Abidi Pharmaceutical Co.,

Iran) over 30min (single

dose). In the mannitol

group, if a moderate

and severe pain

persisted for 12h later,

a sodium diclofenac

suppository 100mg

was administered and

recorded.

VAS

Mohsen

Mohamed El –

guoshy (2018)

**Egypt**

randomized

study

A prospective -

-

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Patients with a history of ischemic

heart disease, pregnancy‐induced

cardiac, vascular, liver and renal

impairment, or any other severe or

disabling medical condition were

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

hypertension, chronic hypertension, section under

spinal anaesthesia

American Society

of Anesthesiologists

excluded from the study. Individuals (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.

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

A 5‐point visual analogue -

**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**

**Table 1: Continued**

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

in the study.

VAS was used to assess

the pain severity. In this

consent to participate 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

before spinal anaesthesia

Patients of the placebo

group also received a

placebo the night before

dose of 150mg the night spinal anaesthesia

VAS

Joseph Botros

(2019)

Egypt

double

18-35

Patients of the

sumatriptan (S)

group were given oral

50mg tablet twice in

the first day and then

50mg once daily for

the next 2 days. While

those of the naratriptan

(N) group were given

naratriptan (Naredrix®)

2.5mg tablet twice daily

in the first day then

2.5mg tablet once daily

in the next 2 days

Patients of the control

(C) group were given

multivitamin tablets

sumatriptan (Imigran®) in the same dosage

regimen.

VAS

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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)

**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**

**Table 1: Continued**

Patients with a history of chronic

cerebral infection, asthma,

hepatic disease, known allergy

to gabapentin or theophylline,

previous or current history of

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 or migraine, hypertension, headache due to

spinal anaesthesia

and with caesarean

delivery, whose body

mass index (BMI)

preeclampsia, stroke, sub-arachnoid was in the range of

20-24.9 Kg/m2 in

the first trimester

of pregnancy, were

included in the study.

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 24h, 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.

of age

patients 20 to 30 years Measurement of pain

assessment every 8h 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 25mg to 4

doses every 8h orally to

patients were given the

first dose of 2h before

sumatriptan

The control group

was given a placebo

at the same intervals.

Placebo pharmaceutical

company model was

anaesthesia (a dose every prepared containing all

8h is 25mg prophylactic 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.

not

200mg intravenous

theophylline (200mg

theophylline in 100mL 5

% dextrose) was infused

over a period of 30min.

Visual analogue scales

(VAS) were assessed at 0,

30 and 60min after the

initiation of infusions,

while in the sitting

position.

not

VAS

Hamideh

Gholami (2021)

Iran

double

17-42

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 24h

after the onset of pain, as

well as intervention

balance block

randomization

Group B: Theophylline

200mg, each 8h.

Patients were taught

how to use the VAS

scale. Medications were

given every 8h and the

maximum dose was

three doses.

Group A: Gabapentin

400mg, each 8h

patients were taught

how to use the VAS

scale. Medications were

given every 8h and the

maximum dose was

three doses.

VAS

Amini, *et al.*: Drug therapy on PDPH after spinal anaesthesia

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[Downloaded free from http://www.jwacs-jcoac.com on Saturday, February 4, 2023, IP: 2.28.143.76]



Exclusion criteria included patients

with NPRS score <5, ASA

physical status >II, age <21 years

or >50 years, pregnant women,

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 24h, 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

history of; chronic headache, cluster 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

using a Numeric Pain

Rating Scale (NPRS),

which is a psychometric

response scale for

measuring subjective

characteristics; baseline,

before drug treatment

(T0), 2h (T2), 6h (T6),

12h (T12), 18h (T18),

24h (T24), then every

12h till 48h (T48)

after drug treatment,

where 0 = no pain, and

10 = worst possible pain

was performed

by the online

≥5, American Society sitting upright for 15min, application

(https://www.

randomizer.

org/) and

sealed, opaque

envelopes

Randomization In group T; oral 150mg

theophylline anhydrous

tablet (Quibron- T/

SR, 300mg dividose

tablet, SmithKline

Beecham Egypt

L.L.C) every 12h. All

concealed using patients in both groups

received conservative

management for 48h,

which consisted of

nursing in the supine

position, hydration with

continuous infusion of

30mL/kg/day Ringer’s

acetate solution, 1g

paracetamol (Perfalgan,

Bristol-Myers Squibb

Pharmaceuticals)

IV every 6h. 75mg

diclofenac sodium

(Voltaren, Novartis)

IM every 12h. The

intervention was

treatment.

in group S; oral 25mg

sumatriptan succinate

tablet (Sumigran 25,

25mg tablet, Sigma

pharmaceutical

industries, Egypt)

every 12h. All patients

in both groups

received conservative

management for 48h,

after hospital admission, after hospital admission,

which consisted of

nursing in the supine

position, hydration with

continuous infusion of

30mL/kg/day Ringer’s

acetate solution, 1g

paracetamol (Perfalgan,

Bristol-Myers Squibb

Pharmaceuticals)

IV every 6h. 75mg

diclofenac sodium

(Voltaren, Novartis)

IM every 12h. The

intervention was

continued until achieving continued until

an NPRS score ≤3 or for achieving an NPRS

a maximum of 48h after score ≤3 or for a

maximum of 48h after

treatment.

**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**

**Table 1: Continued**

Salama (2018)

Egypt

-

18-40

Patients with history of migraine

or other type of headache, patients

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

with history of previous intolerance 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 1h of medication

then every 6h till

complete resolution of

headache.

-

*Group 2:* Theophylline

group (GpT): (n=30

patients): Patients

form of (theophylline

250mg orally/8h +

paracet-maol 500mg/8h

orally).

*Group 1:* Ergotamine

group (GpE): (n=30

pa-tients): Patients

received treatment in the received treatment in the

form of (erogotamine

1mg/8h orally +

paracetamol 500mg/8h

orally). *Group 3:*

Control group (Gp C):

(n=30 patients): Patients

received treatment in the

form of paraceta-mol

500mg/8h orally.

NRS

Ahmed

Mohamed Shaat

(2021)

Egypt

double

21-50

Amini, *et al.*: Drug therapy on PDPH after spinal anaesthesia

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[Downloaded free from http://www.jwacs-jcoac.com on Saturday, February 4, 2023, IP: 2.28.143.76]

Amini, *et al.*: Drug therapy on PDPH after spinal anaesthesia

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



the patients were

allocated into three

equal groups (n = 50,

each group) to receive

orally either a single

dose 150mg of

pregabalin (group 1) or

1000mg paracetamol

(group 2) or a combined

dose of paracetamol

1000mg and pregabalin

150mg (group 3). All

the patients received

the same drug that they

originally received,

if required, and were

followed up for 4 days

**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**

**Table 1: Continued**

VAS

*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]

patients who

developed PDPH

subsequently after

undergoing elective

surgeries, patients

aged 18–55 years,

weighing between

45 and 70kg, and

belonging to the

American Society

of Anesthesiologists

physical status I and

II

scored using the visual

analogue scale (VAS)

where the pain intensity

major gynaecological of headache ranged from

0 to 100mm (0 = no pain,

100 = worst possible

pain).

A patient’s headache was block

randomization

method

paracetamol

**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 168h. 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.

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.

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5.00 4.71 4.38 4.03 2.96

2.50

1.70

3.70 3.35 1.65 1.00 0.60

0.26

0.13

**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 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

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

(2020)

Hesameddin Modir 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

0.73

0.26

Control group

40

0/40

29.80

6.72

0.06

0.06

El –guoshy (2018)

Mohsen Mohamed 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

(2021)

TOHID KARAMI 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

Amini, *et al.*: Drug therapy on PDPH after spinal anaesthesia

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[.

Amini, *et al.*: Drug therapy on PDPH after spinal anaesthesia

**Discussion**

combined

paracetamol and

pregabalin

**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**

**Table 2: Continued**

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]

0

0

1.53

0

1.53

0

0

0

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 1–2h when compared to a placebo. In this review, it was shown that caffeine can reduce the incidence of PDPH within 1–2h 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.

(2021)

Hamideh Gholami 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

Control (suma)

30

11/19

30.50

7.10

6.17

5.37

5.20

4.40

3.47

Intervention (suma)

30

11/19

30.50

7.10

6.17

5.37

5.20

4.40

3.47

Control (Theo)

30

9/21

29.33

7.27

5.90

4.03

2.60

1.20

0

Dipasri

Bhattacharya

(2016)\*

pregabalin

50

39.52

paracetamol

50

39.52

50

39.52

\*Pain score is not reported in this article

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

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cases.[53] A study showed that sumatriptan was more effective in PDPH treatment than the group receiving naratriptan 6 and 12h 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 24h 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 16h 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 12h. It also showed lower VAS scores compared to conservative treatment at 8, 16, and 24h 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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