Original Article

Trans-Nasal Sphenopalatine Ganglion Block Versus Intravenous Aminophylline Injection for Treating Postdural Puncture Headache After Cesarean Section Under Spinal Anesthesia

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Abstract

Background: Postdural puncture headache (PDPH) is a severe and debilitating complication in the obstetric population after regional anesthesia. It affects the parturient and delays home discharge. The epidural blood patch (EBP) is the gold standard treatment; however, it is an invasive and risky procedure. The trans-nasal sphenopalatine ganglion block (SPGB) and intravenous aminophylline are promising modalities for PDPH treatment.

Materials and Methods: In a prospective, double-blinded, and controlled trial, Seventy-five obstetric participants (ASA I and II, aged 18 to 40 years) complaining of PDPH within five days after spinal anesthesia for cesarean section using 22G Quincke needle) were randomized into three groups. Group C received conservative therapy, Group A received intravenous aminophylline plus conservative therapy, and Group S received trans-nasal SPGB plus conservative therapy. Headache severity (VAS score), patient global impression of change (PGIC) scale and the incidence of adverse events were recorded.

Results: Showed that SPGB and intravenous aminophylline significantly reduced the median values of VAS (at 30 minutes,1, 6, 12, and 24 hours) with P≤0.001 and improved 24-hour PGIC with P≤0.001 compared to control. Moreover, SPGB significantly reduced VAS at 30 minutes compared to aminophylline with P=0.004; No significant differences in adverse events.

Conclusion: It is reasonable to offer trans-nasal SPGB, intravenous aminophylline, and conservative therapy as simple, safe, and non-invasive modalities for treating PDPH before EBP.

Keywords: Aminophylline, Cesarean section, Epidural blood patch, Postdural puncture headache, Sphenopalatine ganglion block, Spinal anesthesia

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Introduction

Postdural puncture headache (PDPH) is a severe, debilitating, and well-known iatrogenic complication of the neuraxial block (spinal and epidural anesthesia). The International Headache Society described PDPH as a severe, dull, and frontal or occipital headache that

occurs within five days after a dural puncture with a cerebrospinal fluid leak and usually associated with neck pain, neck stiffness, nausea, tinnitus, muffled hearing, and photophobia. Headache is aggravated in the upright position and dramatically relieved when lying flat. It prevents early mobilization, increases the risk of thromboembolism and neurological complications, and prolongs hospital stay (1, 2).

The pathophysiology of PDPH is uncertain. However, cerebrospinal fluid (CSF) leakage and intracranial hypotension lead to cerebral and meningeal vasodilation that may cause or contribute to headaches (3). The incidence of PDPH varies with the type and size of the spinal needles (4). It may reach 80% with an 18G epidural needle in an unintentional dural puncture (5, 6).

The epidural blood patch is the gold standard treatment of PDPH, in which 20ml of the patient's blood is injected into the epidural space to seal the dural hole and cease the leakage of CSF. Up to 75% of headaches resolve after the initial treatment, although some may require another epidural blood patch (EBP) for unresolved headache or headache recurrence. Conservative treatments such as bed rest, abdominal binder, hydration, or caffeine are usually recommended, although they have been reported ineffective by multiple studies (7).

The sphenopalatine ganglion (SPG) is a complex extracranial ganglion in the pterygopalatine fossa that involves autonomic (sympathetic and parasympathetic) and somatic sensory neural components (8). Through transcutaneous, transoral, or trans-nasal approaches, SPG block (SPGB) has been used to manage chronic pain conditions such as cluster headaches, migraine headaches, and trigeminal neuralgia (9).

The trans-nasal SPGB is a simple, safe, non-invasive, and easily performed procedure. It is supposed that blocking the parasympathetic outflow to the intracranial vasculature helps the cerebral vessels to return to their normal diameter and relieve the headache (10).

Aminophylline, a methylxanthine derivative, has been used to manage PDPH. The exact mechanism is unclear; However, it might be related to the constriction of intracranial vasculature through adenosine receptor inhibition and blocking of pain transmission. It also can induce CSF secretion by increasing the intracellular cAMP, inhibiting calcium uptake by the endoplasmic reticulum of endothelial cells, and stimulating sodium and potassium pumps (11).

PDPH is a common complication among parturients, and the standard treatment (EBP) is invasive, risky, and refused by many patients. This study was designed to evaluate and compare SPGB and intravenous aminophylline against control as promising modalities for relieving headache severity (primary outcome), with a lack of current sufficient evidence to recommend effective, safe, well-tolerated, and non-invasive treatment.

Methods

Ethics: A prospective, randomized**,** and parallel research was registered and approved by the Ethics Committee of the Faculty of Medicine ((FMASU R 124/ 2022) on 25.08.2022), registered at ClinicalTrials.gov (NCT05552404), and conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All participants signed written informed consent.

The study was conducted in the University Obstetric Hospital between 1st October 2022 and 31st December 2022. Obstetric patients who complain of headaches after spinal anesthesia for cesarean section and fulfill the inclusion criteria were randomly assigned in this study into one of the following three groups using computer-generated codes placed in opaque sealed envelopes with a 1:1 ratio by a physician not directly involved in the research or patient care.

Group (C) received conservative therapy (CT). Group (A) received conservative therapy plus Aminophylline (250 mg of Aminophylline dissolved in 100 ml normal saline for intravenous infusion over 30 minutes) to manage PDPH. Group (S) received conservative therapy plus sphenopalatine block (SPGB) using a hollow cotton swab with a local anesthetic solution in each nare to manage PDPH. Follow-up was done by a physician unaware of the group allocation. Therefore, the participants, allocating physicians, and follow-up physicians were blinded.

The participants who fulfill the inclusion criteria were involved: ASA I–II, 18 - 40 years old female,

underwent spinal anesthesia with 22G Quincke needle for cesarean section, and complained of PDPH as defined by the international classification of headache disorders, 3rd edition criteria (Orthostatic headache within five days of a lumbar puncture that significantly worsens in sitting or standing, and improves after lying flat and may be associated with neck pain, tinnitus, changes in hearing, photophobia, and/or nausea; After exclusion of other causes such as hypertension, preeclampsia, tension headache, and migraine).

Participants were excluded if there was a history of headaches that could interfere with the PDPH diagnosis, central nervous system diseases (including intracranial hemorrhage, seizures, intracranial hypertension, or hydrocephalus), cardiovascular diseases (including coronary heart disease, arrhythmias, or hypertension), allergy to or contraindication for using aminophylline, coagulopathy, nasal septal deviation, polyp, or nasal bleeding, and general anesthesia after failed spinal anesthesia.

The anesthesiologist was informed when the patients complained of PDPH within five days after spinal anesthesia. The participants were randomly recruited using computer computer-generated programs into three groups. Participants in group (C) received conservative therapy such as bed rest, fluids, abdominal binder, oral paracetamol, and caffeine (12), whereas group (A) received conservative therapy plus Aminophylline (250mg of Aminophylline dissolved in 100 ml normal saline for intravenous infusion over 30 minutes) (11), and group (S) received the conservative therapy plus sphenopalatine ganglion block SPGB, that has been performed in the emergency room where non-invasive blood pressure, ECG and saturation probe were attached to the patient. Under strict protective and safety measures against COVID-19, SPGB has been performed by a trans-nasal approach. A Few drops of lidocaine 2% were instilled into both anterior nares. Then a hollow cotton swab soaked in lidocaine 2% was passed through each nare, and the end of the swab was positioned just superior to the middle turbinate and anterior to the pterygopalatine fossa and sphenopalatine ganglion for 5 minutes then 0.5ml of lidocaine 2% was injected slowly through the hollow swab and was repeated once after another 5 minutes where the patient stayed in the supine position (13, 14).

After 10 minutes, the patient was asked to sit up, and the presence of a headache was assessed using a Visual Analogue score (VAS) (0–no pain to 10–worst pain imaginable). Intravenous paracetamol 1 g every 8 hours (11) and intravenous ketorolac 30 mg every 12 hours (16) were added when the pain score remained ≥4 after 24 hours.

Pain severity was assessed before the procedure, 30 minutes, 1, 6, 12, and 24 hours after using a Visual Analogue score (VAS) bedside card. VAS scores were recorded with the patient in a sit-up position for 5 minutes after lying flat for more than 10 minutes.

Heart rate (HR) and mean arterial pressure (MAP) were documented simultaneously. The participants' side effects were recorded at 24 hours, including arrhythmias, agitation, nasal bleeding, and nausea and vomiting.

The participants were offered EBP if there was no adequate pain relief within 48 hours.

- The primary outcome is the headache severity in the form of Visual Analogue score (VAS) 12 hours after treatment.
- The secondary outcome:

1. Patient Global Impression of Change (PGIC) Scale: The participant encircles a number that matches the degree of change since the beginning of care, where 0 is much better, 10 is much worse, and 5 has no change at 24 hours.
2. Adverse effects: Recording of adverse effects, arrhythmias, agitation, nasal bleeding, and nausea and vomiting within 24 hours.

The sample size was calculated by using PASS 11 for sample size calculation, setting power at 80%, alpha error at 5% and after reviewing previous study results (Fawaz et al., 2022) (11) showed that Mean VAS scores for postdural puncture headache intensity were statistically significantly lower in patients took IV Aminophylline compared to those took conservative treatment at 12 hours (2.75 ± 2.42 versus 4.79 ± 2.06 respectively) and with considering dropout rate 10%; based on that, a sample size of at least 75 patients undergoing cesarean section under spinal anesthesia divided randomly into three groups (25 patients in each group) was sufficient to achieve study objective.

The data were analyzed using Statistical

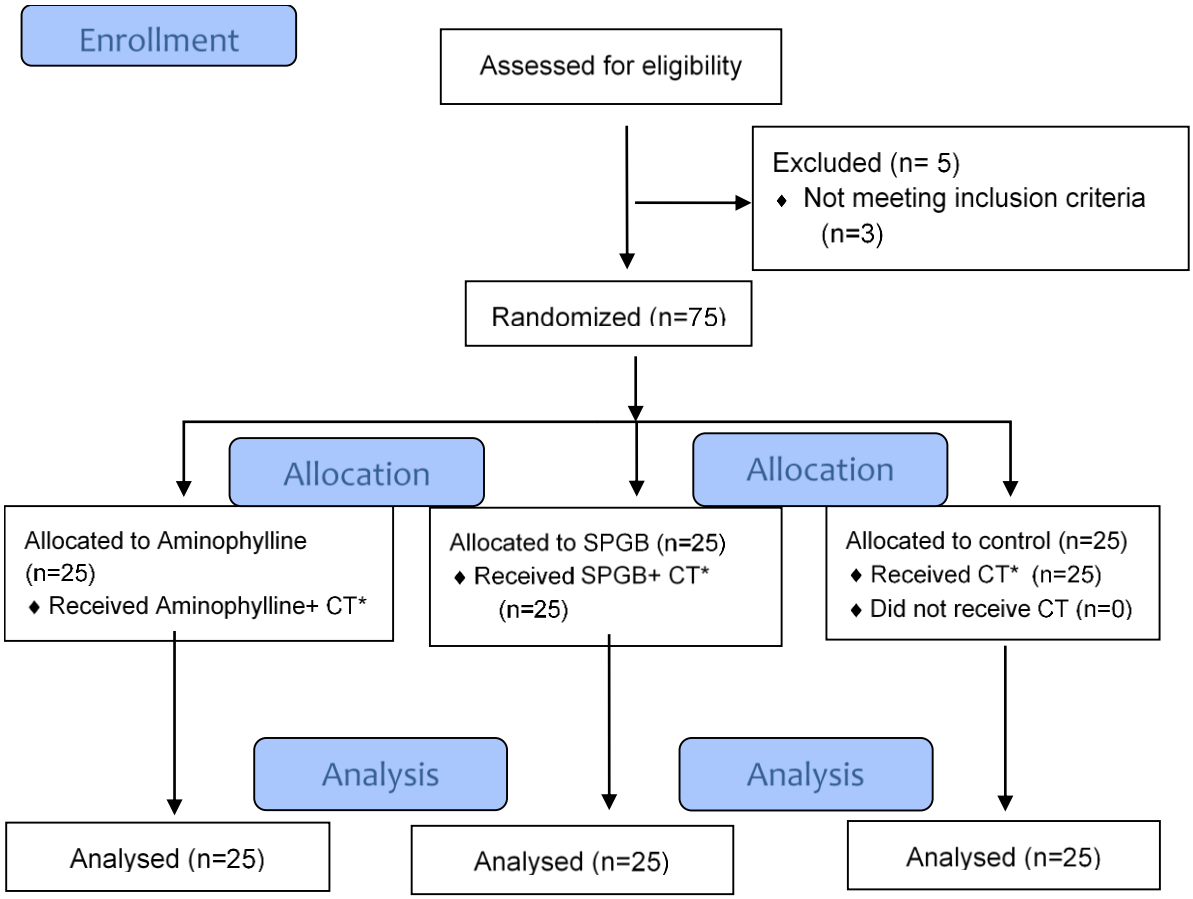

Figure 1. CONSORT Flow Diagram.

Package for Social Science (SPSS) version 27.0., Quantitative data were expressed as mean± standard deviation (SD) or median and interquartile range (QR). Qualitative data were expressed as frequency and percentage. Two-way analysis of variance (ANOVA) is used to test the difference between the means of several variable subgroups; the post-hoc test is used for pairwise comparison of subgroups when the ANOVA test is positive. The Chi-square (X2) significance test was used to compare proportions between qualitative parameters. The Kruskal-Wallis test for several subgroups' comparisons in non-parametric data. Pairwise comparison of subgroups when the test is positive. The confidence interval was 95%, and the accepted error margin was 5%. P-value <0.05 was considered significant.

Results

Eighty participants were screened for eligibility, and five were excluded (2 refused to participate, and three did not meet the inclusion criteria). The 75 participants were randomized into three equal groups, and all were available for final analysis (Fig. 1).

There were no significant differences in terms of demographic data (age and ASA) and hemodynamic (HR and MAP) at baseline, 30 minutes, 1, 6, 12, and 24 hours between the three groups with P-value> 0.05 (Table 1).

The results showed a statistically non-significant baseline VAS score (median=8) in all groups, where SPGB significantly reduced VAS median values to 3 at all-time points with P≤0.001 compared to control. Moreover, SPGB significantly reduced VAS at 30 minutes (median=3 and IQR=2.75-4.25) in comparison to aminophylline (median=6 and IQR=5-7) with P=0.004 (Table 2 and Fig. 2).

Table 1: Demographic data, hemodynamic parameters, and 24-PGIC.

		Group A (n=25)	Group C (n=25)	Group S (n=25)	f	p
AGE		31.8±4.05	31.4±4.1	31.84±4.0	0.07	0.91
ASA	**I**	17 (68%)	15 (60%)	19 (76%)	X2=1.5	0.48
	II	8 (32%)	10 (30%)	6 (24%)		
HR baseline		104.08±4.6	107.12±5.2	106.76±4.8	2.92	0.06
HR 30min		99.12±4.9	101.08±3.6	98.24±4.9	2.63	0.08
HR 1hr		99.24±1.9	99.72±2.6	98.52±2.4	1.71	0.19
HR 6hrs		96.64±2.1	97.44±2.8	95.96±2.6	2.17	0.12
HR 12hrs		87.24±4.2	89.16±3.0	87.28±4.8	1.81	0.17
HR 24hrs		84.6±4.5	86.68±3.1	84.96±5.0	1.68	0.19
MAP baseline		100.72±7.2	100.76±6.8	100.56±5.7	0.01	0.99
MAP 30min		91.36±6.4	91.08±9.4	87.92±7.2	1.51	0.23
MAP 1hr		87.04±5.4	87.6±7.8	85.04±6.1	1.07	0.35
MAP 6hrs		84.4±5.3	85.44±7.8	83.12±6.2	0.79	0.46
MAP 12hrs		82.88±5.1	83.04±6.7	80.4±4.6	1.79	0.18
MAP 24hrs		81.8±5.1	83.64±6.7	80.8±4.6	1.68	0.19
PGIC 24hrs		4.08±3.3	7.84±2.5	3.16±3.2	16.8	<0.001

Data expressed as mean ± SD, f=one-way ANOVA, X2= Chi-square test. P-value> 0.05 is considered statistically non-significant.

Table 2: VAS score comparison.

	A			C			S			P Value
	range	Median	IQR	range	Median	IQR	range	Median	IQR	
VAS baseline	6-9	8	7-8	6-9	8	7-8	6-9	8	7-8	0.91
VAS 30min	5-9	6	5-7	7-9	8	7-9	2-9	3	2.75-4.25	<0.001
VAS 1hr	3-7	4	3-6	5-9	7	6-8	2-9	3	3-4	<0.001
VAS 6hrs	2-7	3	3-6	5-8	7	6-7	2-8	3	2-4	<0.001
VAS 12hrs	1-7	3	2-4.25	3-9	7	4.75-8	1-9	3	2-3.25	<0.001
VAS 24hrs	0-7	3	1-4	4-9	6	4.75-7	0-9	3	2-3	<0.001

Post hoc analysis

	A-C	S-C	S-A
VAS 30min	0.001	0.000	0.004
VAS 1hr	0.000	0.000	0.418
VAS 6hrs	0.000	0.000	0.406
VAS 12hrs	0.000	0.000	0.875
VAS 24hrs	0.000	0.000	0.875
PGIC 24hrs	0.000	0.000	0.532

Data expressed as range, median, interquartile range (IQR), P value Kruskal-Wallis test, and Post hoc Tukey test. P<0.05 is considered statistically significant.

Otherwise, there were no significant differences between SPGB and Aminophylline at 1, 6, 12, and 24 hours with P=0.418, 0.406, 0.875, and 0.875 respectively (Table 2).

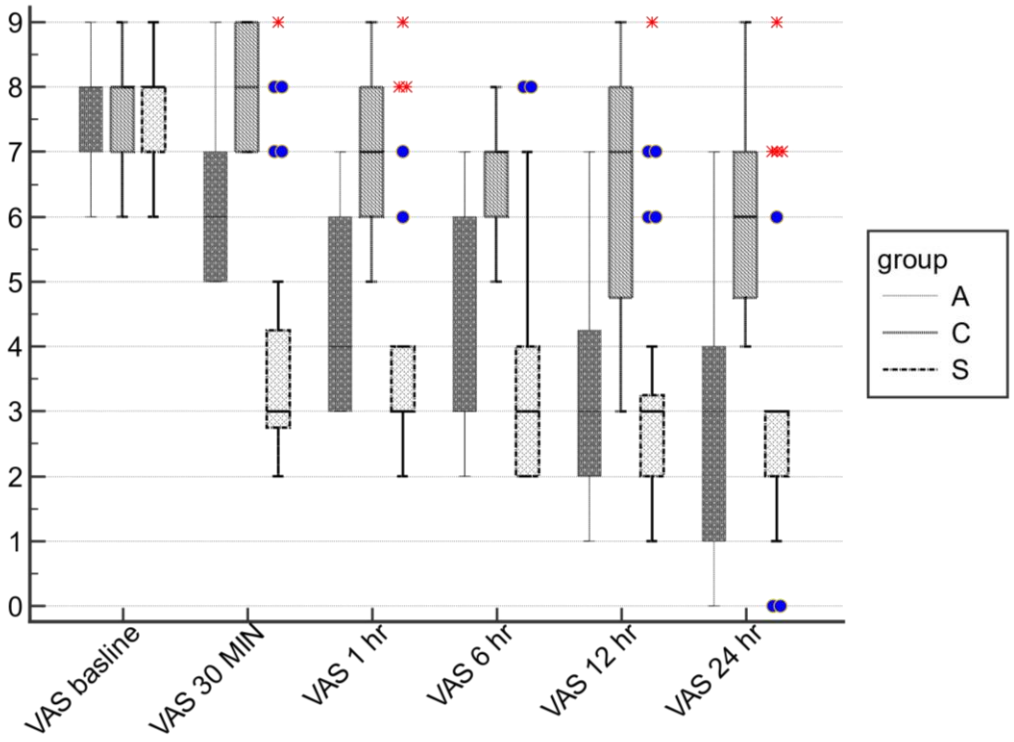

Figure 2. Visual Analogue Scale (VAS). Whiskers show minimum and maximum values; the line shows the median; the box shows the inter-quartile range; ⁕ and • represent the outlier.

Table 3: Adverse events.

	Group A (n=25)	Group C (n=25)	Group S (n=25)	X2	p
Arrhythmia	3(12%)	2(8%)	2(8%)	0.3	0.85
Agitation	2(8%)	3(12%)	2(8%)	0.3	0.85
Nasal bleeding	1 (4%)	2(8%)	3(12%)	1.1	0.58
Nausea & vomiting	2(8%)	4(16%)	3(12%)	0.76	0.69

Data expressed as frequency (percentage). P-value> 0.05 is considered statistically non-significant.

Also, intravenous aminophylline significantly reduced VAS median values to 6, 4, 3, 3, and 3 at 30 minutes,1, 6, 12, and 24 hours, respectively, with P≤0.001 compared to the control (Table 2 and Fig. 2).

The results showed a statistically significant difference and improvement of 24-hour PGIC with SPGB and Aminophylline in comparison to control (Mean±SD=3.16±3.2, 4.08±3.3, and 7.84±2.5 respectively) with P≤0.001 (Table 1); No difference found between SPGB and Aminophylline group P=0.532 (Table 2). Regarding adverse events (arrhythmia, agitation, nasal bleeding, and nausea and vomiting), there were no significant differences between the three groups (Table 3).

Discussion

Our prospective randomized controlled study was designed to evaluate and compare SPGB and intravenous aminophylline for treating PDPH as effective, safe, well-tolerated, and non-invasive promising modalities.

Our results showed a significant reduction of VAS score (as a primary outcome) in SPGB and aminophylline groups compared to the control at all time points. No significant differences in VAS score were recorded between aminophylline and SPGB groups except at the 30-minute time (P=0.004), indicating earlier response to SPGB. There was a statistically significant improvement in 24-hour PGIC in aminophylline and SPGB groups compared to the control. Also, no significant differences in hemodynamic parameters (HR and MAP) nor adverse events were recorded.

The CSF leakage and intracranial hypotension may cause cerebral and meningeal vasodilation to maintain a constant intracranial volume, in addition to the loss of CSF support and subsequent positional traction on intracranial pain-sensitive structures. Both mechanisms may cause and contribute to PDPH (3).

Conservative treatments such as bed rest, abdominal binder, hydration, caffeine, and simple analgesia are usually recommended (7) as more than 85% of patients are relieved within 48 hours (6), although they have been reported to be ineffective, especially in severe cases (7). The epidural blood patch is the gold standard treatment of PDPH (7). Epidural abscesses, wet tap, meningitis, radiculopathy, convulsions, and neurological deficits have been reported after EBP (17). After a review of the previous publications, the SPGB technique was formulated (13), And a single dose of 250 mg aminophylline was chosen; it is lower than the regular therapeutic doses and produces a low plasma aminophylline concentration in comparison to those produced the adverse events (18).

The trans-nasal SPGB is a simple, safe, non-invasive, and easily performed procedure. It is supposed that blocking the parasympathetic outflow to the intracranial vasculature helps the cerebral vessels to return to their normal diameter and relieve the headache (10). The mechanism of aminophylline might be related to the constriction of intracranial vasculature and induction of CSF secretion (11).

In agreement, a systematic review among obstetric patients with PDPH treated with SPGB found significant pain relief in 60% of patients and an initial improvement in the remaining 40% who needed more interventions. The review reported that lidocaine 2% was the most common and effective local anesthetic used, and the response to SPGB after surgery was better than epidural anesthesia (13-16).

Also, 93 obstetric participants with PDPH were enrolled in a randomized comparative trial, where 47 participants received bilateral greater occipital nerve block (GONB), and 46 participants received trans-nasal SPGB and reported that both techniques reduced NRS statistically ($P < 0.000$) and clinically less than four after 30 minutes and improved neck rigidity with no adverse events (17-19). Twenty parturients with PDPH were treated by SPGB either by the applicator or nasal spray and found significant improvement in pain score in the applicator group compared to the nasal spray group (20).

Moreover, seventeen years retrospective comparative study was conducted on 81 obstetric participants with PDPH following wet tap with an epidural needle for labor treated with SPGB (repeated every 15 minutes for three times if needed) or EBP and reported that pain score significantly reduced at 30 and 60 minutes in SPGB group in comparison to EBP group but failed to detect any difference at 1,2,7 days (21). Trans-nasal SPGB in 3 obstetric participants complaining of PDPH showed immediate pain relief after the procedure and at 48 hours in a case report (14).

SPGB was compared against 1gm paracetamol every 8 hours in obstetric PDPH and showed a reduction of headache severity in 89% of participants ($P < 0.001$) with no adverse events (22). Forty urological participants with PDPH were randomized into control (conservative treatment) and trans-nasal SPGB (0.25% ropivacaine) groups, and there was a statistically significant reduction of pain score up to 54 hours, better satisfaction score, and less analgesic requirements in SPGB group (23).

In contrast, a prospective randomized trial conducted on 40 participants with PDPH treated with trans-nasal SPGB (4% lidocaine and 0.5% ropivacaine) versus placebo (saline) after 24 hours on conservative treatments and reported transient reduction at 30 minutes in VAS score (median difference= 5mm, P=0.53) in both groups with no statistically significant difference at 1 hour and one week. The different outcomes might be due to a small amount of local anesthetic, improper technique, heterogeneous causes of dural puncture and population, inter-hospital variations, variable needle sizes and types, and dural puncture attempts. However, transient relief of headache has been explained as mechanical stimulation of SPG by the cotton swab; further SPGB trials assessing intracranial vasculature (as transcranial Doppler) and a sham block are required (15).

In agreement, one dose of intravenous aminophylline 250mg was compared against acetaminophen 1gm over 30 minutes for treatment of PDPH in 70 participants after different surgical interventions, and aminophylline showed a reduction

of VAS scores at 2, 6, and 12 hours in addition to improvement of PGIC in comparison to acetaminophen (12).

A multicentre study in China evaluated 126 participants with PDPH after different surgical interventions. Within 3 hours of symptoms onset, the active group received intravenous aminophylline 250mg over 30 minutes once daily for two days in comparison to placebo and found statistically significant improvement of VAS scores at 8 hours and PGIC at 48 hours with no difference in the incidence of adverse effects (18).

Other studies evaluated theophylline to treat PDPH and reported the same results (24, 25). Also, aminophylline has been evaluated for prevention of PDPH; One hundred twenty parturients who underwent cesarean section under combined spinal epidural anesthesia were enrolled, and 60 participants received intravenous aminophylline 250mg over 30 minutes immediately after baby delivery for prevention of PDPH and were observed 24 hours for adverse events and seven days for incidence of PDPH; The results showed that aminophylline reduced the incidence of PDPH for seven days with no adverse events in comparison to placebo (26).

Three hundred obstetric participants were randomized into three groups for prevention of PDPH, where 1mg/kg aminophylline, 0.15mg/kg ondansetron, or placebo were given during CS, and the results showed that aminophylline did not decrease the incidence of headache nor severity at 24, 48, and 72 hours after spinal anesthesia, probably due to the small dose of aminophylline (1mg/kg) (27).

Further studies are required to compare aminophylline and SPGB with the gold standard treatment (EBP); the effects of intravenous versus oral aminophylline for home treatment of PDPH, in addition to comparing SPGB with a local anesthetic against a sham block to exclude the effects of mechanical stimulation.

Conclusion

It is reasonable to offer trans-nasal SPGB, intravenous aminophylline, and conservative therapy as simple, safe, and non-invasive modalities for treating PDPH before EBP.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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