Randomized Control Trial

Comparative Study Between the Analgesic Effect of Prednisolone and Pregabalin in Managing Post Dural Puncture Headache After Lower Limb Surgeries

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Background: Post dural puncture headache (PDPH) is a major challenging complication and may be a cause of morbidity after spinal anesthesia. Currently there is no definitive management for PDPH, so the search for effective treatment continues.

Objectives: Our aim was to investigate the analgesic effectiveness of oral prednisolone vs oral pregabalin for managing PDPH subsequent to spinal anesthesia for lower limb surgeries.

Study Design: A prospective controlled double-blind randomized study.

Setting: Academic University Hospitals.

Methods: A total of 63 patients who had lower limb surgeries and suffered PDPH after spinal anesthesia were randomly allocated into one of 3 groups. Group C patients received conservative treatment and to maintain blinding, a tablet of vitamins was given to them twice per day for 3 days; Group P patients received conservative treatment and oral prednisolone 20 mg once daily plus one tablet of vitamins (in order to ensure blinding) for 3 days; Group G patients received oral pregabalin 150 mg twice daily for 3 days in addition to conservative treatment. The primary outcomes we measured were the Visual Analog Scale (VAS) score and modified Lybecker score. The secondary outcomes we measured were the total dose of rescue analgesia, the need for an epidural blood patch (EBP), and adverse effects from the study drugs.

Results: When comparing the intensity of headaches assessed through both the VAS and the modified Lybecker score, no statistically significant disparities were observed in relation to baseline measurements. While after starting treatment by 12 hours and 24 hours, the headache intensity was statistically significantly lower in Group G compared to Group P and Group C, but there was no significant difference between Group C and Group P at 12 hours. The headache intensity was statistically significantly higher in Group C compared to Group P and Group G, but there was no significant difference between Group P and Group G at 48 hours and 72 hours. Ketorolac consumption was statistically significantly higher in group C than the other groups. However, it was statistically significantly lower in group G than group P. Only 2 patients in group C were indicated for EBP while no patients in either Groups P or G required an EBP.

Limitations: Our study's limitations include the paucity of literature studying prednisolone and pregabalin use in PDPH, our study's small sample size, and the lack of sufficient studies for comparing results may limit the generalization of our findings.

Conclusion: Both oral prednisolone and pregabalin were effective in reducing PDPH severity; oral pregabalin is superior to prednisolone.

Key words: Spinal anesthesia, post dural puncture headache, prednisolone, pregabalin

Trial registration: Institutional Review Board (IRB#6324-26-8-2020) and ClinicalTrials.gov (NCT:04662125)

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As one of the earliest documented complications of neuraxial blocks and over a century after being first described by Dr. August Bier in 1898, post dural puncture headache (PDPH) remains a challenging clinical problem for anesthesiologist. Meningeal puncture headache is a common, irritating, unpleasant complication with an estimated incidence between 0.3%-40% of patients following spinal anesthesia (1,2).

The pathophysiology of PDPH is not completely understood. However, it is postulated to be due to the disturbance of normal cerebrospinal fluid (CSF) homeostasis resulting from persistent CSF loss through a hole in the meninges (3,4). Although there is a massive search for effective PDPH treatment that dates to Bier's time, most recommended treatments are symptom-based and supportive including fluid therapy, supine bed rest, and caffeine, which are all of doubtful value and may not be able to completely cure the symptoms.

Epidural blood patch (EBP) is the only confirmed treatment and universally accepted as the cornerstone PDPH treatment, even though it has possible serious effects, such as unintentional additional dural puncture, meningitis, and seizures. Recent literature has reported that total or partial PDPH remission occurred only in about 50%-80% of patients treated with EBP (4). Despite all the advances in treating and preventing meningeal puncture headache, this iatrogenic complication remains a common problem and many questions about the optimal measures for its treatment are still unanswered.

A variety of pharmacological treatments have been developed to address PDPH, encompassing gabapentin, pregabalin, aminophylline, corticosteroids, and magnesium (5-7). Incorporating corticosteroids in multimodal analgesia strategies for managing postoperative pain is supported by strong evidence (8-10). Prednisolone is commonly utilized in managing low-pressure headaches stemming from the syndrome of spontaneous intracranial hypotension (11-14). The clinical indications and symptomatology of spontaneous intracranial hypotension-related headache bear a striking resemblance to those observed in PDPH (15). Pregabalin, a synthetic derivative of gamma-aminobutyric acid (GABA), is also one of the drugs used to treat PDPH. It is an antiepileptic medication that has a beneficial effect in reducing hyperalgesia and may play a role in mitigating early postoperative pain by coupling to $\alpha 2\delta$calcium channels (16).

In order to avoid the need for an invasive EBP, both oral prednisolone and pregabalin have been recognized in many studies to improve PDPH. Hence, our study aimed to draw a comparison of the analgesic efficacy of oral prednisolone vs oral pregabalin in PDPH treatment following spinal anesthesia in patients undergoing lower limb surgeries.

The primary outcomes were the Visual Analog Scale (VAS) and modified Lybecker scores for evaluating the analgesic efficacy of oral prednisolone and oral pregabalin in treating PDPH. The secondary outcomes were total dose of ketorolac as a rescue analgesia, the need for an EBP, adverse effects of the study medications, and associated symptoms of PDPH: dizziness, diplopia, tinnitus, sleepiness, neck stiffness, nausea, and vomiting.

Methods

Study Design

This prospective, controlled, comparative, double-blind, randomized trial was carried out at our University Hospitals from December 10, 2020 through August 30, 2023. Ethical approval was secured from our University's Institutional Review Board (IRB#6324-26-8-2020). The study was also registered on ClinicalTrials.gov, bearing the identifier NCT:04662125.

Population

Prior to enrollment, written informed consent was acquired from all patients. The study included 63 patients, aged between 18 and 65 years old, with a body mass index (kg/m^2) of 20-30 and classified as having an American Society of Anesthesiologists (ASA) physical status I or II. All study patients were undergoing lower limb surgery under spinal anesthesia and were diagnosed with PDPH during the postoperative phase.

Exclusions included patients with a history of chronic headache or migraine, an allergy to any of the study drugs, prior cerebrovascular accidents or neurological disorders, were pregnant, had uncontrolled diabetes mellitus, had hepatic disease, and those who refused to participate and those who were uncooperative. Any patient could withdraw from the study at any time.

For all patients undergoing lower limb surgery during our study period, an intrathecal block was performed by an anesthesiologist not involved in this study. The block was done in an operating room after attaching the standard monitors (electrocardiogram, pulse oximetry, noninvasive blood pressure) as well

as securing an appropriate intravenous access with a fluid co-load of 15 mL/kg lactated Ringer's solution. While the patient was sitting, under strict aseptic procedures, and after skin infiltration with lidocaine 2% (3 mL),spinal anesthesia was performed at the L3/L4 or L4/L5 intervertebral spaces using a 25G disposable Quinke spinal needle using the paramedian approach. Then, after CSF free flow, the anesthetic drugs (hyperbaric bupivacaine 0.5% 10-15 mg [2-3 mL] according to the surgery plus 25 µg fentanyl) were intrathecally injected without barbotage.

In the recovery room and for the next 5 postoperative days, any patient who reported having a headache was assessed for eligibility for our study and was interviewed by one of the investigators. During the interview, the aim, advantages, and potential disadvantages of the study drugs were discussed and written informed consent was obtained.

PDPH was diagnosed according to the criteria of the International Headache Society: a headache that occurs within 5 days of a lumber puncture which notably worsens within 15 minutes of sitting upright or standing and exhibits improvement within 15 minutes of reclining flat. This distinctive postural aspect serves as its identifying hallmark. PDPH is usually described as a severe, dull nonthrobbing, fronto-occipital pain occurring bilaterally in the temporal, frontal, or occipital regions and is often accompanied by backache, nausea, neck stiffness, cranial nerve symptoms, and localized muscle spasms (17).

All patients experiencing PDPH were provided with an explanation of the Visual Analog Scale (VAS) and instructed to represent their headache intensity by drawing a perpendicular line to the 10 cm VAS line and to determine the score, a ruler was used to measure the distance (cm) on the VAS line between 0 and the patient's mark, providing a range of scores from 0 to 10 where 0 is no headache and 10 is the most horrible headache which is then graded as follows: 0-1 indicating no headache, 2-4 signifying mild headache, 5-7 representing moderate headache and 8-10 denoting severe headache (18).; we requested they report their headache intensity after sitting upright for 15 minutes. Additionally, headache intensity was assessed using the modified Lybecker score: grade one, patients with mild headache not affecting activities of daily living and relieved by oral analgesics; grade 2, moderate headache restricting activities of daily living and requiring bed rest for most of the day as well as requiring injectable analgesia; grade 3, severe headache with associated symptoms, completely restricted activities of daily living and being bed-bound all day. Associated symptoms include dizziness, diplopia, tinnitus, sleepiness, neck stiffness, nausea, and vomiting (19).

Enrolled patients were hospitalized and followed from their study enrollment and up to 3 days through their treatment course in order to detect and document the study intervention's effects and to guarantee complete resolution of their PDPH symptoms.

Randomization

Patients who reported a VAS score of 4 or greater and a modified Lybecker score of 2 or greater were included in our study. Computer generated randomization numbers were produced by the website Research Randomizer (https://www.randomizer.org/) and were placed in sealed, opaque envelopes to allocate the 63 study patients into 3 equal groups (each group 21 patients).

Group C (control group): These patients were managed with conservative treatment. Conservative treatment included good hydration by administering a 1,000 mL crystalloid infusion during the first 4 hours and increased oral fluid intake, recumbent positioning, administering 2 acetaminophen (500 mg) and caffeine (65 mg) combination tablets every 8 hours for 3 days and administering a stool softener twice a day for 3 days. The stool softener was administered in order to maintain blinding since a tablet of vitamins was given to the other groups twice per day for 3 days.

Group P (prednisolone group): These patients received the same conservative treatment as Group C; they also were administered a daily dose of oral prednisolone (20 mg) plus one vitamin tablet for 3 days.

Group G (pregabalin group): These patients received the same conservative treatment as Group C; they also were administered an oral pregabalin tablet (150 mg) twice per day for 3 days.

Double blinding was maintained since the patients were not aware of their group assignment, and the investigator responsible for data collection was blinded to each patient's group allocation.

Headache intensity and severity were measured by the VAS and modified Lybecker score at 0 (baseline) then at 12, 24, 48 and 72 hours after commencement of the drug therapy for each group. If the VAS score was ≥ 4 in any group after 12 hours, intravenously administered ketorolac (30 mg) was given as a rescue analgesia and if required, was repeated every 12 hours. The total dose of ketorolac was recorded in each group. EBP was

deemed appropriate if the symptoms persisted with a VAS≥ 4 and modified Lybecker score > 2 after 48 hours and after collecting patients' consent for this invasive procedure.

Data Collected

All data collected were for all enrolled patients including the 3 groups (control, prednisolone and pregabalin group).

Data were collected on the secondary outcomes were: total dose of ketorolac as rescue analgesia; the number of patients needing an EBP; possible adverse effects of the study medications including sedation, blurred vision, sleepiness, and dizziness. The sedation level was assessed using the Ramsay Sedation Scale score (one = anxious or agitated, 2 = cooperative and oriented, 3 = responds to commands only, 4 = brisk response to light tap or loud auditory stimulus, 5 = sluggish response to light tap or loud auditory stimulus, 6 = no response to pain) (20). Associated symptoms of PDPH, such as dizziness, diplopia, tinnitus, sleepiness, neck stiffness, nausea, and vomiting were assessed and recorded in each group.

Sample Size Calculation

Determining the sample size was accomplished before starting the study by utilizing the OpenEpi program (Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com) according to the previously published data assuming the mean (SD) VAS score at 24 hours between the control group was 6.16 ± 0.9 and prednisolone group was 5.53 ± 0.7 (15). So, at power of study 80%, 95% CI and an interventional to control group ratio 2:1 the sample size was calculated to be 63 patients, 21 in each group.

Statistical Analysis

Data were entered using the IBM SPSS Statistics 28.0 (IBM Corporation). Data are expressed as mean and SD for normally distributed quantitative variables or median and interquartile range for non-normally distributed quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables.

Comparisons between groups were done using analysis of variance with multiple comparisons, post hoc test in normally distributed quantitative variables, while nonparametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. For comparing categorical data, a χ^2 test was performed. Fisher exact test was used when the expected frequency was less than 5. Correlations between quantitative variables were done using the Spearman rank correlation coefficient. *P* values less than 0.05 were considered statistically significant.

Results

A cohort of 65 patients who developed PDPH after elective lower limb surgery under spinal anesthesia were evaluated to determine their eligibility for inclusion in our study. Two of them were excluded from participation: one patient declined to participate and the other had a history of stroke. The remaining 63 patients were randomly divided into 3 groups (21 patients in each group) as shown in the CONSORT (Consolidated Standards of Reporting Trials) flow chart (Fig. 1). There were no significant statistical differences among the 3 groups regarding age, gender, body mass index, ASA physical status, and type of surgery (Table 1).

Comparing headache intensity as measured by the VASamong the 3 studied groups, there was no statistically significant difference regarding baseline pain intensity (*P* = 0.61). At 12 hours and 24 posttreatment, pain intensity was statistically significantly lower in Group G than both Group P and Group C (*P* < 0.001), while there was no statistically significant difference between Group C and Group P at 12 hours posttreatment (*P* = 0.26).

The headache intensity was statistically significantly higher in Group C than both Group P and Group G (*P* < 0.001) with no significant difference between Group P and Group G at 48 hours, and 72 hours (*P* = 0.28 and *P* = 1.00 respectively) (Fig. 2).

Additionally, the Modified Lybecker score exhibited no statistically significant difference among the 3 studied groups at the baseline readings (*P* = 0.76). However, there was a statistically higher significant difference in Group C at 24 hours, 48 hours, and 72 hours posttreatment than the other 2 groups (*P* < 0.001). While comparing Group P to Group G showed significantly lower headache severity in Group G at 12 hours, and 24 hours posttreatment (*P* = 0.005 and *P* < 0.001 respectively), and no statistically significant difference at 48 hours, and 72 hours posttreatment (*P* = 0.87 and *P* = 1.00 respectively) (Table 2).

Comparing the 3 groups regarding co-existing symptoms shows that there was no statistically significant difference among the 3 groups (*P* = 1.00) (Table 3).

The need for and consumption of ketorolac as rescue analgesia was found to be significantly higher

in Group C than the other 2 groups. The mean (SD) total dose of ketorolac needed in Group C was (111.43 ± 16.82) which was statistically highly significant than in Group P and Group G (70.00 ± 14.49 and 35.71 ± 12.07 respectively). However, the analgesic consumption was statistically significantly lower in Group G when compared to Group P ($P < 0.001$). The need for an EBP showed no statistically significant difference among the 3 groups ($P = 0.32$). In Group C, EBP was indicated for only 2 patients, whereas neither Group P nor Group G patients required an EBP intervention (Table 4).

Regarding adverse effects, no statistically significant difference was found among the 3 groups ($P = 0.32$). In Group G, only one patient reported blurred vision and another one reported sleepiness. Regarding Ramsay Sedation Scale scores, there was no significant difference among the 3 groups ($P = 0.64$) (Table 5).

There was a strong positive correlation between total rescue analgesia, VAS scores at 12, 24, 48, and 72 hours and modified Lybecker scores at 12, 24, 48, and 72 hours (Table 6).

Discussion

PDPH is a major, challenging complication and may be a cause of morbidity after spinal anesthesia; it delays hospital discharge, increases costs, and increases hospital staff workloads. Its treatment is mainly supportive, including bed rest, good hydration, caffeine, abdominal binders, and analgesics, but currently there is no definitive treatment for this common iatrogenic complication, so the search for effective pharmacological treatment continues (1-4).

Both oral prednisolone and pregabalin were proven to be effective in PDPH management in many studies (15,16). Hence, we designed our study to draw a comparison between the analgesic efficacy of oral prednisolone vs oral pregabalin in treating patients

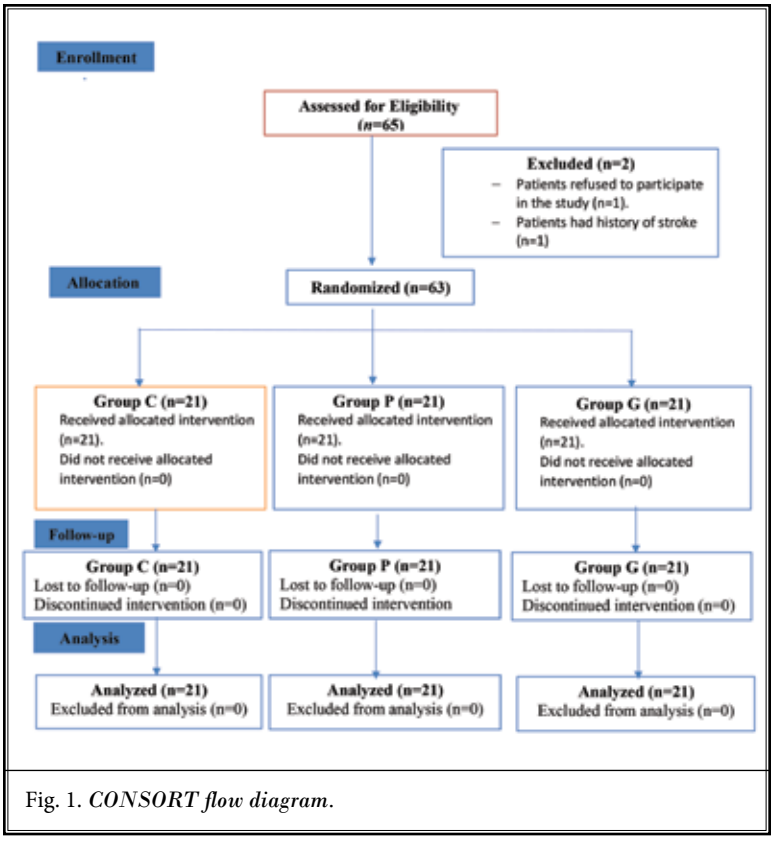

Fig. 1. *CONSORT flow diagram.*

Table 1. *Patients' characteristics and type of surgery in the 3 studied groups.*

Variables	Group C (n = 21)	Group P (n = 21)	Group G (n = 21)	χ^2/F	*P* Value
Age (years)	45.38±12.29	47.33±10.44	46.24±12.07	0.14	0.862*
Gender					
Men	13 (61.9%)	11 (52.4%)	11 (52.4%)	0.51	0.773†
Women	8 (38.1%)	10 (47.6%)	10 (47.6%)		
BMI (kg/m^2)	26.10 ± 3.06	25.48 ± 3.37	25.10 ± 3.36	0.50	0.609*
ASA Physical Status					
ASA I	8 (38.1%)	11 (52.4%)	10 (47.6%)	0.89	0.639
ASA II	13 (61.9%)	10 (47.6%)	11 (52.4%)		
Type of Surgery					
GS	5 (23.8%)	4 (19.0%)	3 (14.3%)	1.07	0.911†
Orthopedic	8 (38.1%)	10 (47.6%)	11 (52.4%)		
Vascular	8 (38.1%)	7 (33.3%)	7 (33.3%)		

Group C = Control Group, Group P = Prednisolone Group, Group G = Pregabalin Group, n = total number of patients in each group, BMI = Body Mass Index, ASA = American Society of Anesthesiologist, GS = General Surgery
Data are expressed as mean ± SD, number, and percentage.
*F: One way analysis of variance (ANOVA) test
† χ^2: Chi square test.
$P < 0.05$ is significant.

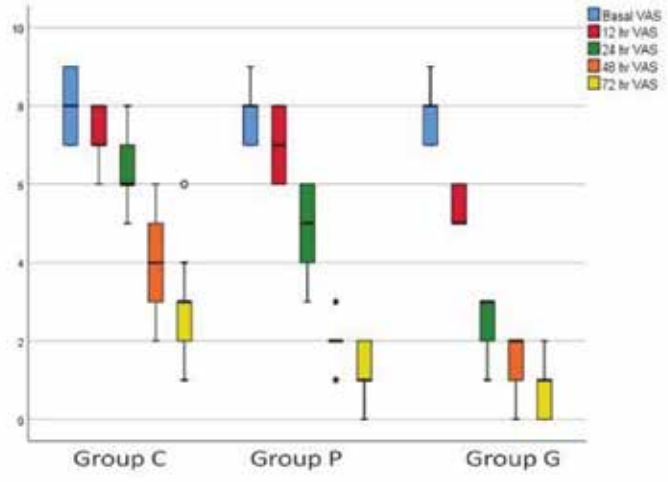

Fig. 2. *VAS score at different times among the 3 groups*.
VAS = Visual Analog Scale; Group C = Control Group; Group P = Prednisolone Group; Group G = Pregabalin Group.
P value at different time intervals among 3 groups: baseline *P* value=0.61, *P* values at 12, 24, 48 and 72 hours were < 0.001
$P < 0.05$ is significant.

with PDPH who underwent lower limb surgeries under spinal anesthesia.

Our study showed that the severity of PDPH was significantly lower in the intervention groups (Group P and Group G) than in Group C based on VAS and modified Lybecker scores at most of the time points. Favorable effects of oral pregabalin on PDPH severity were observed when compared to oral prednisolone as it was evident statistically by a significant reduction of VAS scores, modified Lybecker scores, and the lowest dose of rescue analgesia needed.

We opted to use oral prednisolone in our study as it is widely used with a good response in spontaneous intracranial hypotension treatment. Gentile, et al (11) reported good response to oral prednisolone in managing spontaneous low-CSF pressure headache in 3 cases. Symptoms and signs, headache presentation, and mechanism of action are similar in both spontaneous intracranial hypotension and PDPH (11). The exact mechanism of action of steroids in reducing headache severity is still unclear. The proposed mechanism depends mainly on the anti-inflammatory action of steroids at the dural puncture site as several inflammatory mediators have been found to be released from immune cells in the CSF in response to the puncture-site healing process. These mediators stimulate pain receptors, causing headaches. The analgesic effect of steroids in PDPH may be attributed to their ability to suppress the production of these inflammatory mediators. Moreover, steroids promote an increase in CSF volume by aiding its reabsorption from the extradural space (21).

Gupta, et al (15), in their study of 60 urological patients who suffered PDPH after spinal anesthesia, reported that 20 mg prednisolone once daily was effective in reducing headache severity and duration depending on the VAS score and the number of diclofenac tablets needed, which were significantly lower in their prednisolone group vs the conventional group (15).

Also, Afridi, et al (22) found that prednisolone 20 mg administered once daily reduced pain scores and headache severity in 60 women who underwent elective cesarean delivery and had PDPH after spinal anesthesia (6.3 ± 0.4 in the prednisolone group vs 7.2 ± 0.7 in the placebo group) at 24 hours post dural puncture (*P* = 0.000). Moreover, it was helpful in decreasing PDPH duration and limiting its associated adverse events (22). Prednisolone 20 mg once daily was used in our study keeping in view its dosage in most of the previous studies used it in spontaneous intracranial hypotension and PDPH (11-15,21,22).

Pregabalin is also one of the drugs used for managing PDPH. Its efficacy, verified in many studies, may be due to its analgesic, antihyperalgesic, and anxiolytic effects (16,23-25). Pregabalin acts by blocking hyperalgesia and central sensitization. It is 6 times greater than gabapentin for binding to the $\alpha 2\delta$ subunits of voltage-gated calcium channels, leading to a reduction of excitatory neurotransmitters production, such as glutamate. Additionally, it suppresses excitatory activity within regions of the central nervous system abundant in synaptic connections, including the amygdala, the hippocampus, and the neocortex (26-28).

In their research, Huseyinoglu, et al (29) observed that patients with PDPH who received a daily dose of 300 mg pregabalin for 3 days, followed by 150 mg daily for 2 more days, showed a significantly lower VAS score than the control group from the second day post PDPH. Additionally, Moghaddam, et al (30) reported that both pregabalin and gabapentin effectively reduced pain severity in patients with PDPH and that pregabalin seemed to be more efficient compared to gabapentin. Also, in an analysis of 86 randomized controlled trials

examining the outcome of prophylactic pregabalin on PDPH incidence after spinal anesthesia, EL Rahmawy, et al (31) concluded that preoperative oral pregabalin 150 mg decreased PDPH incidence and severity with no effect on its onset.

Karami, et al (32) studied the effect of a 150 mg pregabalin preoperative dose on 136 parturients and found that pregabalin decreased both the incidence and severity of PDPH (32). Mahoori, et al (16) compared the effects of pregabalin, gabapentin, and acetaminophen on PDPH, concluding that pregabalin and gabapentin were effective and safe, however pregabalin was more efficacious (16). Similarly, El–guoshy, et al (33), in a study involving 400 gravidas who were ASA physical status I or II who underwent elective cesarean delivery under spinal anesthesia, concluded that preoperative administration of oral pregabalin 150 mg decreased PDPH incidence with earlier onset of motor block and increased analgesia duration without affecting the baby (33). As well, Rasool, et al (25) conducted a study to compare the efficacy of pregabalin and acetaminophen in managing PDPH among patients undergoing lower abdominal and pelvic surgeries under spinal anesthesia. They found pregabalin to be superior to acetaminophen (25).

In a recent systematic review, Amini, et al (34) endorsed pregabalin use for PDPH management because it was found to significantly lower pain scores compared to placebo. Overall, it can be stated that oral pregabalin is effective in reducing the severity of PDPH.

In our study, Group G received 150 mg of oral pregabalin twice daily for 3 days. Numerous prior studies have investigated other pregabalin doses. In Huseyinoglu, et al (29), research patients received 300 mg pregabalin daily for 3 days followed by 150 mg for 2 more days. Their results were consistent with our findings (29). Lin, et al (35) showed that patients with PDPH recovered after

Table 2. *Modified Lybecker score among the 3 studied groups at different time points.*

Modified Lybecker score	Group C (n = 21)	Group P (n = 21)	Group G (n = 21)	χ^2	*P* Value
Baseline					
2	15 (71.4%)	17 (81%)	16 (76.2%)	0.52	0.76
3	6 (28.6%)	4 (19%)	5 (23.8%)		
12 hr					
1	0 (0%)	0 (0%)	9 (42.9%)	21.85	< 0.0001
2	15 (71.4%)	17 (81%)	10 (47.6%)		
3	6 (28.6%)	4 (19%)	2 (9.5%)		
24 hr					
1	0 (0%)	6 (28.6%)	18 (85.7%)	35.11	< 0.001
2	16 (76.2%)	13 (61.9%)	3 (14.3%)		
3	5 (23.8%)	2 (9.5%)	0 (0%)		
48 hr					
1	6 (28.6%)	17 (81%)	20 (95.2%)	24.5	< 0.001
2	13 (61.9%)	4 (19%)	1 (4.8%)		
3	2 (9.5%)	0 (0%)	0 (0%)		
72 hr					
1	11 (52.4%)	20 (95.2%)	21 (100%)	20.1	< 0.001
2	8 (38.1%)	1 (4.8%)	0 (0%)		
3	2 (9.5%)	0 (0%)	0 (0%)		

Group C = Control Group, Group P = Prednisolone Group, Group G = Pregabalin Group, n = total number of patients in each group. Modified Lybecker score includes grade 1: patients with mild headache not affecting daily activity and relieved by oral analgesics; grade 2: moderate headache restricting daily activity and requiring bed rest for most of the day and injectable analgesia is required; grade 3: severe headache with associated symptoms, completely restricting daily activity and keeping patients bedbound throughout the entire day.
Data are expressed as number and percentage.
χ^2: Chi square test, $P < 0.05$ is significant, $P \leq 0.001$ is highly significant.

Table 3. *Co-existing symptoms of PDPH in the 3 studied groups.*

Variables	Group C (n = 21)	Group P (n = 21)	Group G (n = 21)	χ^2	*P* Value
Co-existing symptoms					
Yes	6 (28.6)	5 (23.8)	5(23.8)	0.168	0.92
No	15 (71.4%)	16 (76.2%)	16 (76.2%)		
Types of co-existing symptoms					
Diplopia	1 (4.8%)	0 (0%)	1 (4.8%)	2.552	0.863
Dizziness	2 (9.5%)	2 (9.5%)	1 (4.8%)		
Nausea & Vomiting	3 (14.3%)	2 (9.5%)	2 (9.5%)		
Neck Stiffness	0 (0%)	1 (4.8%)	1 (4.8%)		

Group C = Control Group, Group P = Prednisolone Group, Group G = Pregabalin Group, n = Total number of patients in each group.
Data are expressed as number and percentage.
χ^2: Chi square test. $P < 0.05$ is significant, $P \geq 0.05$ is no significance.

Table 4. *Total dose of rescue analgesia and the need for an EBP in the 3 studied groups.*

Variables	Group C (n = 21)	Group P (n = 21)	Group G (n = 21)	χ^2/F	*P* Value
Total Dose of Rescue Analgesia (mg)	111.43 ± 16.82*	70.00 ± 14.49	35.71 ± 12.07†	141.8	< 0.001
EBP Need					
Yes	2 (%)	0 (0%)	0 (%)	4.13	0.323
No	19 (90.5%)	21 (100%)	21 (100%)		

Group C = Control Group; Group P = Prednisolone Group; Group G = Pregabalin Group; n = total number of patients in each group; EBP = epidural blood patch.
Data are expressed as mean ± SD, number, and percentage.
F: One way analysis of variance (ANOVA) test. χ^2: Chi square test.
$P < 0.05$ is significant, $P \leq 0.001$ is highly significant.
*The consumption of rescue analgesia was significantly higher in Group C than in both Group P and Group G.
† The consumption of rescue analgesia was significantly lower in Group G than Group P.

Table 5. *Adverse effects of the study drugs among the 3 studied groups.*

Adverse Effects	Group C (n = 21)	Group P (n = 21)	Group G (n = 21)	χ^2	*P* Value
No Symptoms	21 (100%)	21 (100%)	19 (90.5%)	4.13	0.32
Blurred Vision	0 (0%)	0 (0%)	1 (4.8%)		
Sleepiness	0 (0%)	0 (0%)	1 (4.8%)		
Ramsy Sedation Score					
1	6 (28.6%)	5 (23.8%)	3 (14.3%)	3.12	0.64
2	15 (71.4%)	16 (76.2%)	17 (81%)		
3	0 (0%)	0 (0%)	1 (4.8%)		
4	0 (0%)	0 (0%)	0 (0%)		
5	0 (0%)	0 (0%)	0 (0%)		

Group C = Control Group; Group P = Prednisolone Group; Group G = Pregabalin Group; n = total number of patients in each group.
Data are expressed as number and percentage.
χ^2: Chi square test.
$P < 0.05$ is significant, $P \leq 0.001$ is highly significant.

receiving pregabalin 400 mg daily for 3 days. In another study, Mahoori, et al (16), 100 mg pregabalin was administered every 8 hours for 3 days. Their findings indicated that in the pregabalin group, the VAS scores were significantly lower at 24, 48, and 72 hours compared to the other groups; in addition, no side effects were noted in their study (16). In general, our results are consistent with the above-mentioned studies with the use of the lowest pregabalin dose.

To the best of our knowledge, this is the first randomized controlled study that aimed to compare the therapeutic effects of oral prednisolone and oral pregabalin in PDPH treatment. Our study revealed a decreased trend of VAS scores and modified Lybecker scores in both Group P and Group G compared to Group C. Notably, the reduction in pain scores was more significant in Group G, underscoring pregabalin's superior efficacy in managing PDPH. Furthermore, the need and consumption of rescue analgesia (ketorolac) was significantly lower in Group G. Also, our findings showed fewer patients in Group G developed minor side effects in the form of blurred vision and sleepiness. In addition, none of the patients in Group P or Group G required an EBP; 2 patients in Group C were indicated for this invasive procedure.

Limitations

First, there is a paucity of literature studying the use of prednisolone and pregabalin in treating PDPH. Second, our study evaluated only the therapeutic value of prednisolone and pregabalin. These drugs might have a preventive value; future studies are required to evaluate if they have any preventive value. Lastly, our small sample size and the lack of sufficient studies for comparing the results may limit the generalization of our findings. Therefore, large sample size randomized studies are highly advised in the future to verify our results.

Conclusion

In conclusion, PDPH management includes various pharmacological agents currently undergoing investigation. Our results verified the efficacy of both oral prednisolone and pregabalin in relieving PDPH severity compared to placebo, with the superiority of pregabalin over prednisolone in reducing the severity of PDPH and lowering the need for and consumption of rescue analgesia. In addition, there were no significant adverse effects. Thus, clinicians should consider administering pregabalin in PDPH treatment to avoid the use of an invasive EBP.

Author Contributions

Dr. Dina Abdelhameed Elsadek Salem: This author helped in conceiving, registering, writing, editing, and approving the final manuscript.

Dr. Mahmoud M Elnady: This author helped in designing the study, analyzing the data, and approving the final manuscript.

Dr. Sherif A. Alagamy: This author helped in designing the study, and editing and approving the final manuscript.

Dr. Sherif M. S. Mowafy: This author helped in collecting data, writing, editing, and approving the final manuscript.

Table 6. *Correlation between total dose of rescue analgesia, VAS, and modified Lybecker score among the studied patients.*

Variables	Total Dose of rescue Analgesia	
	Correlation Coefficient (n = 63)	*P* Value
VAS Score		
Baseline	0.058	0.65
At 12 hrs	0.699	< 0.001
At 24 hrs	0.829	< 0.001
At 48 hrs	0.817	< 0.001
At 72 hrs	0.705	< 0.001
Modified Lybecker Score		
Baseline	0.15	0.22
At 12 hrs	0.51	< 0.001
At 24 hrs	0.71	< 0.001
At 48 hrs	0.65	< 0.001
At 72 hrs	0.54	< 0.001

VAS = Visual Analog Scale; n = total number of patients.
$P < 0.05$ is significant, $P \leq 0.001$ is highly significant.

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