Pain Physician 2025; 28:39-49 • ISSN 1533-3159

Randomized Control Trial

Adjuvants to Conventional Management of Postdural Puncture Headache Following Obstetric Surgery Under Spinal Anesthesia: Mirtazapine vs. Sumatriptan

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Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 05-14-2024
Revised article received: 08-05-2024
Accepted for publication: 09-26-2024

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Background: Postdural puncture headache (PDPH) is a debilitating, life-altering complication of the administration of obstetric spinal anesthesia (SA). The lack of evidence-based treatment for PDPH necessitates the implementation of new treatment modalities. Mirtazapine is a noradrenergic and specific serotonergic antidepressant that has been used as a prophylactic treatment for chronic tension-type headaches. Few previous studies have assessed the efficacy of sumatriptan in the treatment of PDPH.

Objectives: The purpose of this study was to assess the hypothesis that an adjunctive therapy that involved adding mirtazapine or sumatriptan to conventional management (CM) would be more effective in reducing the incidence of refractory PDPH after obstetric surgery under SA than would CM alone.

Study Design: A prospective randomized study.

Setting: This study was carried out at Ain-Shams University Maternity Hospital.

Methods: Two hundred and ten American Society of Anesthesiologists (ASA) physical status II women who complained of PDPH after obstetric SA were randomly allocated to one of 3 groups. Each group consisted of 70 women. The intervention treatment for every group was continued for 3 days, as was the CM of PDPH. Every day at 8 p.m., patients in the mirtazapine group (the M-group) took 30 mg mirtazapine tablet, patients in the sumatriptan group (the S-group) took 50 mg sumatriptan tablet, and patients in the control group (the C-group) took placebo tablets. The primary outcome was the incidence of refractory headache 72 hours after the ingestion of the first dose of the intervention drugs. The incidences of side effects of the study drugs, the hospital length of stay (LOS), and the patient satisfaction score were secondary outcomes.

Results: Patients in the C-group had higher means of headache intensity, lower rates of complete response to medical treatment, more increased incidences of refractory PDPH 72 hours after intervention, and a greater need for epidural blood patches than did patients in either of the intervention groups ($P < 0.001$), with comparable efficacy between the M- and S-groups ($P > 0.05$). Incidences of nausea, vomiting, and the need for antiemetics were least frequent in the M-group ($P < 0.001$). More patients in the C-group had a high prevalence of photophobia and neck stiffness than did patients in the other 2 groups ($P < 0.001$). Meanwhile, patients in the M- and S-groups had lower hospital LOS and higher patient satisfaction scores ($P < 0.001$), with no significant differences between the intervention groups ($P > 0.05$).

Limitations: This was a single-center study. This study did not determine the optimal dose of mirtazapine.

Conclusions: Adding either mirtazapine or sumatriptan to the CM of PDPH following obstetric SA was associated with lower means of headache intensities, higher rates of complete response to medical treatment, and decreased incidence of refractory headaches. As an antiemetic drug, mirtazapine was found to be effective, inexpensive, safe, well-tolerated, and capable of being used on an outpatient basis.

Key words: Obstetric, surgery, spinal anesthesia, postdural puncture headache, conventional, refractory, mirtazapine, sumatriptan

Pain Physician 2025: 28:39-49

Spinal anesthesia (SA) is commonplace among laboring women around the world. Due to economic considerations, SA remains an important procedure for developing countries (1). Despite the overwhelming safety and efficacy of SA, postdural puncture headache (PDPH) is a common complication of the technique, estimating to occur in up to 36% of cases (2). The occurrence of PDPH is due to intracranial hypotension (IH), a decrease in pressure caused by the leakage of cerebrospinal fluid (CSF) from subarachnoid space (SAS), followed by a subsequent inability to compensate for the lost volume and the traction of painfully sensitive nerve and vascular structures, factor that starts the process of nociception (3). PDPH may also take place due to compensatory cerebral vasodilation, which occurs in response to the loss of CSF volume (3). α-2 adrenergic receptors are present in the cerebrovascular system, and they are linked to vasodilation mediated by endothelial cells (4).

Despite the self-terminating nature of PDPH, the condition may limit a patient's daily activities, extend the patient's hospital length of stay (LOS), and increase the incidence of long-term residual symptoms (chronic headache, backache and neckache) and rising health care costs (5). With a highly variable level of evidence, the treatment options for PDPH vary greatly from one health institution to another (6). Finding an efficient adjuvant therapy to add to the conventional management (CM) of PDPH and searching for better treatment solutions may reduce the consequences of PDPH.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that inhibits the central presynaptic α-2 adrenergic receptors, which increase the release of serotonin and norepinephrine. This antidepressant acts as an antagonist of H1 histamine receptors and 5-HT2A, 5-HT2C, and 5-HT3 serotonin receptors (7). Mirtazapine may treat PDPH through the activation of 5-HT1 receptors (notably 5-HT1B/1D), which results in the constriction of dilated cerebral blood vessels (8).

Meanwhile, several case reports recommended the use of sumatriptan in the treatment of PDPH (9,10) and it is also used in the treatment of migraine (11). As a 5-HT1B vascular receptor agonist, sumatriptan decreases migraine symptoms through the vasoconstriction of dural and meningeal vessels and sets bounds for the breakdown of vasoactive neuropeptides (11).

The purpose of this study was to assess the hypothesis that an adjunctive therapy that involved adding mirtazapine or sumatriptan to CM would be more effective in reducing the incidence of refractory PDPH after obstetric surgery under SA than would CM alone.

Methods

Ethics

This prospective randomized double-blind study was performed after getting the approval of the ethics committee (FMASU MD 209/2021) and was prospectively registered at ClinicalTrials.gov (NCT05108688). The investigators of this study recruited patients from 15th November 2021 to December 20th 2023 at Ain-Shams University Maternity Hospital. Every recruited patient signed an informed consent form before any research procedures started. This study followed the regulations and standards for research of the 2013 Declaration of Helsinki.

Study Population

The study included 210 women who were 18 to 40 years of age and met the American Society of Anesthesiologist (ASA) physical status II. These patients complained that they had developed PDPH within 4 days after dural puncture and a visual analog scale (VAS) score $\geq$ 4 (12) after SA for obstetric surgeries. The International Classification of Headache Disorders criteria (3) were adapted to diagnose the PDPH. Patients with a history of pregnancy induced hypertension, eclampsia, chronic hypertension, psychiatric illness, migraine, hypersensitivity to study drugs, and contraindication of oral intake were excluded. Similarly, patients who had impaired cardiac, vascular, liver or renal functions and were using ergotamine, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors were excluded from study design criteria. If patients refused to participate in this clinical research, withdrew from the research intervention, or violated the treatment protocol during the study period, they were excluded from the final statistical analysis of this study.

Technique of Spinal Anesthesia

All study patients underwent preanesthesia evaluations prior to surgery. Patients consumed no solid food or clear fluids for 8 hours before the obstetric procedure. Anesthesia providers administered aspiration prophylaxis routinely before surgery to prevent aspiration. Before the SA began, an intravenous (IV) device, an IV fluid preload of 10 mL/kg lactated Ringer's solution (LRS), a sterile environment, and adequate monitors were established for each patient. Certified anesthesiologists, not involved in this clinical trial, performed SA at the L3-L4 or L4-L5 level with each patient in the sitting position. Each anesthesiologist used a 25-gauge or 27-gauge Quincke spinal needle with different doses of hyperbaric bupivacaine 0.5% according to the various obstetric procedures included in this study.

Randomization and Blinding

Patients with postoperative (PO) PDPH that had developed within 4 days after dural puncture and a VAS score ≥ 4 were randomly allocated to one of 3 treatment groups (mirtazapine [M], sumatriptan [S], and control [C] groups) (70 each), using computer-generated random numbers. Those numbers were concealed in opaque sealed envelopes from the researchers who enrolled and assessed the patients. In accordance with our institutional protocol, patients in all 3 groups received CM, which consisted of bed rest, hydration with an intravenous infusion (IVI) of 30 mL/kg/day LRS or normal saline solution (NSS), 2 tablets of Abimol Extra® every 6 hours (each tablet consisting of 30 mg caffeine and 500 mg acetaminophen), ,3 mg IV granisetron every 24 h, and 40 mg IV omeprazole every 24 h. Every day at 8 p.m. over a 72-hour period, patients in the M group took a 30 mg mirtazapine tablet and a placebo for the S tablet, patients in the S group took a 50 mg sumatriptan tablet and a placebo for the M tablet, and patients in the C group (negative placebo-control) took 2 placebo tablets that substituted for M and S.

Intervention drugs, including M and S, were provided, with Remeron® tablets (Organon & Co.) containing M and Imigran® tablets (GlaxoSmithKline) containing S. The hospital pharmacists were responsible for preparing the study medications. Progress notes were documented by anesthesia residents. Patients, ward nurses, obstetricians, and anesthesia residents were blinded to the patients' group allocation. The patients were told to withhold breastfeeding during the study period until 48 hours after the last dose of intervention drugs and to use a breast pump to relieve breast engorgement.

Outcomes

Anesthesia residents reported the VAS scores for the severity of PDPH for every patient after sitting upright for 15 minutes at 0 hours (the starting point of the study and the ingestion of the first dose of the intervention drug) and at one, 2, 6, 12, 24, 36, 48, and 72 hours (the endpoint of the study). The hemodynamics of the patients, including heart rate (HR) and mean arterial pressure (MAP), were documented at the same time points. The patients' demographic data, including patient-related factors, factors related to the anesthesia providers, and current PDPH characteristics were recorded. Patients who complained of PDPH after starting conventional and interventional treatments were treated with 30 mg ketorolac diluted in an infusion of 100 mL NSS over 15 minutes as a rescue analgesia and not given more than 120 mg/day. The incidence of refractory PDPH after 72 hours and the total dose of ketorolac (in mg) over 24 hours were reported. Incidences of nausea, vomiting, photophobia, neck stiffness, tinnitus, dry mouth, somnolence, elevated liver enzymes, chest tightness, bradycardia and hypotension were also documented. Nausea and vomiting were treated with IVs of 10 mg metoclopramide.

By the end of this study, patients either achieved VAS scores < 4 or had refractory PDPH (meaning the conservative and intervention treatments had failed). Patients who had refractory PDPH were offered complete supportive CM of PDPH or the opportunity to receive a lumbar epidural blood patch (EBP). The EBP was administered in the operating room (OR) by a senior anesthetist under strict aseptic techniques and standard monitoring, and the procedure was recorded. The patient`s satisfaction with the PDPH management using a 5-point Likert scale (13) and the hospital length of stay (LOS) were recorded.

The primary outcome of this study was the incidence of refractory headache after 72 hours, while the incidences of side effects of the study drugs, hospital LOS, and patient satisfaction score were considered secondary outcomes.

Power of the Study

We based our sample size on the results from a prior study that showed that percentages of persistent headache after 72 hours following interventions in sumatriptan, naratriptan and control groups were 4.7%, 7.9% and 25.4% respectively (14). After considering those findings, setting power at 80% and alpha error at 0.017 for comparisons of the 3 groups (15) and using the PASS 11 program for sample size calculation (16), we determined that a minimal sample size of 57 patients in each group would be required to get a statistically significant difference. This sample size was raised to 70 patients per group for possible attrition.

Data Analysis

The collected data were analyzed using IBM SPSS

Statistics (Statistical Package for Social Sciences) version 28.0 (IBM Corp.). Quantitative data were expressed as mean ± SD and compared using an ANOVA test. Qualitative data were expressed as number and percentage and were compared using the Chi-square test and Fisher's exact test. The post-hoc Bonferroni test was used for pairwise comparison. The level of significance was taken at P-value ≤ 0.050. This clinical trial was analyzed according to the per protocol (PP) approach.

Results

Among the 210 patients who received the allocated treatment, the final statistical analysis showed that 15 patients were excluded for various reasons (Fig. 1). There were no statistically significant differences in the patients' demographic data (patient-related factors, factors related to the anesthesia providers, and current PDPH characteristics) among randomized groups ($P > 0.05$) (Table 1).

Pre procedure and first-hour readings of HR and MAP were comparable between the treatment and control groups ($P > 0.05$). More patients in the M group had lower HR and MAP readings at 2, 6, 12, 24, 36, 48, and 72 hours after the first dose of mirtazapine than did the other 2 groups ($P < 0.001$) (Fig. 2), with no significant differences between the S and C groups at the same time points ($P > 0.05$) (Fig. 2).

Patients in the M and S groups showed significantly lower means of headache intensities on the VAS at 2, 6, 12, 24, 36, 48 and 72 hours after the first dose of intervention drugs than did patients in the C- group ($P < 0.001$) (Fig. 3), with comparable efficacy between the M and S groups at the same time points ($P > 0.05$) (Fig. 3).

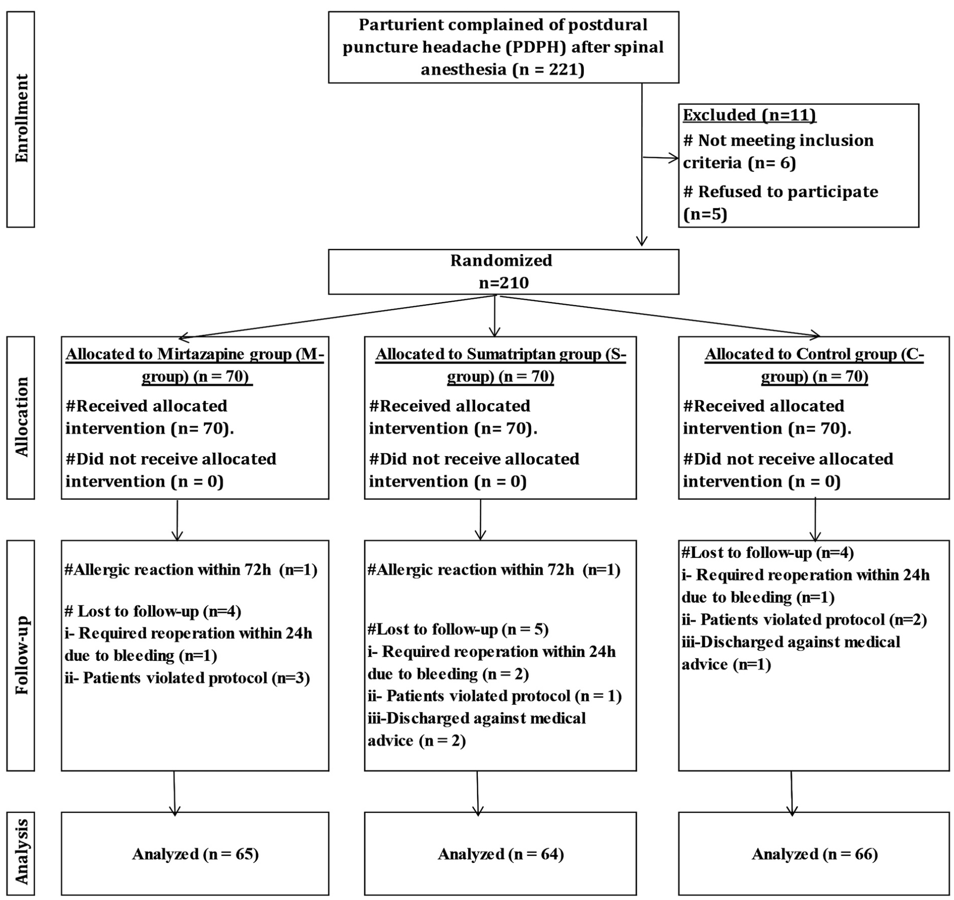

Fig. 1. *CONSORT flow chart of the studied patients.*

The rate of complete response to medical treatment was significantly lower in the C group ($P < 0.001$) than in the other 2 groups, with no significant differences between the intervention groups ($P > 0.05$) (Fig. 4).

The incidences of refractory PDPH 72 hours after the first dose of intervention drugs, the need for EBP, the number of rescue doses (of ketorolac) every 24 hours, and the total dose of rescue analgesia every 24 hours were significantly more frequent in the C group than in the intervention groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively), with comparable efficacy between the M and S groups ($P > 0.05$) (Table 2).

Incidences of nausea, vomiting, and need for antiemetics were significantly less frequent in the M group than in the other 2 groups ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively), with comparable differences between the S and C groups ($P > 0.05$) (Table 2). More patients in the C group had a high prevalence of photophobia and neck stiffness compared to the other 2 groups ($P < 0.001$ and $P < 0.001$, respectively) with comparable efficacy between the M and S groups ($P > 0.05$) (Table 2). Incidences of tinnitus, bradycardia, hypotension, dry mouth, somnolence, elevated liver enzymes and chest tightness were comparable among randomized groups ($P > 0.05$) (Table 2).

Table 1. *Demographic data of the patients.*

Variables		M group (n = 65)	S group (n = 64)	C group (n = 66)	*P*-value
Patient-related factors					
Age (years), Mean ± SD		31.1 ± 2.6	30.1 ± 2.7	30.6 ± 2.6	^0.117
BMI (kg/m²)		31.7 ± 2.1	30.9 ± 2.4	31.2 ± 2.0	^0.145
Parity (n,%)	Nullipara	27 (41.5%)	29 (45.3%)	26 (39.4%)	#0.788
	Multipara	38 (58.5%)	35 (54.7%)	40 (60.6%)	
GA (weeks)		38.7 ± 0.7	38.7 ± 0.8	38.6 ± 0.8	^0.568
Comorbities (n%)		19 (29.2%)	16 (25.0%)	17 (25.8%)	#0.845
Diabetes mellitus only		12 (18.5%)	14 (21.9%)	13 (19.7%)	#0.887
Autoimmune disease only		4 (6.2%)	1 (1.6%)	3 (4.5%)	§0.494
Diabetes mellitus and autoimmune disease		3 (4.6%)	1 (1.6%)	1 (1.5%)	§0.537
Previous cesarean section (n%)		35 (53.8%)	33 (51.6%)	36 (54.5%)	#0.939
History of PDPH (n%)		13 (20.0%)	12 (18.8%)	12 (18.2%)	#0.964
Procedure (n%)	Vaginal delivery	11 (16.9%)	6 (9.4%)	9 (13.6%)	#0.680
	Cesarean section	48 (73.8%)	54 (84.4%)	51 (77.3%)	
	Other Obstetric Procedures ⌂	6 (9.2%)	4 (6.3%)	6 (9.1%)	
Patient's position (n%)	Sitting	53 (81.5%)	57 (89.1%)	57 (86.4%)	#0.466
	Lateral	12 (18.5%)	7 (10.9%)	9 (13.6%)	
Space of spinal block (n%)	L3–L4	28 (43.1%)	27 (42.2%)	27 (40.9%)	#0.969
	L4–L5	37 (56.9%)	37 (57.8%)	39 (59.1%)	
Anesthesia-providers-related factors:					
Experience of physician (n%)	< 3 years of practice in anesthesia	45 (69.2%)	44 (68.8%)	44 (66.7%)	#0.945
	≥ 3 years of practice in anesthesia	20 (30.8%)	20 (31.3%)	22 (33.3%)	
Number of attempts (n%)	Single	13 (20.0%)	18 (28.1%)	18 (27.3%)	#0.503
	Multiple	52 (80.0%)	46 (71.9%)	48 (72.7%)	
Spinal needle size (n%)	25G	57 (87.7%)	59 (92.2%)	60 (90.9%)	#0.674
	27G	8 (12.3%)	5 (7.8%)	6 (9.1%)	
Current PDPH characteristics:					
First presenting day of PDPH (n%)	Day 1	28 (43.1%)	26 (40.6%)	25 (37.9%)	#0.827
	Day 2	24 (36.9%)	23 (35.9%)	20 (30.3%)	
	Day 3	9 (13.8%)	10 (15.6%)	13 (19.7%)	
	Day 4	4 (6.2%)	5 (7.8%)	8 (12.1%)	
Nausea (n%)		54 (83.1%)	53 (82.8%)	50 (75.8%)	#0.487
Vomiting (n%)		52 (80.0%)	51 (79.7%)	47 (71.2%)	#0.400
Neck stiffness (n%)		50 (76.9%)	48 (75.0%)	48 (72.7%)	#0.858

Data are presented as mean ± SD or number of patients (n) and (%). GA: Gestational age. G: gauge. ⌂Other obstetric procedures (manual removal of retained placenta, inspection, and suturing of the perineum). ^ANOVA test. #Chi square test. §Fisher's exact test.

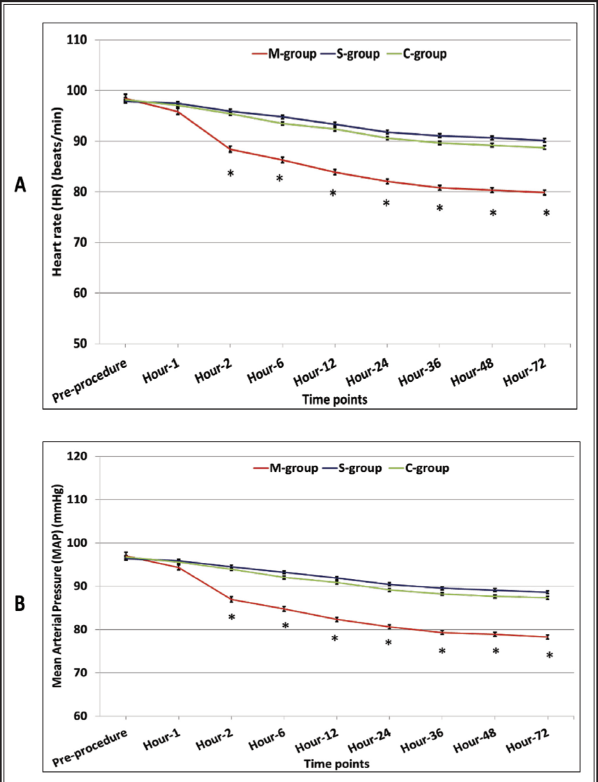

Fig. 2. *Hemodynamic variables: A) Heart rate changes. B) Mean arterial pressure changes among the study groups. (*Significantly different group.)*

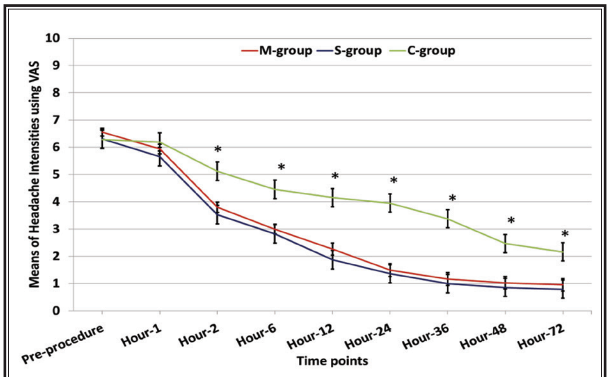

Fig. 3. *Means of headache intensities, measured on a VAS, among the study groups. (*Significantly different group.)*

Patients in the M and S groups had lower hospital LOS and higher patient satisfaction scores than did the C group ($P < 0.001$ and $P < 0.001$, respectively), with no significant differences between the intervention groups ($P > 0.05$) (Table 2).

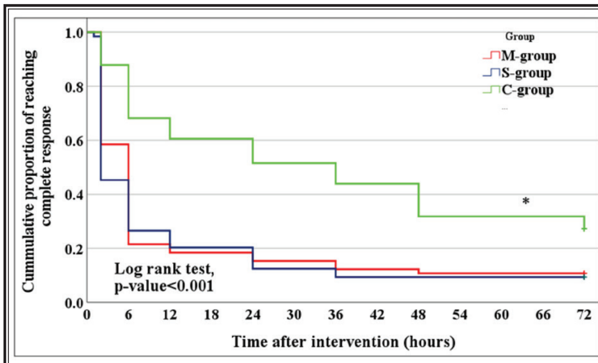

Fig. 4. *Kaplan-Meier curve for rate of complete response among the study groups. (*Significantly different group.)*

Discussion

As far as the authors know, this clinical trial is the first study to evaluate the effects of adding mirtazapine to the CM of PDPH following obstetric surgery under SA. The purpose of the design of this single-center study that used 3 parallel treatment groups was to assess the hypothesis that an adjunctive therapy that involved adding mirtazapine to CM (investigational group, M group) or sumatriptan to CM (active control group, S group) (17) would be more effective in reducing the incidence of refractory headaches of PDPH following obstetric surgery under SA than would CM alone (placebo-control group) (C group). All patients experiencing severe PDPHs received the CM because every patient has the right to the highest attainable standard of treatment given by competent health care providers. Adding either mirtazapine or sumatriptan to the CM of PDPH was associated with lower means of headache intensities, higher rates of complete response to medical treatment, and decreased incidences of refractory headache with priority to mirtazapine due to its antiemetic effects.

High estrogen levels reduce cerebral vascular tone and increase cerebral blood flow, which augments the IH elicited after PDPH (18). Despite the conflicting results on the effectiveness of conservative measures (bed rest and intense hydration) after PDPH (3), they are implemented in our institute standard protocol for management of PDPH in conjugation with drug therapy (caffeine, acetaminophen, and antiemetics). Several treatment protocols for PDPH reported an improvement in headache pain scores, and EBP remains the gold standard treatment for patients who are unresponsive to CM (3). The limited supply of basic medications, poor pain control, debilitating short-term PDPH,

Table 2. ***Treatment outcomes and study safety profile among treatment groups.***

Variables		**M group (n = 65)**	**S group (n = 64)**	**C group (n = 66)**	***P*-value**
PDPH grades after 72 hours (n, %)	No headache	48 (73.8%) a	50 (78.1%) a	32 (48.5%) b	§0.016*
	Grade I	10 (15.4%) a	8 (12.5%) a	16 (24.2%) a	
	Grade II	4 (6.2%) a	4 (6.3%) a	11 (16.7%) a	
	Grade III	3 (4.6%) a	2 (3.1%) a	7 (10.6%) a	
	Grade IV	0 (0.0%) a	0 (0.0%) a	0 (0.0%) a	
Refractory PDPH after 72 hours (n, %)		7 (10.8%) a	6 (9.4%) a	18 (27.3%) b	#0.008*
Need for EBP (n, %)		7 (10.8%) a	6 (9.4%) a	18 (27.3%) b	#0.008*
Number of rescue doses (of ketorolac) /24 hours (n, %)	One	51 (78.5%) a	56 (87.5%) a	32 (48.5%) b	#< 0.001*
	2	14 (21.5%) a	8 (12.5%) a	16 (24.2%) a	
	More than 2 doses	0 (0.0%) a	0 (0.0%)a	18 (27.3%) b	
Total dose of rescue analgesia (ketorolac) (mg)/24 h, mean ± SD		36.5±12.4 a	33.8±10.0 a	55.5±28.9 b	^< 0.001*
Adverse events					
Nausea (n, %)		10 (15.4%) a	34 (53.1%) b	36 (54.5%) b	#< 0.001*
Vomiting (n, %)		6 (9.2%) a	29 (45.3%) b	30 (45.5%) b	#< 0.001*
Antiemetics (n, %)		10 (15.4%) a	34 (53.1%) b	36 (54.5%) b	#< 0.001*
Photophobia (n, %)		5 (7.7%) a	3 (4.7%) a	16 (24.2%) b	#< 0.001*
Neck stiffness (n, %)		4 (6.2%) a	2 (3.1%) a	15 (22.7%) b	#< 0.001*
Tinnitus (n, %)		3 (4.6%)	2 (3.1%)	7 (10.6%)	§0.246
Bradycardia (n, %)		5 (7.7%)	2 (3.1%)	3 (4.5%)	§0.521
Hypotension (n, %)		4 (6.2%)	1 (1.6%)	2 (3.0%)	§0.408
Dry mouth (n, %)		5 (7.7%)	1 (1.6%)	1 (1.5%)	§0.201
Somnolence (n, %)		6 (9.2%)	1 (1.6%)	2 (3.0%)	§0.127
Chest tightness (n, %)		1 (1.5%)	4 (6.3%)	1 (1.5%)	§0.288
Elevated liver enzymes (n, %)		2 (3.1%)	0 (0.0%)	1 (1.5%)	§0.660
Hospital length of stay (LOS) (days)		3.8 ± 0.6 a	3.5 ± 0.5 a	5.2 ± 0.6 b	^< 0.001*
Patient Satisfaction Score (1-5) 72 hours after intervention		3.9 ± 0.7a	4.2 ± 0.4a	1.5 ± 0.6b	^< 0.001*

Data are presented as mean ± SD or number of patients (n) and (%). §Fisher's exact test. #Chi-square test. ^ANOVA test. *Significant. Homogenous groups had the same symbol ("a,b") based on the post-hoc Bonferroni test. EBP: Epidural Blood Patch.

low rates of complete response to medical treatment, and refractory PDPH pose challenges for anesthetists (19,20). Our research team adopted a new treatment modality for this group of patients.

Mirtazapine has unique pharmacological characteristics that target almost every pathophysiological cause of PDPH (Fig. 5). The antidepressant's agonism of 5-HT1 receptors induces cerebral vasoconstriction; mirtazapine's ability to block the activity of presynaptic α-2 receptors promotes analgesia, as does the antidepressant's antagonism toward postsynaptic 5-HT2 receptors; and the antagonism of 5-HT3 receptors creates an antiemetic effect that helps in the management of associated emesis (3,7,21,22). Following oral administration, the mirtazapine is rapidly absorbed from the gastrointestinal (GI) tract, the substance's peak plasma concentration is achieved within 2 hours, and its elimination half-life ranges from 20 to 40 hours. Mirtazapine may be given once per day in the evening before bedtime (23). The safety of mirtazapine in lactation cannot be evaluated properly due to the scarcity of data on the risk of mirtazapine in lactation (24).

Bendtsen et al (21) reported that a daily dose of 30 mg mirtazapine at bedtime was found to be effective in the prophylactic therapy of chronic tension-type headaches. In addition, a previous study documented that reduced frequency and intensity of migraines were found in a case of low-dose mirtazapine used to treat a 25-year-old patient who had recurrent major depression and migraines (22). However, an earlier clinical trial showed that the combination of low-dose mirtazapine and ibuprofen was not an effective therapy

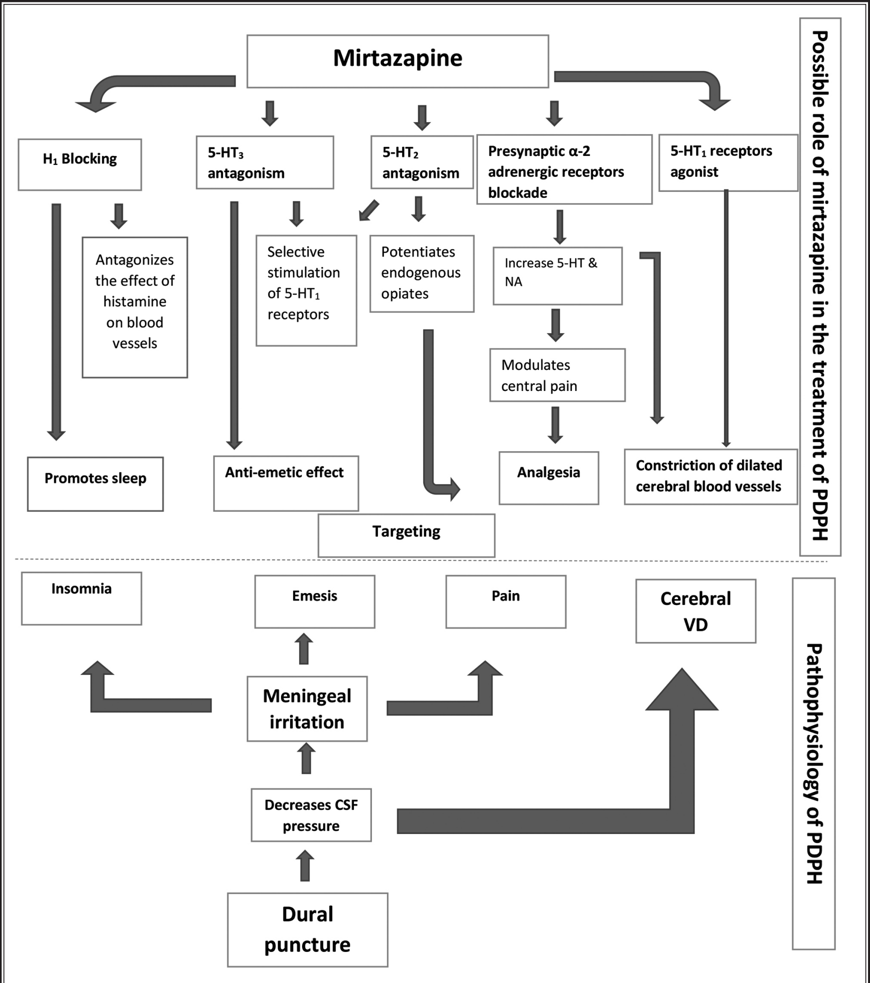

Fig. 5. *Illustration of the unique mechanism of action of mirtazapine and its possible role in the treatment of PDPH (3,8,21,22,27).*

preoperative anxiety and the risk of postoperative nausea and vomiting (PONV) as a result of the blockade of 5-HT2 and 5-HT3 receptors, respectively, in women undergoing gynecological operations under general anesthesia. The authors of this study documented that patients in the M group had lower HR and MAP readings at 2, 6, 12, 24, 36, 48 and 72 hours after the first dose of mirtazapine than did patients in the other 2 groups. The investigators of this clinical trial also reported that incidences of nausea, vomiting, and the need for antiemetics were significantly less frequent in the M group than in the other 2 groups.

Sumatriptan belongs to a group of medicines called triptans, which are 5-HT1B/1D receptor agonists that lead to the vasoconstriction of cerebral blood vessels. Triptans are used as the first-line acute treatment for patients who may experience moderate-to severe migraine attacks (29). Nevertheless, triptans are not recommended for patients with coronary artery disease, uncontrolled hypertension, stroke, hemiplegic migraine, or vasculitis, or for pregnant women (29). Antonaci et al reported that a 50 mg dose of oral sumatriptan may allow a patient with an acute migraine to achieve pain relief and offer the best combination of efficacy and tolerability (30). In addition, treatment with the combination of 50 mg sumatriptan and 10 mg metoclopramide was well tolerated and provided headache relief in some migraineurs who failed to achieve sufficient headache relief with 50 mg sumatriptan alone (31). Láinez et al (32) reported that using an oral antiemetic in combination with NSAIDs or triptans was crucial for the effective management of nausea and vomiting in migraine patients and allowing their outcomes to improve.

Furthermore, Ghanei et al documented that prophylactic sumatriptan reduced the incidence of PDPH during

for chronic tension-type headaches (25). The authors of that research paper explained their results by the small dose (4.5 mg) and the existence of a dose–response relationship for mirtazapine (25).The findings of the previous study could be attributed to a higher affinity of low-dose mirtazapine to histamine receptors than to serotonergic receptors, and it is uncommon for patients with vascular (migraine) headaches to obtain complete pain relief through antihistamine therapy (26,27).

Due to the novelty of this study, reports that examine adding mirtazapine to the CM of PDPH are scarce. Sheen and Ho reported that mirtazapine was an effective treatment in resolving the PDPH of a 55-yr-old woman after accidental dural puncture during epidural anesthesia (8). Chen et al (28) demonstrated that premedication with a 30 mg tablet of mirtazapine decreased the 48 hours after the induction of SA (33). In contrast to the results of the current study, Hunter and Seupaul reported that subcutaneous sumatriptan had no statistically significant benefit in comparison with a placebo for the treatment of PDPH (34). Amundsen et al (35) recorded that among most patients treated with triptans, breastfeeding should be withheld for 24 hours after treatment. A previous study found that the evidence to support using sumatriptan to treat PDPH was weak and inconclusive due to the small sample sizes of most of the clinical trials designed to assess the efficacy of sumatriptan and the inconsistency among those studies (36).

Bussone et al (37) reported results supporting the hypothesis that prophylaxis with oral frovatriptan, used for the treatment and prophylaxis of migraines, may successfully decrease the risk of PDPH. Furthermore, 2 different triptans (naratriptan and zolmitriptan) used as antimigraine drugs demonstrated efficacy and tolerability when deployed in combination with supportive therapy for PDPH relief among parturients given cesarean sections under SA (14,38).

Despite the short elimination half-life of sumatriptan (one–4 hours) (29), the investigators of this clinical trial told the patients to withhold breastfeeding during the study period until 48 hours after their last dose of intervention drugs due to the long elimination half-life of mirtazapine (20–40 hours) (23).

Over 17,000 deliveries were conducted at Ain-Shams University Maternity Hospital during 2015, in which cesarean delivery rates were over 30% (39). The results of the current study are in concordance with those of a previous study regarding the relationship between the overall incidence of PDPH and the use of 25-gauge (G) Quincke spinal needle (40). The research team used 25G needles on most of the patients due to that size's association with the highest incidence of successful dural puncture (40).

PDPH is a disabling problem in our institute that limits breastfeeding, delays hospital discharge, and prolongs the duration of analgesic use. Furthermore, chronic headaches and backaches may develop, and the need for an EBP may increase if CM fails. So, extra costs and additional burdens will be added to an already distressed health care system (5,6,41). Moreover, patients treated with an EBP may have rapid pain relief, but some patients may get rebound headaches, necessitating new EBPs (41). The investigators of this clinical trial focused on the weight effect of currently available (sumatriptan) and investigational (mirtazapine) drugs added to the CM of PDPH. All patients experiencing severe PDPHs received the CM because every patient has the right to the highest attainable standard of treatment given by competent health care providers.

Limitations

This study had some limitations; first, although this research paper presented robust conclusions, only a single center was involved in the data collection. Therefore, multicenter clinical trials are required to ensure the generalizability of the results. Second, the investigators did not assess the results of this study beyond 3 days, because the research team feared that early patient discharge and subsequent losses of the patients' follow-up notes could happen. Third, this study did not determine the optimal dose of mirtazapine, and the long-term effects of the antidepressant on PDPHs warrant further study. Fourth, the optimal reduction of the incidence of PDPHs requires the use of pencil-point 25G Whitacre spinal needles, which are more expensive than 25G Quincke spinal needles, (19). Fifth, cost-benefit analysis of the study drugs and hospital LOS should be discussed in future randomized trials, especially in low- and middle-income countries (LMICs).

Despite advances in the treatment of patients with PDPHs, much work remains. Inadequate treatment of PDPHs among patients who live in LMICs with poor availability of pain treatment options and poor health policies is both perplexing and inexcusable. Lack of access to PDPH treatment, compounded by under-recognition of the burden of headache disorders in these settings, will deter advancements in health care (19,20). This study investigated the effectiveness of mirtazapine as an adjuvant therapy to the CM of PDPH and how refractory PDPH could be markedly improved with safe, simple, relatively cheap, efficacious antiemetic and widely available drug.

Conclusions

Adding either mirtazapine or sumatriptan to the CM of PDPH after obstetric SA was associated with lower means of headache intensities, higher rates of complete response to medical treatment, and decreased incidences of refractory headaches. Mirtazapine was an effective antiemetic drug as well as inexpensive, safe, and well tolerated and could be used on an outpatient basis.

Acknowledgments

The investigators of this study thank the anesthesia residents and the nursing staff for their valuable contributions.

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