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A Multimodal Analgesic Protocol with Gabapentin-dexmedetomidine for Post-operative Pain Management after Modified Radical Mastectomy Surgery: A Randomized Placebo-Controlled Study

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Abstract

BACKGROUND: Modified radical mastectomy (MRM) is accompanied by severe acute post-operative pain.

AIM: This study evaluated the safety and efficacy of oral gabapentin plus dexmedetomidine infusion as an analgesic multimodal protocol in patients undergoing MRM.

METHODS: This prospective randomized, double-blind, placebo-controlled study included 30 females scheduled for MRM from June 2021 to December 2021. They were randomly divided into two groups. GD group (n = 15) received oral gabapentin 400 mg and IV infusion of dexmedetomidine 0.4 μg/kg/h over 10 min after a bolus of 0.5 μg/kg before induction of general anesthesia. Placebo group (n = 15) received a placebo capsule and saline infusion identical to the GD group. The primary outcome measure was total morphine consumption, and secondary outcomes were pain and sedation scores and intraoperative fentanyl consumption.

RESULTS: Pain score was significantly lower in the GD group than in the placebo group, starting immediately post-operative up to 24 h except after 18 h. The total intraoperative fentanyl consumption and post-operative morphine consumption were significantly lower in the GD group. The sedation score was significantly higher in the GD group compared to the placebo group immediately postoperatively and after 2 h. The heart rate and mean arterial pressure were within the clinically accepted ranges intra- and postoperatively in the two groups.

CONCLUSION: Preemptive oral gabapentin plus dexmedetomidine IV infusion is a safe and effective analgesic alternative for patients undergoing MRM.

Introduction

Breast cancer is the most common women malignancy in Egypt, accounting for nearly 39% of cancers in women [1]. Treatment of breast cancer is mainly surgical. Modified radical mastectomy (MRM) has been the gold standard and is preferred when conservative surgery is impossible. However, it is a mutilating procedure commonly accompanied by severe acute post-operative pain [2].

Severe pain is fairly common in patients undergoing mastectomy, with an incidence of approximately 60% [3]. Acute post-operative pain is frequently followed by persistent chronic pain. A systematic review of 187 studies with 297,612 breast cancer patients showed a median prevalence of 37%; axillary lymph node dissection was associated with a higher prevalence [4]. Opioids are considered the gold standard analgesic, but multiple side effects are frequently encountered [5]. Hence, appropriate pain control is essential to reduce acute pain and avoid post-mastectomy chronic pain syndrome [6].

Dexmedetomidine (Dex) is a highly selective α2-adrenergic receptor agonist with anxiolytic, sedative, analgesic, and sympatholytic properties [7]. The α2-adrenergic receptors act on the locus ceruleus area, resulting in inhibition of nociceptive neurotransmission through the spinal cord [8]. They also inhibit norepinephrine release from the presynaptic membrane, causing hyperpolarization, and blocking pain signals to the brain [9]. Besides, Dex stimulates acetylcholine release from spinal interneurons, enhancing nitric oxide synthesis that could be involved in analgesia regulation [10].

Gabapentin was presented as an adjunct in the multimodal analgesia after breast cancer surgery. It is an anticonvulsant agent that binds to the α-2-δ-subunit of presynaptic voltage-gated calcium channels, reducing the calcium influx into presynaptic terminals [11], [12]. A meta-analysis of nine RCTs indicated that pre-operative gabapentin was associated with reduced pain for 24 h and total morphine consumption after breast cancer surgery. It was also associated with a reduction in the incidence of chronic post-operative pain [13].

The notion of multimodal analgesia depends on the administration of two or more drugs with different mechanisms of action. It aims to improve pain relief while reducing opioid requirements and their undesirable adverse effects [14]. Therefore, this study aimed to evaluate the impact of combining oral gabapentin and dexmedetomidine infusion on opioid consumption, hemodynamic parameters, and pain scores within the first 24 h in patients undergoing MRM.

Patients and Methods

This prospective randomized, double-blind, placebo-controlled study was conducted from June 2021 to December 2021. The study included 30 adult female patients below 65 years of age scheduled for MRM surgery. Written informed consent was obtained from each patient before enrollment in the study. The study implemented the principles of the Declaration of Helsinki (1964) and its following revisions. The Institutional Review Board approved the study (approval no. 2101-501-005), and the study was registered on Clinical Trials.gov with study ID NCT04976374.

Inclusion criteria were the American Society of Anesthesiologists (ASA) Physical Status I–II. Exclusion criteria were known allergy to study drugs, renal or hepatic dysfunction, and current treatment with oral gabapentin, narcotics, antihypertensives, benzodiazepines, α2-agonists, antiepileptics, or antipsychotics.

The day before surgery, the patients were assessed for their medical status in addition to performing laboratory investigations. All patients were instructed how to report pain on the visual analog scale (VAS) for pain (0 = No pain to 10 = The worst pain).

Two hours before induction of anesthesia, patients were randomly divided using computer-generated randomization numbers. Random assignment was protected in sealed, closed opaque envelopes. The patients were allocated to one of the two groups: The GD group (n = 15) received oral gabapentin 400 mg (Conventin 400 mg, Eva Pharma, Egypt) and the placebo group (n = 15) received a placebo capsule. An intravenous (IV) cannula was inserted under local anesthesia on arrival at the preparation room, and sedation was given. Standard anesthesia monitoring was applied. Then, in the patients of the GD group, an IV infusion of Dex (Precedex 100 μg/mL, Hospira) was started at a dose of 0.4 μg/kg/h after a bolus of 0.5 μg 1 kg intravenously over 10 min. Patients of the placebo group received a bolus of saline followed by saline infusion identical to the GD group. Patients and investigators recording data in the operating room were blinded to the treatment given.

All patients in both groups receive standard anesthetic techniques in the form of fentanyl (1 μg/kg) IV. Anesthesia was maintained by sevoflurane 2% in 50% oxygen and air and 0.025 mg/kg atracurium every 20 min. Additional bolus doses of fentanyl (0.5 μg/kg) were given if the mean arterial pressure (MAP) or the heart rate (HR) rose above 20% of baseline. Fluids were given according to their deficit, maintenance, and losses. The patients were mechanically ventilated at an appropriate setting to keep end-tidal CO_2 at 30–25 mmHg. Hypotension was treated with 0.9% normal saline and/or 5 mg ephedrine in incremental doses to maintain mean blood pressure above 70 mmHg. Recovery was carried out after closing the surgical wound by turning off sevoflurane and reversal when the TOF ratio became 0.7, and fully awake extubation was done. Then, the patients were transferred to the post-anesthesia care unit (PACU).

In the PACU, pain was evaluated using VAS score immediately postoperative and then 2, 4, 6, 12, 18, and 24 h post-extubation. If the VAS was above 3, the patient was treated with 2 mg morphine slowly IV that was repeated if required. The level of sedation was assessed every 2 h in the PACU using Ramsay sedation score (RSS). Nausea and vomiting were recorded and treated by metoclopramide 10 mg/8 h slowly IV.

The primary outcome measure of the study was the total morphine consumption during the first 24 post-operative hours. The secondary outcome measures were pain and sedation scores, intraoperative fentanyl consumption, post-operative nausea and vomiting, and hemodynamic variables.

Sample size estimation

A previous study [15] reported a difference in total opioid consumption of 27 mg with a pooled standard deviation of 20 mg between patients under gabapentin analgesia and those receiving placebo. Based on these findings, a sample size of 12 patients for each group is required to achieve a power of 90% at an alpha level of 0.5 for detecting a true difference in means between groups. The sample was increased by 25% to compensate for non-parametric tests. A sample of 15 patients was enrolled in each group.

Statistical analysis

Statistical analysis was done using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was made using independent sample t-test or Mann–Whitney U-test. Comparison of repeated measures

was done using Friedman test followed by Wilcoxon signed-ranks test. $p < 0.05$ was considered statistically significant.

Results

All randomized patients completed the study protocol (Figure 1).

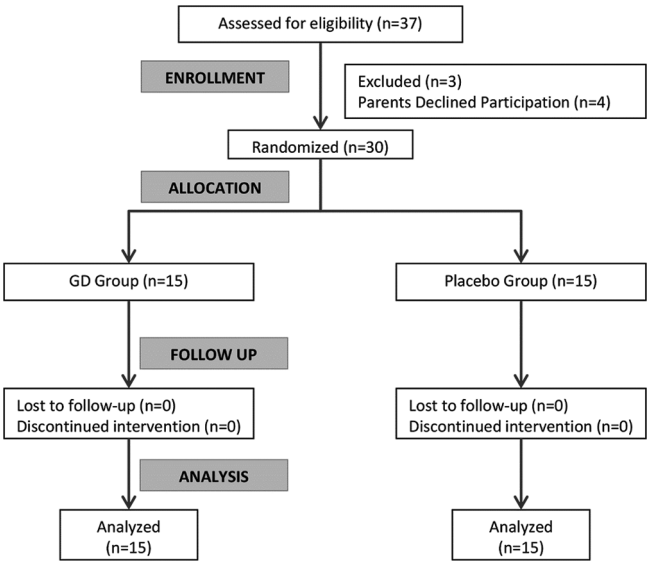

Figure 1: CONSORT flowchart

The two studied groups were comparable in baseline characteristics (Table 1).

Table 1: Baseline characteristics of the two studied groups

Parameters	GD group, n = 15	Placebo group, n = 15	p value
Age (years)	47.3 ± 5.7	48.1 ± 4.6	0.652
ASA class (I/II)	12/3	11/4	1.000
Weight (kg)	70.3 ± 10.9	71.9 ± 10.6	0.699
Height (cm)	161 ± 6	162 ± 5	0.663
BMI (kg/m^2)	26.9 ± 2.3	27.2 ± 2.5	0.734
Heart rate (beats/min)	75 ± 5	75 ± 5	0.891
Mean arterial pressure (mmHg)	88 ± 7	88 ± 9	0.893
Duration surgery (min)	92 ± 8	94 ± 8	0.635

Data are expressed as mean ± SD.

The VAS score was significantly lower in the GD group than in the placebo group, starting immediately postoperatively up to 24 h except after 18 h (Table 2). In the two groups, the VAS score increased significantly after 2 h up to 24 h compared to the immediate post-operative readings. Furthermore, the total intraoperative fentanyl consumption and post-operative morphine consumption were significantly lower in the GD group. The sedation score was significantly higher in the GD group compared to the placebo group immediately postoperatively and after 2 h. Then, the sedation score of all patients in the two groups was 2 up to 24 h.

Table 2: VAS score for pain, intraoperative fentanyl consumption, and post-operative morphine consumption and sedation score in the two studied groups

Parameters	GD group, n = 15	Placebo group, n = 15	p value
VAS score			
Immediate post-operative	1 (0–1)	2 (1–3)	<0.001
After 2 h	2 (1–3)	3 (2–4)	<0.001
After 4 h	3 (2–4)	4 (3–4)	0.002
After 6 h	3 (2–3)	3 (3–4)	0.007
After 12 h	2 (2–3)	3 (3–4)	<0.001
After 18 h	3 (3–4)	3 (3–4)	0.775
After 24 h	2 (2–3)	3 (3–4)	<0.001
Fentanyl consumption (μg)	48 ± 18.6	92 ± 22.6	<0.001
Morphine consumption (mg)	9.6 ± 1.4	20.5 ± 4.1	<0.001
Sedation score			
Immediate post-operative	3 (3–4)	2 (2–3)	<0.001
After 2 h	3 (2–3)	2 (2–2)	<0.001

Data are expressed as median (range) or mean ± SD.

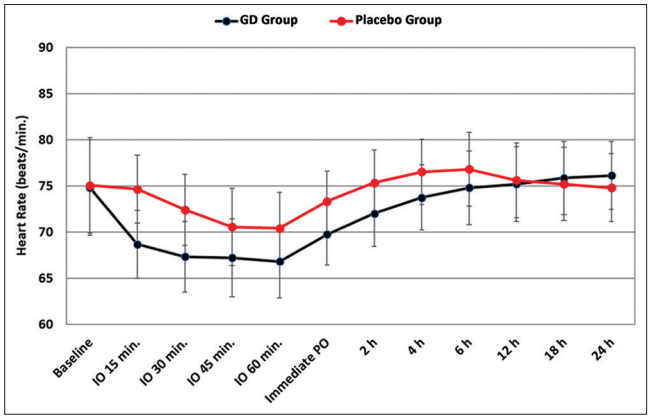

Figure 2: Changes in heart rate during the intraoperative (IO) and post-operative (PO) periods in the two studied groups

Heart rate decreased significantly 15 min after starting surgery in the two studied groups. The heart rate was significantly slower in the GD group till the end of surgery. Heart rate was significantly slower in the GD group postoperatively up to 4 h after surgery, and then, the two groups were comparable (Figure 2). However, the heart rate was within the clinically accepted range intra- and post-operatively in the two groups. The MAP decreased significantly 15 min after starting surgery in the two studied groups. The MAP was significantly slower in the GD group until the end of surgery and up to 2 h after surgery, and then, the two groups were then comparable (Figure 3). The MAP was within the clinically accepted range intra- and post-operatively in the two groups.

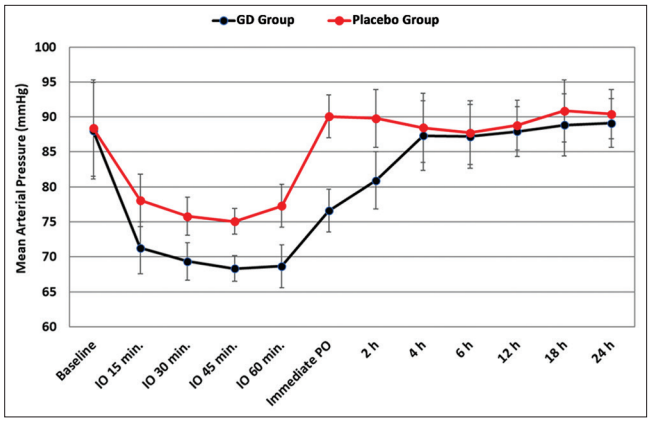

Figure 3: Changes of the mean arterial pressure during the intraoperative (IO) and post-operative (PO) periods in the two studied groups

Discussion

This study demonstrated that oral gabapentin 400 mg plus IV infusion of dexmedetomidine 0.4 μg/kg/h before anesthesia induction decreases post-operative opioid consumption and intraoperative fentanyl consumption and reduces post-operative pain while maintaining stable intraoperative hemodynamics in patients undergoing MRM.

The idea of the present study was to test a novel combination of two drugs in a preemptive multimodal model. The two drugs are not classical analgesic drugs. Gabapentin is an anticonvulsive used originally as a muscle relaxant and anti-spasmodic medication [16], [17] Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist with anxiolytic, sedative, and analgesic properties [18].

The previous studies on perioperative use of gabapentinoids have reported conflicting evidence of its analgesic benefit and rate of adverse effects [19], [20] Significant opioid-sparing benefits of gabapentinoids have been demonstrated in many studies [19], [21], [22], [23]. In a large retrospective study including 4046 patients subjected to total knee arthroplasty, adjuvant gabapentin use was associated with a significant reduction in opioid consumption [17]. A recent meta-analysis indicated a minimal decrease in pain scores with perioperative gabapentinoids despite a significant opioid reduction during the first 72 post-operative hours [19]. Gabapentinoids may decrease central sensitization with consequent reduction of surgical pain [24]. The current randomized controlled trial demonstrates the safety and efficacy of preemptive gabapentin. A large RCT including different surgical procedures showed a post-operative opioid reduction with perioperative gabapentin in a pre-operative dose of 1200 mg and 10 doses of 600 mg 3 times daily postoperatively [25]. A meta-analysis was performed to determine the efficacy and safety of the pre-operative gabapentin administration in managing acute and chronic post-operative pain after breast cancer surgery. The study included nine RCTs and indicated that gabapentin use reduced pain scores for 24 h after surgery and reduced total morphine consumption [13].

Other studied opioid-sparing systemic analgesics include the α2-adrenergic receptor agonists Dex and clonidine. These drugs induce central analgesia and reduce agitation and sympathetic tone without significant respiratory depression [26]. Perioperative use of Dex provides analgesia and sedation through multiple locations within the central nervous system, and it induces sympatholysis and dampens the neuroendocrine and hemodynamic response to surgery [27], [28]. Perioperative IV Dex can suppress the release of epinephrine and norepinephrine through activation of medullary vasomotor receptors. Reducing blood catecholamine levels keep intraoperative hemodynamic stability [29]. Recently, Ye *et al.* found that intravenous infusion of Dex 0.6 μg/kg before induction in patients undergoing laparoscopic cholecystectomy can maintain hemodynamic stability and relieve post-operative pain [30]. Intraoperative hemodynamic stability decreases the risk of adverse cardiac events, including myocardial ischemia [31].

Many studies provide mixed results about the post-operative analgesic effect of perioperative administration of Dex [32], [33], [34], [35]. One systematic review, including six studies comparing Dex versus Placebo, reported reduced opioid consumption in the first 24 h after surgery. However, the authors found the quality of evidence to be very low due to imprecision of results and the risk of bias [36]. A combination of Dex and lidocaine was investigated in 240 women subjected to elective abdominal hysterectomy. This combination reduced post-operative pain score and fentanyl requirement and enhanced recovery of bowel function [37].

Adverse effects of Dex are limited to hemodynamic alterations, including hypo- or hypertension and bradycardia due to α2-receptor activation causing vasodilatation, vasoconstriction, and reflex bradycardia [38]. In the present study, we did not record any cases of disturbance of heart rate or blood pressure as an adverse effect of tested drugs.

Conclusion

We can conclude that preemptive oral gabapentin plus dexmedetomidine IV infusion is a safe and effective analgesic alternative for patients undergoing MRM. This combination reduces post-operative pain and opioid consumption and decreases intraoperative fentanyl consumption. It maintains stable intraoperative hemodynamics.

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