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Impact of Combining Dexamethasone and Ketamine with Bupivacaine for Ultrasound-guided Serratus Plane Block for Controlling Pain in Major Breast Surgeries: A Prospective Randomized Double-blind Trial

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Abstract

Background: Breast surgeons need to deliver optimal pain relief to patients following breast surgeries. The purpose of this study was to assess the analgesic efficacy of ketamine and dexamethasone (DEX) when combined with bupivacaine in ultrasound-guided serratus anterior plane block (US-guided SAPB) for simplified radical mastectomy (MRM) procedures.

Methods: This randomized, double-blind trial was conducted on 60 females between 20 and 60 years old with an American Society of Anesthesiologists (ASA) physical status classification of I to III undergoing MRM. Participants were randomly assigned to one of two equal groups that received US-guided SAPB with a solution of bupivacaine 0.25% and 4 mg of DEX in group A and plus 50 mg ketamine in group B.

Results: Group B exhibited a significant reduction in pain score, total morphine consumption throughout the initial twenty-four hours following the procedure, and patients requiring morphine compared to group A. Group B exhibited a significant reduction in hemodynamic measurements compared to group A. Group B exhibited a significantly delayed time to the first analgesic request compared to group A.

Conclusions: For patients undergoing MRM under general anesthesia, adding ketamine and DEX to bupivacaine enhances the US-guided SAPB analgesia with stable hemodynamics and minor adverse effects.

Keywords: Breast Surgeries; Bupivacaine; Dexamethasone; Ketamine; Ultrasound; Serratus plane block.

Introduction:

Among surgical interventions worldwide, breast cancer surgery takes the predominant position [1]. Advances in surgical techniques have led to more conservative approaches that maintain therapeutic effectiveness while enhancing aesthetic results. These surgical advancements have been complemented by significant improvements in anesthetic-analgesic management, facilitating faster recovery and minimizing postoperative discomfort [2].

Postoperative pain after modified radical mastectomy (MRM) is linked with slower recovery, extended hospitalization, and higher chances of developing chronic pain [3]. Several procedures have been developed to alleviate postoperative pain, enhance patient outcomes, and lower the chances of chronic pain [4].

Ultrasonography has made describing various interfascial analgesic blocks at the thoracic level easier. It may replace central regional treatments because they are safer, more straightforward to execute, and more effective [5].

Ultrasound-guided serratus anterior plane block (US-guided SAPB) alleviates pain along the side and front of the chest (anterolateral chest wall). In the US-guided SAPB approach, LA is administered into the fascial plane separating the serratus anterior and latissimus dorsi muscles aiming to reach the lateral cutaneous intercostal nerve branches. So, SAPB effectively minimizes pain in the aforementioned region [6].

Analgesics administered via SAPB during mastectomy procedures are more widely utilized as a result of its safety profile and straightforward administration [7]. The analgesic effects of SAPB typically last for several hours. Prolonging the duration of postoperative analgesia can successfully mitigate moderate to severe pain experience following surgical procedures [8].

Adding dexamethasone (DEX) and ketamine to bupivacaine can be done to improve the effectiveness of the LA [9]. DEX, a medication with well-established anti-inflammatory properties, has been shown to delay the duration of bupivacaine's analgesic effect [10].

Ketamine has been found to increase the efficacy of pain relief and decrease the requirement for opioid drugs [11]. The combination of ketamine and bupivacaine in anesthesia not only boosts its potency but also extends its duration [12].

There is a scarcity of literature assessing DEX -ketamine combination to bupivacaine US-guided SAPB. Thus, this study aimed to assess the analgesic efficacy of ketamine and DEX when combined with bupivacaine in US-guided SAPB for simplified MRM procedures.

Patients and Methods:

This randomized, prospective, double-blind trial was conducted on 60 female patients between 20 and 60 with an American Society of Anesthesiologists (ASA) physical status classification of I-III undergoing MRM.

The research was conducted with approval from the Ethical Committee of the National Cancer Institute Hospitals at Cairo University, Egypt (IRB:2202-301-007). The patient provided informed written consent.

Exclusion criteria included rejection for SAPB, suspected coagulopathy, injection site infection, and previous allergic reactions to bupivacaine or DEX or ketamine.

Randomization and Blinding:

Participants were assigned randomly to one of two equal groups in a parallel design. Group A received US-guided SAPB with a solution composed of bupivacaine 0.25% and 4 mg of DEX, while Group B received the same with an additional 50 mg of ketamine in the solution. The randomization process involved computer-generated numbers, and the allocation codes were concealed in sealed opaque envelopes.

The medications for both groups were prepared by an anesthesiologist who was not involved in the study. The intervention was concealed from the patients and the outcome assessors to

maintain blinding. Before the procedure, each patient underwent a medical history assessment, clinical examination, laboratory tests, and hemodynamic evaluation. They were also informed about the study's objectives and the use of the Visual Analog Scale (VAS) for pain assessment. Patients received pre-oxygenation with pure oxygen for three minutes during the surgical procedure. Anesthesia was initiated through intravenous administration of propofol (2 mg/kg), fentanyl (200 μg), and atracurium (0.5 mg/kg) to facilitate endotracheal intubation. Anesthesia was sustained using isoflurane (1-2%) in a mixture of oxygen and air. Atracurium was periodically administered for muscle relaxation, and fentanyl (1 μg/kg) was administered if the heart rate surpassed 20% of the initial measurement. Mechanical ventilation was utilized to maintain end-tidal CO2 tension around 35 mmHg. After surgery, inhalation anesthesia was terminated, and neuromuscular blockade was reversed via IV injections of neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg) after satisfying extubation criteria. After extubation, patients were transmitted to the post-anesthesia care unit (PACU).

Superficial SAPB

Following the induction of general anesthesia, patients were positioned laterally with the affected side facing upwards. In the sagittal plane, a 10–12 MHz linear ultrasound transducer (manufactured by Sonosite M-turbo) was positioned over the mid-clavicular region of the thoracic cage. The location of the fifth rib along the midaxillary line was determined. The latissimus dorsi, teres major, and serratus muscles were easily identified from superficial to deep. The thoracodorsal artery was an additional reference point for locating the superficial plane of the serratus muscle. An in-plane insertion of a 22-gauge, 50-mm Tuohy needle was performed, targeting the plane just above the serratus muscle under ultrasound guidance. An LA solution was injected and disseminated using a fanning method under continuous ultrasound supervision.

All patients were given intravenous paracetamol (1 g) every 6 hours, then morphine (3 mg) if necessary to maintain the VAS score below 3 for postoperative pain management. Morphine consumption as a rescue drug was recorded during the first 24 postoperative hours. The VAS pain score was recorded every 2 hours once the patient was alert.

The primary outcome measured was the duration of analgesia, defined as the time to first request for postoperative analgesia. Secondary outcomes included total morphine consumption in the first 24 postoperative hours and total intraoperative fentanyl consumption.

Sample size calculation:

G Power *3.1.9.4 was applied to determine the sample size. In a prior investigation [13], the addition of ketamine to LA resulted in a 5.2-hour extension of analgesic effect duration, with an aggregated standard deviation of 2.8. Based on these results, it was necessary to reject the null hypothesis with 29 patients in each group at an alpha level of 0.05 and a power of 80%.

Statistical analysis

Statistical analysis was performed using SPSS V 28. The Shapiro-Wilks test and histograms assessed the normality of data distribution. The unpaired Student's t-test assessed quantitative parametric data reported as mean ± standard deviation. The Mann-Whitney U test assessed quantitative nonparametric data, which were reported as median (interquartile range). The chi-square test or Fisher's exact test, as appropriate, assessed qualitative variables, which were reported as frequency. A two-tailed p-value less than 0.05 was considered statistically significant.

Results:

This study evaluated 79 patients for eligibility, of which 11 were excluded, 8 declined to contribute, and the remaining patients were randomized into two equal groups, each consisting of 30 participants. All patients in both groups were followed up and included in the statistical analysis. Figure 1

Demographic characteristics and surgical durations were comparable between the two groups. Table 1

Intraoperative measurements of heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SpO2) were comparable at baseline and 10, 20, 30, 40, 50, 60, 90, 120, and 150 minutes between groups A and B. Figure 2

VAS scores at rest and during movement were comparable between both groups at 2 and 24 hours. However, in group B, VAS scores were significantly lower at 4, 6, 8, 10, 12, and 18 hours compared to group A ($P < 0.05$). Figure 3

Postoperative HR, MAP, and SpO_2 measurements were comparable between groups at 2 and 24 hours. However, these measurements were significantly decreased at 4, 6, 8, 10, 12, and 18 hours in group B than in group A ($P < 0.05$). Figure 4

Patients required fentanyl, total intraoperative fentanyl consumption, incidence of nausea and vomiting, hypotension, and bradycardia were comparable between both groups. The time until the first request for analgesia, the number of patients requiring morphine and the total morphine consumption during the first 24 postoperative hours were significantly decreased in group B than in group A ($P < 0.001$). No cases of cardiac arrhythmia or local anesthetic toxicity were reported in either group A or group B. Table 2

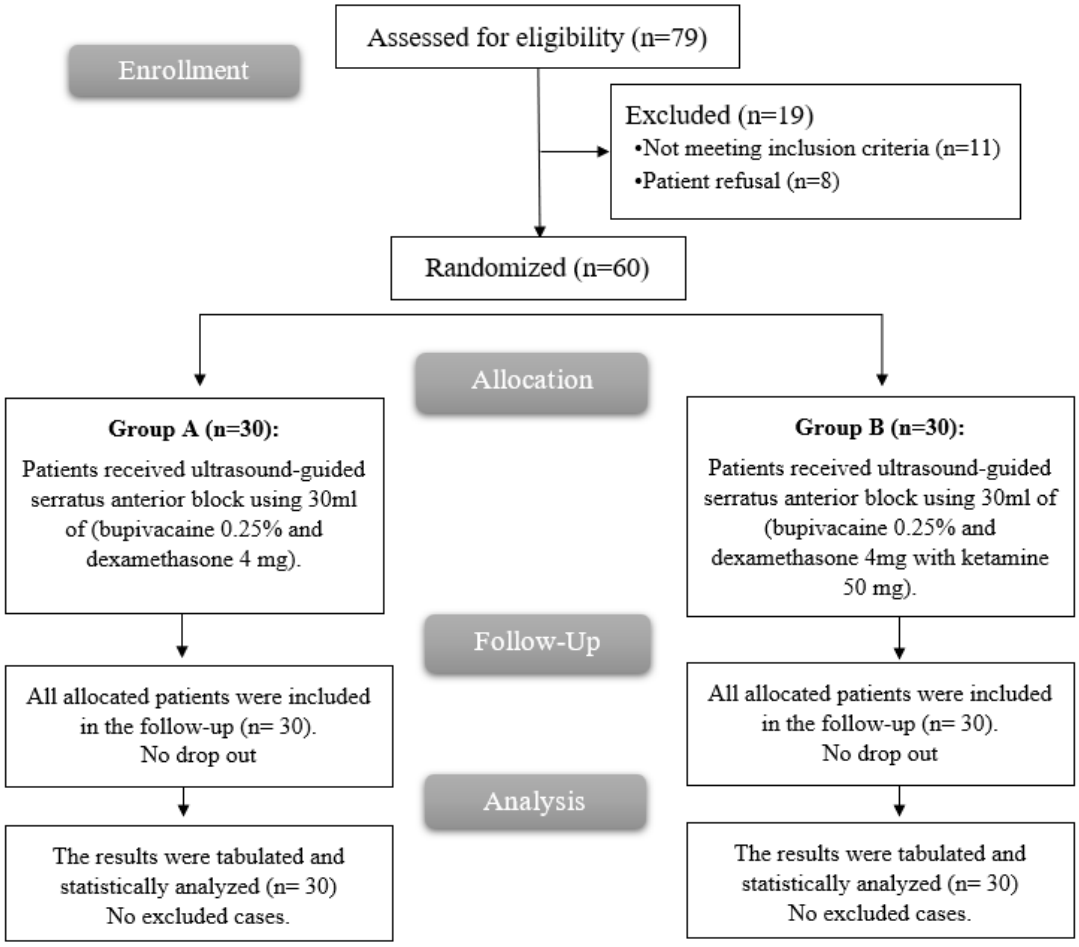


Figure 1: CONSORT flowchart of the enrolled patients

Table 1: Demographic data and duration of surgery of the studied groups

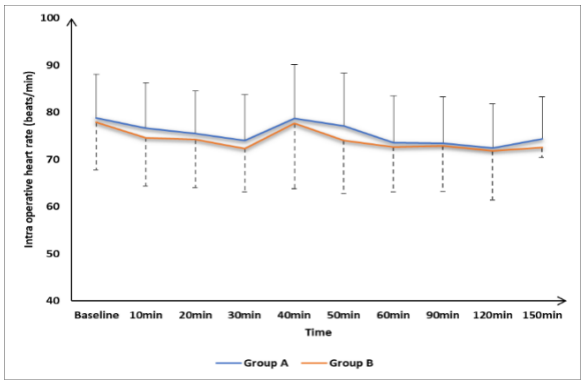
		Group A (n=30)	Group B (n=30)	P value
Age (years)		38.9 ± 11.58	40.3 ± 10.46	0.625
Weight (kg)		70.3 ± 8.05	72.83 ± 7.49	0.212
Height (m)		1.65 ± 0.05	1.64 ± 0.08	0.625
BMI (kg/m^2)		25.91 ± 3.47	27.19 ± 3.67	0.169
ASA physical status	**II**	23 (76.67%)	26 (86.67%)	0.506
	III	7 (23.33%)	4 (13.33%)	
Duration of surgery (min)		116.67 ± 23.43	115 ± 23.01	0.782

Data are presented as mean ± SD or frequency (%). ASA: American Society of Anesthesiologists, BMI: body mass index.

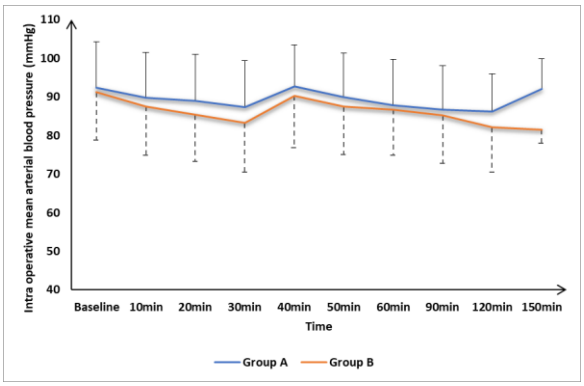
Table 2: Analgesia and adverse effects of the studied groups

		Group A (n=30)	Group B (n=30)	P
Number of patients required fentanyl		2 (6.67%)	5 (16.67%)	0.423
Total intraoperative fentanyl consumption (µg)		4.8 ± 18.31	12.8 ± 29.16	0.208
Time to first analgesic request (h)		9.83 ± 4.01	13.57 ± 4.27	**<0.001***
Number of patients required morphine		28 (93.33%)	21 (70%)	**0.041***
Total morphine consumption during the first 24 postoperative hours (mg)		8.57 ± 1.43	6.11 ± 1.91	**<0.001***
Adverse effects	**Nausea and vomiting**	6 (20%)	3 (10%)	0.471
	Hypotension	3 (10%)	1 (3.33%)	0.612
	Bradycardia	5 (16.67%)	2 (6.67%)	0.423
	Cardiac arrhythmia	0(0%)	0 (0%)	--
	Local anesthetic toxicity	0(0%)	0 (0%)	--

Data are presented as mean ± SD or frequency (%). *: significant as P value <0.05.



(A)



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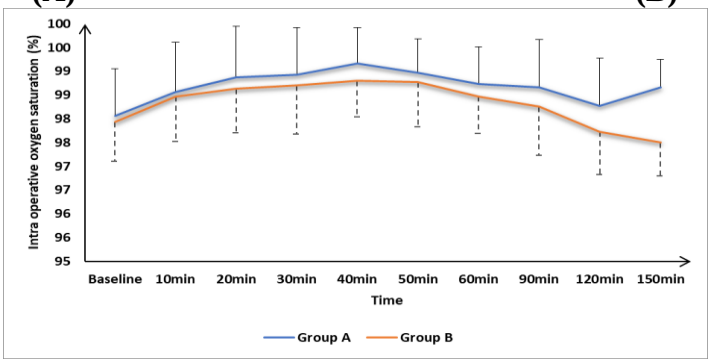
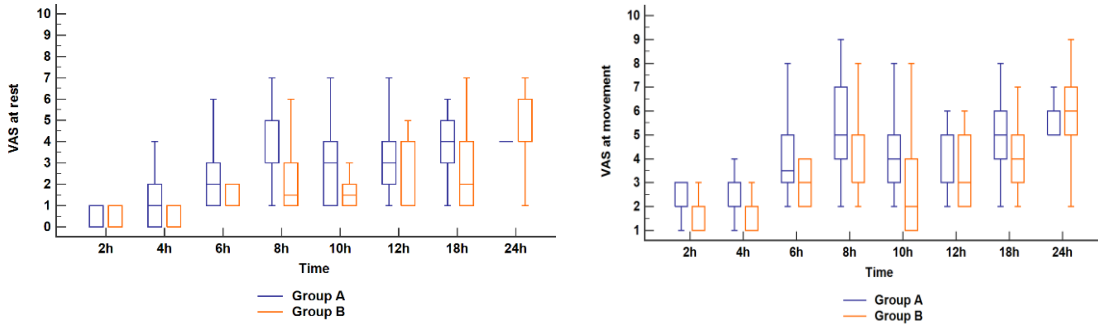


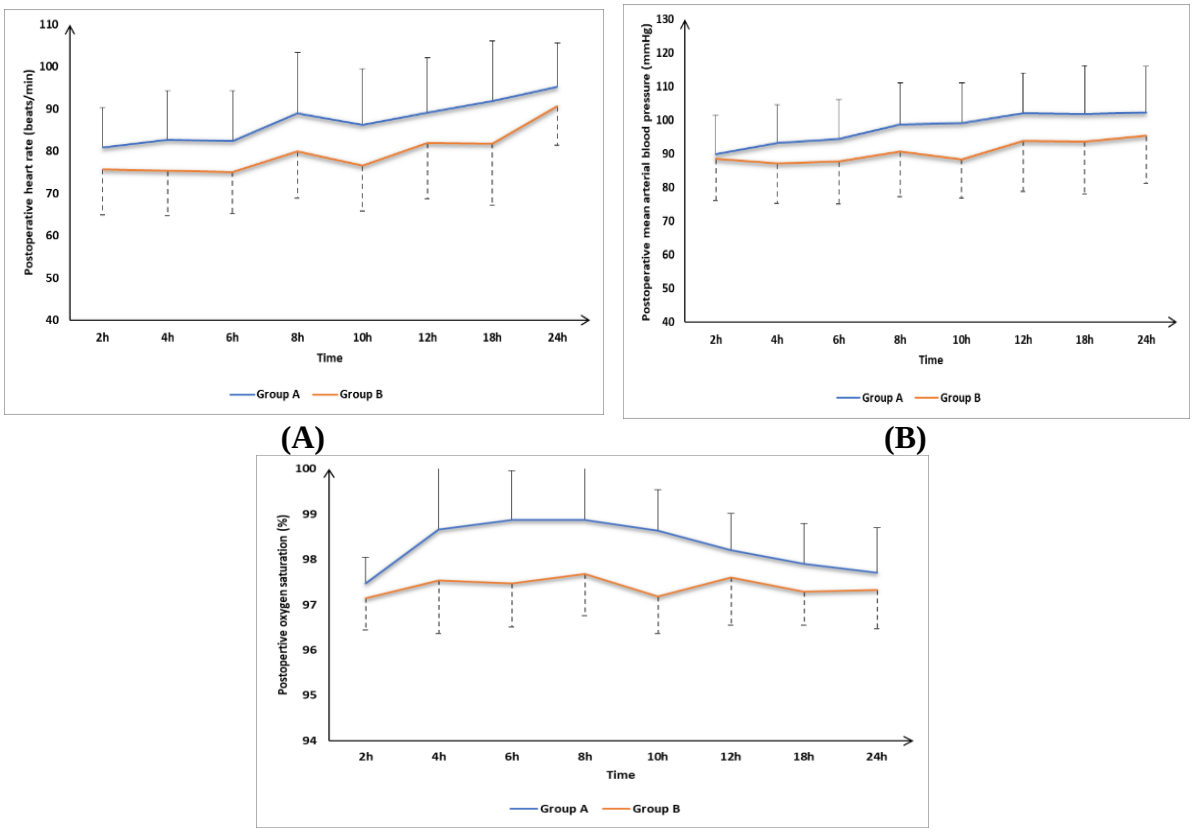
(C)

Figure 2: Intraoperative (A) heart rate, (B) mean arterial blood pressure and (C) oxygen saturation of the studied groups



(A) **(B)**

Figure 3: Visual analog scale (VAS) (A) at rest and (B) at movement of the studied groups



(A) **(B)**

(C)

Figure 4: Postoperative (A) heart rate, (B) mean arterial blood pressure and (C) oxygen saturation of the studied groups

Discussion

We hypothesized that adding ketamine to the DEX bupivacaine combinations might enhance the analgesic efficacy because of their distinct mechanisms of action.

Ketamine's antinociceptive impact is achieved by blocking N-methyl-D-aspartate (NMDA) receptors, enhancing the opioid system sensitivity, and activating aminergic pathways while

inhibiting their reuptake. Ketamine directly inhibits nitric oxide synthase, perhaps contributing to its pain-relieving properties [14].

Ketamine has been studied as an adjunct to LA in epidural analgesia with positive results, while its pain-relieving impact in peripheral nerve blocks has shown inconsistent impacts [15]. Ketamine was shown to have an LA-like effect by interacting with the sodium channel in rat myocytes. Ketamine inhibits the N-methyl-D-aspartate receptors involved in the pain pathway [13, 16, 17].

The synergistic effect of ketamine and DEX as bupivacaine additives has been attributed to their complementary mechanisms of action. Ketamine's NMDA receptor antagonism may reduce central sensitization and hyperalgesia [18], while DEX's anti-inflammatory effects may reduce peripheral sensitization and inflammation [19]. The combination of these two drugs may provide longer-lasting pain relief compared to using them individually.

DEX delayed the initiation of patient-controlled analgesia and resulted in substantially reduced pain ratings for up to 72 hours after surgery [10]. Multiple studies have demonstrated that DEX is a safe adjuvant to regional anesthetics; it did not increase the probability of adverse events [20].

The mechanism via which DEX may extend regional block duration is not fully understood [10]. By binding to glucocorticoid receptors, DEX obstructs potassium exchange in unmyelinated C fibers, which mediate pain signals [21]. DEX can hinder LA absorption via vasoconstriction and lower capillary permeability via increased catecholamine sensitivity [22]. Another systemic approach involves inhibiting local cyclooxygenase activity after trauma, which decreases the synthesis of pain-inducing molecules such as prostaglandins [23].

The present study found that patients who received ketamine had significantly lower VAS scores, both at rest and during movement, compared to the control group. The ketamine group also had significantly lower HR, MAP, and SpO_2 measurements than the control group. The time to the first request for analgesia was significantly reduced, and the need for morphine and the total morphine consumption during the first 24 postoperative hours was significantly lower in the ketamine group compared to the control group.

Consistent with our findings, Xiang et al. [24] performed a systematic review and meta-analysis of 20 studies on 1011 patients. The administration of ketamine as a supplement to LA resulted in an extended duration of analgesia, particularly in the context of peripheral nerve blocks.

Consistent with our investigations, Abdelhamid et al. [25] included 50 mg of ketamine in 0.25% bupivacaine for preoperative US-guided SAPB in females undergoing MRM with general anesthesia resulted in a decrease in postoperative morphine consumption during the first 24 hours and the requirement for intraoperative fentanyl.

Also, a study by El Mourad and Amer [26] was carried out to compare the impact of supplementing bupivacaine with DEX or ketamine in thoracic paravertebral block in MRM patients. They exhibited that administering either 50 mg of ketamine or 4 mg of DEX in combination with bupivacaine, 0.5%, prolonged the time to the initial request for analgesia without causing any significant adverse effects. These findings suggest that the combined use of DEX and ketamine with bupivacaine in the thoracic paravertebral block for MRM patients is both secure and effective.

Additionally, Othman et al. [13] investigated the analgesia of combining 0.25% bupivacaine (30 mL) with ketamine (1 mg/kg) during ultrasound-guided modified pectoral blocks on patients undergoing MRM. They showed that this combination resulted in a longer time to the initial request for analgesia and reduced total morphine consumption compared to the control group. Therefore, the study suggests that adding ketamine to bupivacaine in the modified pectoral block can enhance postoperative pain management for MRM patients.

Also, Kumar et al. [14] illustrated that postoperative pain scores, both at rest and during movement, were improved in the DEX group compared to the control group. The number of

patients requiring rescue analgesics was significantly reduced in the DEX group, and the median latency to first-rescue analgesia was longer in the DEX group compared to the control group.
The small sample size and single-center location limit our study. Additional research is demanded to verify the ideal concentration and dose of DEX and ketamine. Further studies to compare the use of dexamethasone and ketamine to other anesthetic agents in different blocks and surgeries are recommended.

Conclusions:

Ketamine-DEX combination with bupivacaine in the US-guided SAPB for patients undergoing MRM enhances the block analgesia with table hemodynamics and minor adverse effects as evidenced by longer duration before the initial request for analgesia, lower consumption of morphine 24h after surgery, and lower pain score both at rest and during movement parameters.

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Conflict of Interest: Nil

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