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Effects of Adding Dexamethasone Plus Ketamine to Bupivacaine for Ultrasound-guided Serratus Plane Block as Analgesia in Major Breast Surgery: A Randomized, Double-blind Trial

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Abstract

BACKGROUND: Post-operative pain after mastectomy is associated with poor recovery, prolonged hospital stays, and increased liability for chronic persistent pain.

AIM: This work aimed to test the analgesic efficacy of adding ketamine to a dexamethasone bupivacaine combination in ultrasound-guided serratus anterior plane block (SAPB) in patients undergoing modified radical mastectomy (MRM).

METHODS: This randomized, double-blind trial included 60 females aged 20–60 undergoing MRM. They were randomized into two groups: Group DB (n = 30) received SAPB using 30 ml of bupivacaine 0.25% and dexamethasone 4 mg. Group KD (n = 30) received the same block with the addition of ketamine 50 mg.

RESULTS: The time to the first analgesic request was significantly delayed in Group KD than in Group DB ($p < 0.001$). The number of patients requiring morphine and its total consumption during the first 24 post-operative hours in Group KD were significantly less than in Group DB ($p = 0.001$ and $p < 0.001$, respectively). Visual Analog Scale scores at rest and movement at 4, 6, 8, 10, 12, and 18 h were significantly lower in Group KD than in Group DB.

CONCLUSIONS: Adding ketamine to bupivacaine plus dexamethasone in ultrasound-guided SAPB is associated with better analgesic outcomes in patients undergoing MRM, including prolonged duration of analgesia and decreased post-operative morphine consumption and pain scores at rest and movement.

Introduction

Despite the strides made in the surgical management of breast cancer, slight advancement has been made to improve post-operative pain control after modified radical mastectomy (MRM), with pain remaining one of the most common symptoms encountered in up to 50% of patients [1]. Post-operative pain after mastectomy has several complications, such as poor recovery, prolonged hospital stays, and even increased liability to chronic persistent pain. Acute post-operative pain is complicated by persistent chronic post-surgical pain in 25-60% of women undergoing MRM [2].

Various methods are suggested to manage post-operative pain, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, local anesthetic (LA) infiltration, and regional blocks [2]. Regional anesthesia techniques provide excellent pain control, improve pulmonary function, and reduce perioperative narcotic requirements [3]. Novel ultrasound-guided interfascial plane blocks have been described as safe, easy, and reliable alternatives in breast surgery. One of these techniques is serratus anterior plane block (SAPB), in which the lateral cutaneous branches of the intercostal nerves are blocked by injecting LA above or below the serratus anterior muscle in the mid-axillary line, sparing the pectoral nerves [4].

The limited duration of analgesia provided by LAs has warranted the use of various adjuvants, such as tramadol, dexmedetomidine, dexamethasone, or ketamine, aiming to enhance analgesia quality synergistically [5]. Dexamethasone adjuvant for LAs has been shown to boost and prolong various types of nerve block [6]. Ketamine, an NMDA antagonist, has an analgesic effect by blocking NMDA-induced pain sensitization and enhancing opioid receptor sensitization [7]. Ketamine added to bupivacaine in Pecs block was shown to prolong analgesia and reduce opioid consumption [8].

This work aimed to assess the analgesic efficacy of adding ketamine to bupivacaine plus dexamethasone in ultrasound-guided SAPB in patients undergoing MRM.

Patients and Methods

This randomized, double-blind trial included 60 females aged 20–60 years of ASA physical status class I-III undergoing MRM from February 2022 to January 2023. The study was approved by the Ethical Committee National Cancer Institute, Cairo University, Egypt. Written informed consent was obtained from the patients. Exclusion criteria were refusal for SAPB, defective coagulation, infection at the injection site, and history of allergy to the study drugs.

Patients were randomized in a parallel manner at 1:1 by computer-generated numbers into two equal groups. Their allocation code was kept in a closed, opaque envelope. Group DB (n = 30) received ultrasound-guided SAPB using 30 ml of bupivacaine 0.25% and dexamethasone 4 mg. Group KD (n = 30) received SAPB with 30 ml of bupivacaine 0.25%, dexamethasone 4 mg, and ketamine 50 mg.

All patients were subjected to history taking and clinical examination and assessed for hemodynamic abnormalities in the pre-operative room. They were continuously monitored with a five-lead electrocardiogram (ECG), pulse oximetry, non-invasive blood pressure monitoring (NIBP), end-tidal CO_2, and Train-of-four (TOF).

General anesthesia

A uniform anesthetic technique was used in the two groups. After pre-oxygenation with 100% oxygen for 3 min, induction of anesthesia was done by IV propofol 2 mg/kg, fentanyl 200 μg, and atracurium 0.5 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane 1–2% in 50% air in oxygen mixtures. An intermittent dose of atracurium for muscle relaxation and fentanyl 1 μg/kg was used if the heart rate (HR) increased more than 20% of the initial reading. All patients were mechanically ventilated to maintain end-tidal CO_2 tension around 35 mmHg. Inhalation anesthetic was discontinued at the end of the surgery, and neuromuscular blockade was reversed by IV injection of neostigmine 0.05 mg/kg with atropine 0.01 mg/kg after fulfilling the criteria for extubating. Patients were extubated and transferred to the post-anesthesia care unit (PACU).

Superficial SAPB

The block was done after induction of general anesthesia with the patient in the lateral position and the diseased side up. A linear ultrasound transducer (10–12 MHz) by Sonosite M-turbo machine was placed over the mid-clavicular region of the thoracic cage in a sagittal plane. The fifth rib was identified in the mid-axillary line. The following muscles are identified easily overlying the fifth rib: the latissimus dorsi (superficial and posterior), teres major (superior), and serratus muscle (deep and inferior). The thoracodorsal artery was used to identify the plane superficial to the serratus muscle as an extra-reference point. A 22G, 50-mm Tuohy needle was introduced in-plane with the ultrasound probe targeting the plane superficial to the serratus muscle. Under continuous ultrasound guidance, the LA solution was injected, and fanning of the LA was observed.

Post-operative management

For post-operative pain management, all patients received intravenous (IV) paracetamol 1 g (Injectemol, Pharco B International, Pharmatech) every 6 h, then morphine IV (3 mg) if required to keep Visual Analog Scale (VAS) score < 3. Morphine consumption as a rescue drug was calculated during the first 24 post-operative hours. As soon as the patient was alert, the VAS pain score (10 mm vertical scale from 0 to 10 where zero means no pain and 10 is the worst pain) was recorded every 2 h.

The primary outcome measure was the duration of analgesia, defined as the time to first request post-operative analgesia. The secondary outcomes were total morphine consumption over the first 24 post-operative hours, total intraoperative fentanyl consumption, hemodynamic characteristics, and adverse effects, including nausea, vomiting, hypotension, bradycardia, and cardiac arrhythmia.

Sample size

There was no similar study to ours in the literature. We supposed that ketamine addition to the dexamethasone bupivacaine combination would induce the same effect if bupivacaine was used alone. A previous study [9] reported an increase in analgesia duration of 5.2 h by adding ketamine to the LA, with a pooled standard deviation of 2.8. Based on these findings, 29 patients in each group were required to reject the null hypothesis at an alpha level of 0.05 and a power of 80%. The sample size was calculated by G Power *3.1.9.4.

Statistical analysis

Statistical analysis was done using the SPSS v26 (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 (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, a comparison between the two groups was done using an independent sample t-test or Mann–Whitney test. A two-tailed $p < 0.05$ was considered statistically significant.

Results

In this study, 84 patients were assessed for eligibility, 18 did not meet the inclusion criteria, and six refused to participate. The remaining patients were randomly allocated into two equal groups (30 patients each). All allocated patients were followed up and analyzed statistically (Figure 1). Demographic data and duration of surgery were insignificantly different between both groups (Table 1).

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

	Group DB (n = 30)	Group KD (n = 30)	p
Age (years)	40.3 ± 11.1	43.3 ± 10.4	0.284
Weight (kg)	72.1 ± 7.7	74.5 ± 7.3	0.225
Height (cm)	166 ± 6	163 ± 7	0.124
Body mass index (kg/m^2)	26.3 ± 3.6	28.1 ± 3.8	0.064
ASA physical status (II/III)	27/3	28/2	1.000
Duration of surgery (min)	124 ± 20	119 ± 20	0.303

Data are presented as mean ± SD, ASA: American Society of Anesthesiologists

Group KD showed a better analgesic profile compared to Group DB. The analgesic duration was significantly longer in Group KD than in Group DB ($p < 0.001$). The number of patients requiring morphine and total morphine consumption during the first 24 post-operative hours were significantly lower in Group KD than in Group DB ($p = 0.001$ and $p = 0.035$, respectively). The number of patients requiring fentanyl was comparable between groups (Table 2).

Table 2: Analgesic profile of the studied groups

Variable	Group DB (n = 30)	Group KD (n = 30)	p
Duration of analgesia (hours)	11.8 ± 4.8	19.3 ± 1.8	<0.001
Patients requiring fentanyl	7 (23.3%)	3 (10.0%)	0.166
Total fentanyl consumption (μg)	74 (67–84)	81 (73–82)	**
Patients required morphine	30 (100.0%)	20 (66.7%)	0.001
Total morphine consumption (mg)	6 (3–9)	4 (2–8)	0.035

Data are presented as mean ± SD, median (range), or number (%), **No *P* value was computed due to the small number of patients in the KD group

VAS scores at rest and movement from 4 to 18 h postoperatively were significantly lower in Group KD than in Group DB. In the early and late post-operative period (2 and 24 h), VAS scores at rest and movement were comparable between groups (Table 3).

Table 3: Post-operative VAS pain score at rest and with movement in the two studied groups

Variable	Group DB (n = 30)	Group KD (n = 30)	p
VAS score at rest			
2 h	1 (0–1)	1 (0–1)	0.605
4 h	2 (0–6)	0 (0–1)	< 0.001
6 h	2 (1–7)	1 (1–2)	< 0.001
8 h	3 (1–6)	2 (1–3)	0.002
10 h	3 (1–7)	2 (1–3)	< 0.001
12 h	3 (1–7)	2 (1–3)	< 0.001
18 h	3 (1–7)	2 (1–6)	0.013
24 h	4 (1–6)	3 (2–7)	0.695
VAS score with movement			
2 h	2 (1–3)	2 (1–3)	0.281
4 h	3 (2–8)	2 (1–3)	< 0.001
6 h	4 (2–9)	3 (2–4)	0.002
8 h	4 (2–7)	3 (2–5)	0.005
10 h	5 (2–8)	3 (2–4)	< 0.001
12 h	5 (2–8)	3 (2–5)	< 0.001
18 h	5 (3–8)	4 (2–7)	0.012
24 h	5 (2–8)	4 (3–8)	0.734

Data are presented as median (range)

During the intraoperative period, the two groups had no significant differences in heart rate

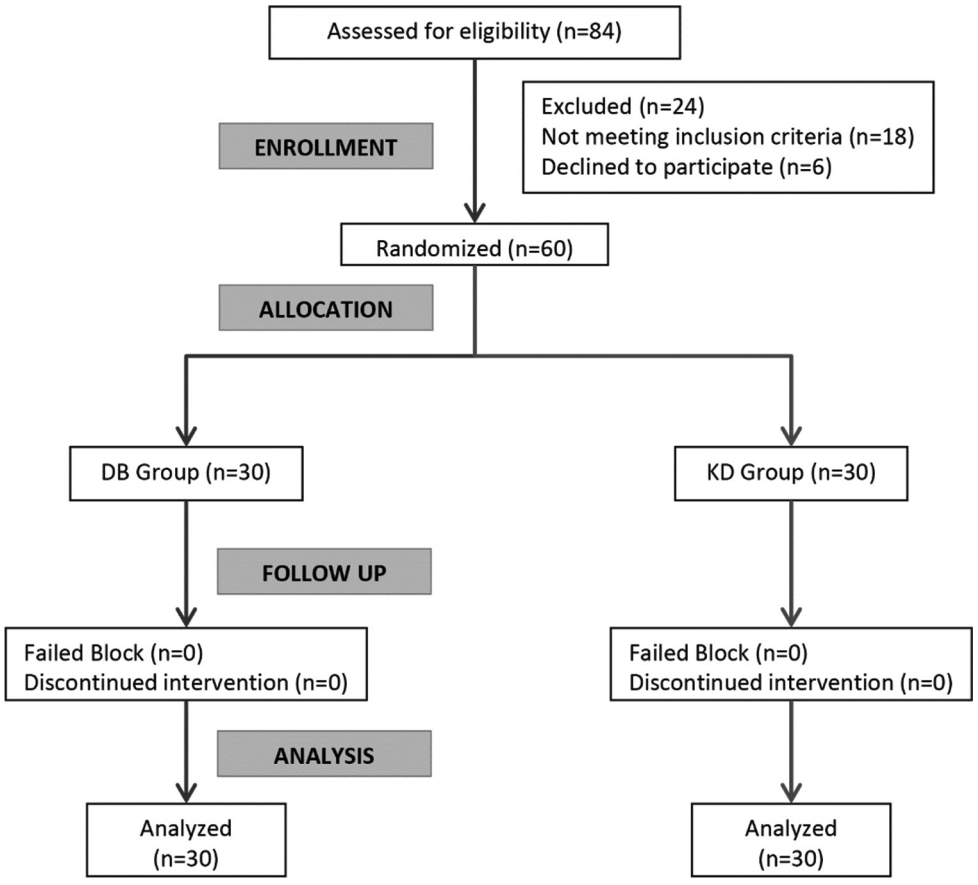

Figure 1: CONSORT flowchart

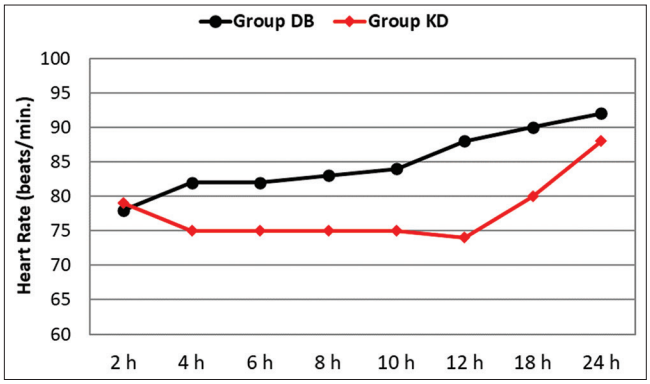

Figure 2: Changes in heart rate during the post-operative period

and mean arterial blood pressure (MAP) (Table 4). Postoperatively, HR in Group KD was significantly slower than in Group DB between 4 and 18 h (Figure 2). Similarly, MAP was significantly lower than in Group DB between 4 and 18 h (Figure 3). However, all readings were within the clinically acceptable ranges.

Table 4: Intraoperative and post-operative hemodynamic profile in the two studied groups

	Group DB (n = 30)	Group KD (n = 30)	p
Heart Rate (beats/min.)			
Baseline	81 ± 10	80 ± 10	0.938
Intraoperative			
10 min	77 ± 10	79 ± 9	0.442
30 min	75 ± 9	77 ± 9	0.422
60 min	74 ± 10	76 ± 9	0.493
90 min	74 ± 10	76 ± 9	0.403
Post-operative			
2 h	78 ± 10	79 ± 10	0.870
4 h	82 ± 12	75 ± 9	0.007
6 h	82 ± 14	75 ± 10	0.031
12 h	88 ± 16	74 ± 10	< 0.001
18 h	90 ± 14	80 ± 12	0.004
24 h	92 ± 13	88 ± 15	0.230
Mean Arterial Pressure (mmHg)			
Baseline	96 ± 13	94 ± 12	0.554
Intraoperative			
10 min	91 ± 13	92 ± 12	0.850
30 min	88 ± 13	90 ± 11	0.564
60 min	89 ± 13	90 ± 11	0.658
90 min	88 ± 13	87 ± 12	0.598
Post-operative			
2 h	92 ± 13	90 ± 12	0.603
4 h	93 ± 15	85 ± 11	0.024
6 h	93 ± 14	86 ± 12	0.043
12 h	98 ± 16	86 ± 12	0.002
18 h	99 ± 18	89 ± 14	0.023
24 h	102 ± 15	94 ± 16	0.059

Data are presented as mean ± SD

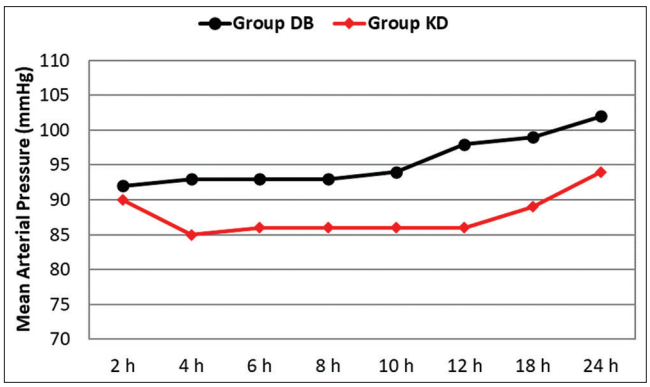

Figure 3: Changes in mean arterial pressure during the post-operative period

The two groups had no significant difference in post-operative nausea and vomiting (PONV), hypotension, and bradycardia (Table 5). Cardiac arrhythmia and LA toxicity did not occur in any patient.

Table 5: Adverse effects encountered in the two studied groups

	Group DB (n = 30) (%)	Group KD (n = 30)	p
Nausea and vomiting	5 (16.7)	2 (6.7)	0.228
Hypotension	2 (6.7)	0 (0.0)	**
Bradycardia	3 (10.0)	0 (0.0)	**

**No P value due to small number in groups

Discussion

Breast cancer is the most common female malignancy worldwide [10]. Surgery is required in almost 80% of patients for tumor resection. Unfortunately, acute post-operative pain following breast surgery is usually moderate-to-severe [11]. Thoracic paravertebral block (TPVB) is widely accepted as the gold standard analgesic technique for breast surgery [12]. However, its routine use is deterred by the likely risks of pneumothorax, hypotension, and neuraxial spread during this invasive block [13].

The SAPB is a novel regional anesthetic technique for the thoracic wall that appears to be a feasible alternative to TPVB. A recent meta-analysis of 12 RCTs of moderate to high quality confirmed the efficacy and safety of SAPB compared to no regional block and its ability to be a possible alternative to TPVB for perioperative analgesia in breast cancer surgery [14]. The application of the SAPB significantly relieves post-operative pain in breast surgery and reduces intraoperative and post-operative consumption of analgesics.

SAPB can be easily performed under ultrasound guidance, where the LA is injected either superficial or deep into the serratus muscle, targeting the lateral cutaneous branches of the thoracic intercostal nerves [15]. In the current study, we have chosen the superficial rather than the deep block, depending on the authors' experience and recommendations from previous studies. Tan *et al*. [16] found that the superficial block achieved better analgesic efficacy for mastectomy with axillary clearance than the deep block, with lower pain scores, longer analgesic time, and reduced morphine consumption. This is probably explained by the need to extend the surgical incision to the lateral aspect of the hemithorax for axillary lymph node dissection. In this situation, superficial but not deep SAPB might give satisfactory analgesic coverage.

In SAPB, like other forms of peripheral nerve blocks, the analgesic effect often lasts for a few hours. Therefore, prolonging the analgesia duration can prevent moderate-to-severe pain in the post-operative period. A larger LA dose exposes the patients to adverse cardiovascular and nervous outcomes [17]. Many drugs have proved helpful as analgesic adjuvants to enhance

the analgesic efficacy. Dexamethasone and ketamine are among these agents. To the best of our knowledge, this study is the first to test the possible analgesic advantage of adding ketamine to bupivacaine plus dexamethasone in ultrasound-guided SAPB in patients undergoing MRM.

This study demonstrated that ketamine addition to dexamethasone bupivacaine combination in superficial SAPB had a better analgesic efficacy compared to dexamethasone bupivacaine mixture. Ketamine addition was associated with longer analgesic duration and reduced post-operative morphine consumption in the first 24 h. However, the number of patients requiring fentanyl was comparable between groups. The post-operative pain scores at rest and with movement were significantly lower in ketamine Group KD up to 18 h. Both groups have exhibited hemodynamic stability with no significant difference in post-operative nausea and vomiting (PONV), hypotension, and bradycardia. It is noteworthy that none of the patients developed cardiac arrhythmia or other LA toxicity manifestations.

Dexamethasone is a long-acting synthetic corticosteroid with anti-inflammatory, anti-allergic, analgesic, and immunosuppressive properties [18]. It was used in many studies to prolong regional anesthesia. In patients who received brachial plexus nerve block, dexamethasone as an adjuvant to ropivacaine prolonged analgesia duration in doses of 1, 2, and 4 mg [19]. A meta-analysis showed a reduction in pain scores and morphine consumption with more prolonged analgesia when LA was combined with dexamethasone in the transversus abdominis plane (TAP) block [20]. In another meta-analysis of 27 studies that compared perineural dexamethasone with a placebo, the analgesic duration was prolonged in the perineural dexamethasone group by 6.5 h [21]. Chen *et al*. studied the analgesic efficiency of dexamethasone as an adjuvant with ropivacaine in continuous SAPB in patients undergoing VATS. Dexamethasone prolonged the time to the first patient-controlled analgesia and was associated with significantly lower pain scores up to 72 h postoperatively [22]. Numerous investigations have provided empirical evidence supporting the relative safety of utilizing dexamethasone as an adjuvant to regional anesthetics without elevating the likelihood of complications [23], [24].

The mechanism by which dexamethasone can prolong regional block is not well understood. Dexamethasone inhibits K^+ exchange in unmyelinated C fibers, transmitting pain through binding to glucocorticoid receptors [25]. Dexamethasone can also delay LA absorption by constricting the blood vessels and reducing capillary permeability by enhancing catecholamine sensitivity [26], [27]. A further systemic mechanism is suppressing local cyclooxygenase activity after trauma, which reduces the production of chemicals causing pain, like prostaglandins [28]. Bravo *et al*. [29] found that 2 mg, 5 mg, and 8 mg of dexamethasone resulted in similar motor and sensory durations in brachial plexus blocks. A meta-analysis showed that 4-10 mg of dexamethasone combined with ropivacaine can effectively extend its analgesic duration. In the current study, we used 4 mg of dexamethasone [24].

We hypothesized that the ketamine addition to the dexamethasone bupivacaine combination would result in a superior analgesic effect based on its different mechanisms of action. It has been used in many previous studies to improve post-operative and chronic pain management. Sub-anesthetic dose ketamine was shown to exert analgesic and anxiolytic benefits, enhancing patient experience and co-operation [30]. When employed as an adjuvant with opioids in patients having thoracic and abdominal surgery, ketamine has been shown to enhance post-operative pain relief and decrease morphine consumption [5].

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with a sedative and surface analgesic effect [30]. The NMDA receptors are critical in terminating post-operative analgesia and preventing rebound pain. Ketamine, as an NMDA antagonist, has been shown to elicit diverse analgesic effects through different routes of administration [31]. When used as an adjuvant for LA, ketamine directly inhibits Na+ channels where action potentials and pain are initially created and maintained [32]. In patients with chronic regional pain syndrome, ketamine, when administered with an LA, demonstrates sympatholytic traits against heat allodynia without adverse side effects in the CNS when injected at 0.5 mg/kg [33].

Adding ketamine to epidural bupivacaine or lidocaine has been shown to prolong regional anesthesia and post-operative analgesia [34]. Simultaneous intraoperative infusion of ketamine and lidocaine during open abdominal surgery provided a significant reduction in pain severity and opioid consumption after surgery [35].

A three-arm, randomized control trial compared 0.375% ropivacaine alone or combined with ketamine 40 mg and a third group who received intravenous ketamine intraoperatively in patients undergoing anterior cruciate ligament reconstruction. The ketamine ropivacaine mixture was associated with significantly reduced post-operative pain and longer analgesic duration. IV-administered ketamine during operation did not produce the same effects as pre-operative administration [36]. Another study compared ketamine vs. dexmedetomidine as adjuvants in supraclavicular nerve block in patients undergoing upper limb surgery. Compared to a control group, both drugs showed reduced pain scores up to 24 h postoperatively. Dexmedetomidine was superior to ketamine in reducing pain and time of the first analgesic request [37].

A recent study evaluated the effect of ketamine addition to ropivacaine in TAP block for cesarean section

as compared to dexmedetomidine or dexamethasone. The authors found that the duration of analgesia was more prolonged in the ketamine-treated group than in dexamethasone and dexmedetomidine. Besides, patient satisfaction was significantly better in the ketamine group, with no significant difference in the incidence of adverse effects between the three groups [38].

Othman *et al*. [8] tested the analgesic efficacy of modified Pecs block with ketamine as an adjuvant to bupivacaine in patients undergoing breast cancer surgery. Adding ketamine to bupivacaine resulted in a prolonged time of first request of analgesia (18.3 ± 2.0 and 12.6 ± 2.6, respectively, $p < 0.001$), reduced morphine consumption (12.5 ± 4.6 and 18.9 ± 6.3, respectively, $p = 0.016$). However, it did not affect pain scores or hemodynamics or increase the side effects.

Abdelhamid *et al*. [39] compared ketamine vs. neostigmine as additives to bupivacaine for ultrasound-guided SAPB in MRM. The post-operative morphine consumption was lower in the ketamine group compared to the neostigmine and control groups. However, the time of the first analgesic request and the number of patients requiring rescue analgesia were comparable between the three groups. Ketamine effectively reduced pain compared to the other groups, but only after 8 and 16 h. There was no significant difference between groups in the frequency of PONV.

El Mourad and Amer [40] compared dexamethasone and ketamine as adjuncts to bupivacaine in TPVB in patients undergoing MRM. They reported that ketamine was associated with a longer time to first analgesic demand than dexamethasone and control groups (18.0 ± 6.0, 10.3 ± 4.5, and 5.3 ± 3.1 h, respectively; $p = 0.0001$). Pain scores were occasionally lower in the ketamine group than in the dexamethasone group. The total opioid consumption was reduced comparably in the ketamine and dexamethasone groups. The authors did not report serious adverse events with stable hemodynamic values at all times of measurements, with no significant intergroup difference.

All of the previous studies used a ketamine dose of 1–2 mg/kg. In the current study, we used a fixed dose of 50 mg in all patients as an additive to dexamethasone. The smaller ketamine dose is supposed to avoid the possible adverse effects of the drug. Injections of ketamine activate the sympathetic system. Thus, patients may experience tachycardia and elevated blood pressure [41]. It may also lead to psychiatric symptoms; however, a low dose of ketamine has been shown to have no significant side effects during the post-operative period [42]. Therefore, the lowest effective dose of dexamethasone plus the low ketamine dose in the current study is supposed to avoid the possible adverse effects of both drugs. In fact, we did not observe any serious side effects in the present study.

This study has some limitations; it was a single-center study with no placebo groups as a control to confirm the effect of the dexamethasone-only group. We followed the patients for only 24 h, while other studies reported the post-operative analgesic effects up to 48–72 h. However, one of our main objectives of adequate analgesia was early ambulation. We did not investigate different doses of adjuvants used in the study; instead, we used an empirical dose of both agents.

Conclusions

The addition of ketamine to a combination of dexamethasone and bupivacaine during ultrasound-guided SAPB in patients subjected to MRM improved the analgesic outcomes, including prolonged time for first request of analgesia, reduced post-operative morphine consumption, decreased VAS score at rest and movement. The use of dexamethasone and ketamine was associated with hemodynamic stability and minimal mild adverse effects.

References

1. Karmakar MK, Samy W, Li JW, Lee A, Chan WC, Chen PP, *et al.* Thoracic paravertebral block and its effects on chronic pain and health-related quality of life after modified radical mastectomy. Reg Anesth Pain Med. 2014;39(4):289-98. https://doi.org/10.1097/AAP.0000000000000113
PMid:24956453
2. Kim SY, Song JW, Park B, Park S, An YJ, Shim YH. Pregabalin reduces post-operative pain after mastectomy: A double-blind, randomized, placebo-controlled study. Acta Anaesthesiol Scand. 2011;55(3):290-6. https://doi.org/10.1111/j.1399-6576.2010.02374.x
PMid:21288209
3. Plunkett A, Scott TL, Tracy E. Regional anesthesia for breast cancer surgery: Which block is best? A review of the current literature. Pain Manag. 2022;12(8):943-50. https://doi.org/10.2217/pmt-2022-0048
PMid:36177958
4. Mayes J, Davison E, Panahi P, Patten D, Eljelani F, Womack J, *et al.* An anatomical evaluation of the serratus anterior plane block. Anaesthesia. 2016;71(9):1064-9. https://doi.org/10.1111/anae.13549
PMid:27440171
5. Prabhakar A, Lambert T, Kaye RJ, Gaignard SM, Ragusa J, Wheat S, *et al.* Adjuvants in clinical regional anesthesia practice: A comprehensive review. Best Pract Res Clin Anaesthesiol. 2019;33(4):415-23. https://doi.org/10.1016/j.bpa.2019.06.001
PMid:31791560
6. Huynh TM, Marret E, Bonnet F. Combination of dexamethasone and local anaesthetic solution in peripheral nerve blocks: A meta-analysis of randomised controlled trials. Eur J

Anaesthesiol. 2015;32(11):751-8. https://doi.org/10.1097/EJA.0000000000000248

PMid:25774458

7. Nath TS. Case report: Effectiveness of low-dose ketamine infusion in opioid refractory cancer pain. Cureus. 2022;14(11):e31662. https://doi.org/10.7759/cureus.31662

PMid:36545179

8. Othman AH, El-Rahman AM, El Sherif F. Efficacy and safety of ketamine added to local anesthetic in modified pectoral block for management of postoperative pain in patients undergoing modified radical mastectomy. Pain Physician. 2016;19(7):485-94.

9. Hefni AF, Eldeek AM, Ismael SA, Shaban AR. Comparing effect of adding ketamine versus dexmedetomidine to bupivacaine in Pecs-ec Block on postoperative pain control in patients undergoing breast surgery. Clin J Pain. 2022;38(9):568-74. https://doi.org/10.1097/AJP.0000000000001055

PMid:35777735

10. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660

PMid:33538338

11. Fecho K, Miller NR, Merritt SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. Pain Med. 2009;10(4):708-15. https://doi.org/10.1111/j.1526-4637.2009.00611.x

PMid:19453965

12. Albi-Feldzer A, Dureau S, Ghimouz A, Raft J, Soubirou JL, Gayraud G, *et al.* Preoperative paravertebral block and chronic pain after breast cancer surgery: A double-blind randomized trial. Anesthesiology. 2021;135(6):1091-103. https://doi.org/10.1097/ALN.0000000000003989

PMid:34618889

13. Hussain N, Brull R, McCartney CJL, Wong P, Kumar N, Essandoh M, *et al.* Pectoralis-II myofascial block and analgesia in breast cancer surgery: A systematic review and meta-analysis. Anesthesiology. 2019;131(3):630-48. https://doi.org/10.1097/ALN.0000000000002822

PMid:31408448

14. Li ZH, Hong WJ, Guo XL, Li XR, Jiang XY, Jiang Y, *et al.* Serratus plane block in breast cancer surgery: A systematic review and meta-analysis. Clin Breast Cancer. 2023;23(1):e1-13. https://doi.org/10.1016/j.clbc.2022.10.009

PMid:36357268

15. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: A novel ultrasound-guided thoracic wall nerve block. Anaesthesia. 2013;68(11):1107-13. https://doi.org/10.1111/anae.12344

PMid:23923989

16. Tan KW, Sayed Masri SN, Musthafa QA, Mohd Azidin A, Nik Mohamed Kamil A, Izaham A, *et al.* Analgesic efficacy of the superficial versus deep serratus plane blocks for mastectomy with axillary clearance: A randomized controlled trial. Medicine (Baltimore). 2022;101(35):e30515. https://doi.org/10.1097/MD.0000000000030515

PMid:36107598

17. El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: Current perspectives. Local Reg Anesth. 2018;11:35-44. https://doi.org/10.2147/LRA.S154512

PMid:30122981

18. Margulis R, Francis J, Tischenkel B, Bromberg A, Pedulla D, Grtisenko K, *et al.* Comparison of dexmedetomidine and dexamethasone as adjuvants to ultra-sound guided interscalene block in arthroscopic shoulder surgery: A double-blinded randomized placebo-controlled study. Anesth Pain Med. 2021;11(3):e117020. https://doi.org/10.5812/aapm.117020

PMid:34540645

19. Gouda N, Zangrilli J, Voskerijian A, Wang ML, Beredjiklian PK, Rivlin M. Safety and duration of low-dose adjuvant dexamethasone in regional anesthesia for upper extremity surgery: A prospective, randomized, controlled blinded study. Hand (N Y). 2022;17(6):1236-41. https://doi.org/10.1177/15589447211008558

PMid:33880959

20. Zhang D, Zhou C, Wei D, Ge L, Li Q. Dexamethasone added to local anesthetics in ultrasound-guided transversus abdominis plain (TAP) block for analgesia after abdominal surgery: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2019;14(1):e0209646. https://doi.org/10.1371/journal.pone.0209646

PMid:30620730

21. Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst Rev. 2017;11(11):CD011770. https://doi.org/10.1002/14651858.CD011770.pub2

PMid:29121400

22. Chen JQ, Chen JR, Wang S, Gao W, Gu H, Yang XL, *et al.* Effect of perineural dexamethasone with ropivacaine in continuous serratus anterior plane block for postoperative analgesia in patients undergoing video-assisted thoracoscopic surgery. J Pain Res. 2022;15:2315-25. https://doi.org/10.2147/JPR.S372071

PMid:35992248

23. Woo JH, Kim YJ, Kim DY, Cho S. Dose-dependency of dexamethasone on the analgesic effect of interscalene block for arthroscopic shoulder surgery using ropivacaine 0.5%: A randomised controlled trial. Eur J Anaesthesiol. 2015;32(9):650-5. https://doi.org/10.1097/EJA.0000000000000213

PMid:25603389

24. Kirkham KR, Jacot-Guillarmod A, Albrecht E. Optimal dose of perineural dexamethasone to prolong analgesia after brachial plexus blockade: A systematic review and meta-analysis. Anesth Analg. 2018;126(1):270-9. https://doi.org/10.1213/ANE.0000000000002488

PMid:28922230

25. Abdallah FW, Johnson J, Chan V, Murgatroyd H, Ghafari M, Ami N, *et al.* Intravenous dexamethasone and perineural dexamethasone similarly prolong the duration of analgesia after supraclavicular brachial plexus block: A randomized, triple-arm, double-blind, placebo-controlled trial. Reg Anesth Pain Med. 2015;40(2):125-32. https://doi.org/10.1097/AAP.0000000000000210

PMid:25629321

26. Rwei AY, Sherburne RT, Zurakowski D, Wang B, Kohane DS. Prolonged duration local anesthesia using liposomal bupivacaine combined with liposomal dexamethasone and dexmedetomidine. Anesth Analg. 2018;126(4):1170-5. https://doi.org/10.1213/ANE.0000000000002719

PMid:29239940

27. Chong MA, Szoke DJ, Berbenetz NM, Lin C. Dexamethasone as an adjuvant for caudal blockade in pediatric surgical patients: A systematic review and meta-analysis. Anesth Analg. 2018;127(2):520-8. https://doi.org/10.1213/ANE.0000000000003346

PMid:29596095

28. Zhu C, Zhang S, Gu Z, Tong Y, Wei R. Caudal and intravenous dexamethasone as an adjuvant to pediatric caudal block: A systematic review and meta-analysis. Paediatr Anaesth. 2018;28(3):195-203. https://doi.org/10.1111/pan.13338

PMid:29436137

29. Bravo D, Aliste J, Layera S, Fernández D, Leurcharusmee P, Samerchua A, *et al.* A multicenter, randomized comparison between 2, 5, and 8 mg of perineural dexamethasone for ultrasound-guided infraclavicular block. Reg Anesth Pain Med. 2019;44(1):46-51. https://doi.org/10.1136/rapm-2018-000032
PMid:30640652
30. Erdman HB, Kornilov E, Kahana E, Zarchi O, Reiner J, Socher A, *et al.* Asleep DBS under ketamine sedation: Proof of concept. Neurobiol Dis. 2022;170:105747. https://doi.org/10.1016/j.nbd.2022.105747
PMid:35550159
31. Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, *et al.* Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology. 2000;92(2):465-72. https://doi.org/10.1097/00000542-200002000-00029
PMid:10691234
32. Reddi D, Curran N. Chronic pain after surgery: Pathophysiology, risk factors and prevention. Postgrad Med J. 2014;90(1062):222-7. https://doi.org/10.1136/postgradmedj-2013-132215
PMid:24572639
33. Sunder RA, Toshniwal G, Dureja GP. Ketamine as an adjuvant in sympathetic blocks for management of central sensitization following peripheral nerve injury. J Brachial Plex Peripher Nerve Inj. 2008;3:22. https://doi.org/10.1186/1749-7221-3-22
PMid:18950516
34. Abdel-Ghaffar ME, Abdulatif MA, Al-Ghamdi A, Mowafi H, Anwar A. Epidural ketamine reduces post-operative epidural PCA consumption of fentanyl/bupivacaine. Can J Anaesth. 1998;45(2):103-9. https://doi.org/10.1007/BF03013246
PMid:9512842
35. Imani F, Bagheri A, Arvin E, Gatt SP, Sarveazad A. Effects of ketamine and lidocaine infusion on acute pain after elective open abdominal surgery, a randomized, double-blinded study. Med J Islam Republ Iran. 2022;36:60. https://doi.org/10.47176/mjiri.36.60
PMid:36128312
36. Zhu T, Gao Y, Xu X, Fu S, Lin W, Sun J. Effect of ketamine added to ropivacaine in nerve block for postoperative pain management in patients undergoing anterior cruciate ligament reconstruction: A randomized trial. Clin Ther. 2020;42(5):882-91. https://doi.org/10.1016/j.clinthera.2020.03.004
PMid:32247522
37. Mohmed A, Hassanein A, Mansour H. Ketamine Versus Dexmedetomidine as an Adjuvant in Ultrasound-guided Supraclavicular Brachial Plexus Block: A Double-blind Randomized Clinical Trial. In Review; 2021. Available from: https://www.researchsquare.com/article/rs-128342/v1 [Last accessed on 2023 Oct 15].
38. Stephan J, Saba H, El Metni A, Kamel K. B353 Comparision of Dexmedetomidine, Dexamethasone, Ketamine as Adjuvants to Ropivacaine in Transverse Abdominis plane Block for Cesarean Section: A Prospective Randomized Study. Postoperative Pain Management. BMJ Publishing Group Ltd.; 2022. p. A253. Available from: https://rapm.bmj.com/lookup/doi/10.1136/rapm-2022-ESRA.428 [Last accessed on 2023 Nov 06].
39. Abdelhamid BM, Samy S, Abdalla A, Saad A, Ollaek M, Ahmed A. Ketamine versus neostigmine as adjuvants to bupivacaine during ultrasound-guided serratus anterior plane block in modified radical mastectomy. A randomized controlled trial. Egypt J Anaesth. 2021;37:356-63.
40. El Mourad MB, Amer AF. Effects of adding dexamethasone or ketamine to bupivacaine for ultrasound-guided thoracic paravertebral block in patients undergoing modified radical mastectomy: A prospective randomized controlled study. Indian J Anaesth. 2018;62(4):285-91. https://doi.org/10.4103/ija.IJA_791_17
PMid:29720754
41. Tan ZL, Zhou ZY, Zhou X, Zhang L, Cao HJ. The protective effect of high heme oxygenase-1 expression induced by propofol on the alveolar II type epithelial cells of rats with acute lung injury induced by oleic acid. J Physiol Pharmacol. 2021;72(3):451-9. https://doi.org/10.26402/jpp.2021.3.13
PMid:34873068
42. Mohammadzadeh Jouryabi A, Sharami SH, Mansour Ghanaie M, Sedighinejad A, Imantalab V, Rafiee Sorouri Z, *et al.* Comparing the effects of low dose of ketamine, tramadol, and ondansetron in prevention of post spinal anesthesia shivering in cesarean section. Anesth Pain Med. 2021;11(4):e116429. https://doi.org/10.5812/aapm.116429
PMid:34692439