EGYPTIAN JOURNAL OF ANAESTHESIA
2024, VOL. 40, NO. 1, 184–192
https://doi.org/10.1080/11101849.2024.2331351

OPEN ACCESS Check for updates

Original research: Dexmedetomidine versus ketamine in erector spinae plane block for postoperative analgesia following modified radical mastectomy: A prospective randomized controlled blinded study

Ehab Hanafy Shaker[a], Ahmed M Soliman[a], Ahmed Abd Elmohsen Bedewy[b] and Suzan Adlan[a]

[a]Department of Anaesthesia, Intensive care and Pain management, National Cancer Institute, Cairo University, Cairo, Egypt; [b]Department of Anaesthesia and Surgical intensive care, Faculty of Medicine, Helwan University, Cairo, Egypt

ABSTRACT

Background: A significant postoperative pain has been documented in numerous breast cancer cases following modified radical mastectomy (MRM). We evaluated the effectiveness of dexmedetomidine (DEX) versus ketamine as adjuvants to local anaesthetic in erector spinae plane block (ESPB) in MRM.

Methods: In this randomized controlled trial, 75 women with breast cancer scheduled for MRM were included. All patients underwent ESPB with 30 ml 0.25% bupivacaine and randomized into three equal groups: group A, ESPB group; group B: received 1 µg/kg DEX with the ESPB; and group C: given 0.5 mg/kg Ketamine with the block.

Results: Compared with group A, VAS score at rest as well as movement were lower considerably in groups B and C ($p < 0.05$) at 6 h, 12 h, and 24 h. Group B had lower VAS scores at rest at 12 h and 24 h and during movement at 6 h, 12 h, and 24 h ($p < 0.05$) than group C. In comparison to A Group; B and C Groups required considerably less time to rescue analgesia and consumed significantly fewer total opioids ($p < 0.05$ and $p < 0.001$, respectively). In addition, total number of patients who required additional analgesia was markedly reduced in groups B and C compared to group A ;($p < 0.05$).

Conclusion: In MRM surgery, the postoperative opioids consumption and VAS values were lower in both groups DEX and ketamine as an adjuvant to bupivacaine which enhanced the analgesic profile and prolonged ESPB duration compared to ESPB alone, with DEX being superior to ketamine.

ARTICLE HISTORY
Received 14 November 2023
Revised 10 January 2024
Accepted 15 February 2024

KEYWORDS
Breast cancer; Dexmedetomidine; ketamine; erector spinae plane block; pain

1. Introduction

In 2020, breast cancer (BC) accounted for 11.7% of all new cases across all ages and sexes. Consequently, surgery is considered as the best management option for BC [1]. A considerable incidence of postoperative pain has been documented in numerous BC patients after major surgical operations. Although patient-controlled analgesia (PCA) opioids are frequently used to manage postoperative pain with systemic respiratory depression, nausea, and vomiting (PONV) are undesirable side effects that may exacerbate comorbidities.

Injections into regional nerves such as pectoral nerve block, interscalene brachial plexus block, thoracic epidural, paravertebral, and erector spinae plane blocks (ESPB), are considered essential features of multimodal analgesia and enhanced postoperative recovery in patients with BC [2,3].

Ultrasound (US)-guided ESPB is a block that exists to deliver local anesthetics (LA) to the facial muscle plane, that effectively delivers (LA) to the erector spinae (ES) muscle. Recent research has shown that ESPB is an alternative analgesic therapy for thoracic pain after surgery, trauma, persistent neuropathic pain, and breast and abdominal procedures, with a high rate of effectiveness in reducing somatic and visceral pain [4]. Combining LA with an adjuvant may extend its analgesic effect, reduce pain postoperatively, and the need for additional I.V. pain management [5].

Dexmedetomidine (DEX) is an effective α-2 agonist that can be used as a regional anesthetic and analgesic adjuvant. When used with LA for nerve block anesthesia, it can enhance its onset and lengthen its duration [6,7].

Ketamine is a known antagonist of the N-methyl-D-aspartate receptor with some LA and analgesic effects [8]. Previous studies reported that combining of ketamine with LA for a nerve block technique can enhances regional anesthesia duration and postoperative analgesia [9,10].

Although prior studies have examined the potential impact of DEX and ketamine as adjuvants to local

CONTACT Ehab Hanafy Shaker ehab.gendy@nci.cu.edu.eg Department of Anesthesia, Intensive care and Pain management, National Cancer Institute, Fom Elkhalig, Cairo University, Cairo, PO 11796, Egypt

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

anesthesia (LA), there is a limited number of controlled trials that directly compare these additives in the context of ESPB during mastectomy procedures. Therefore, this trial was performed to compare the additive effects of DEX versus ketamine to LA in ESPB to control pain postoperatively in patients who had modified radical mastectomy (MRM).

2. Materials and methods

This trial was a prospective, controlled, randomized, that was performed at the National Cancer Institute, Cairo University, Egypt, from January 2023 to June 2023, after approval by the Institutional Ethical Committee (201920022.2P) and registration at clinicaltrials.gov (ID: NCT05727098). Signed consent was obtained from all patients after a detailed preoperative explanation.

Seventy-five adult female patients aged 18–65 years with physical state II or III according to ASA with BC and planned for MRM participated in this trial. Patients with allergy to any of the drugs being used in the trial; infection at the injection site; coagulation abnormalities; disease of the heart, liver, or kidneys; use of immunosuppressant medication; inflammatory breast cancer, breast cancer surgery history, radiation or chemotherapy before surgery, BMI >30 kg/m^2, who were pregnant or breastfeeding, or who were taking pain drugs were not allowed to take part in the research.

3. Randomization and blindness

The numbers of a random computer generator and opaque envelopes were used to distribute the patients in parallel. The cases were divided equally among three categories. Group A received US guided ESPB with 30 ml 0.25% bupivacaine; group B received US guided ESPB with the same volume of bupivacaine added to 1 µcg/kg DEX; group C received ESPB with same bupivacaine volume with 0.5 mg/Kg ketamine. The patients and care providers were blinded about our aim. All medications were produced in identical coated-sterile vials by a pharmacist who was not part of the anesthetic or surgical team.

Routine laboratory tests, physical examinations, and examination of patients' medical histories were performed for all participants. Patients were given instructions on how to estimate the severity of their pain on VAS varying from 0 (no pain) to 10 (the greatest pain imaginable).

An intravenous (IV) line was inserted in all patients in the operating room. All patients underwent usual monitoring (ECG, pulse oximetry, temperature probe, non-invasive blood pressure, and capnography) and midazolam (0.03 mg/kg) were used as premeditations.

Propofol (2–2.5 mg/kg IV) and (0.5 mg/kg) atracurium besylate were used to all patients to induce general anesthesia (GA). 1 gm Paracetamol and 40 mg ketorolac were given to all patients immediately after induction. After securing the airway with a right-sized I gel laryngeal mask airway, Oxygen: air (1:1 total fresh gas flow) was started while isoflurane was titrated to a minimum alveolar level of 1.0 were used to keep the patient under balanced anesthesia. ESPB was performed by the same anesthesiologist after the induction of GA under complete sterilization but was blinded to the injected solution.

4. The US-guided ESPB technique

In lateral position, the T4 vertebra's spinous process was visualized in the midline vertebra down from the spinous process of the C7 vertebra, using a linear US transducer that was placed vertically (craniocaudal orientation). 2–3 ml of 2% lidocaine were injected 3 cm laterally from the midline at needle entry. The rhomboid major muscle, trapezius muscle, and ES muscle lying superficial to the transverse process (TP) were detected using the US probe. A 18-G The ES muscle was accessed using a Tuohy needle placed in-plane until reaching just superficial to the fourth thoracic TP by the needle tip and deep to the ES muscle. Subsequently, 2 mL of normal saline was administered to verify the accurate placement of the needle. The drug was administered through a needle according to group randomization, and the injected fluid was distributed cranially and caudally after negative aspiration.

By the end of surgery. All patients received Atropine (0.02 mg/kg) added to Neostigmine (0.05 mg/kg) for reversal of neuromuscular blockade, and 1 gm/8 hours IV of paracetamol was given as standard analgesic.

VAS score (both at rest and with movement), heart rate (HR), oxygen saturation, and mean arterial pressure (MAP) were monitored immediately after surgery, at 3, 6, 12, and 24 h after surgery. In the case of a VAS score >3, patients were instructed to receive 3 mg IV morphine as rescue analgesia. Total opioid administration, time, and number of patients to first rescue analgesia were also evaluated.

Hypotension (MAP < 20% of baseline readings; managed with 5 mg IV ephedrine and/or infusion of standard saline), and bradycardia (HR < 60 beats/min; dealt with IV atropine 0.5 mg bolus) were also noticed.

1ry outcomes were the time of 1st request of analgesia and total opioid consumption, whereas 2^{ry} outcomes were the postoperative VAS scores at rest and during movement.

5. Sample size calculation

G. power 3.1.9.4 (Universitat Kiel, Germany) determined the needed sample size. The following factors

informed the selection of the sample size: 0.05 α error and 80% research power with an effect size of 0.40, the mean (±SD) time of 1st request of analgesia (the primary outcome) was meaningly prolonged with DEX (10.3 h ± 4.5) and with ketamine (18.0 min ± 6.0) compared to the controls (5.3 h ± 3.1) according to El Mourad and Amer [11] Three cases were added to each group to balance for expected losses. Therefore, 25 patients were enrolled in each group.

6. Statistical analysis

SPSS v27 (IBM, Chicago, IL, USA) was used for statistical analysis of this study. To check for a normal distribution, we employed histograms and the Shapiro–Wilk test. Quantitative parametric data were evaluated using an ANOVA (F) test and post hoc test (Tukey's) for means and standard deviations. We utilized the Kruskal–Wallis test and the Mann–Whitney U test to compare groups based on quantitative and non-parametric data shown as median and IQR. Chi-square analysis was performed to provide percentages and frequencies for the qualitative variables. Two-tailed P-values <0.05 were considered statistically significant.

7. Results

Ninety-six patients were initially screened for participation in the trial; 14 did not meet the requirements, and 7 refused. All remaining patients were equally allocated into three groups (25 patients each). The patients were followed up systematically for statistical analysis (Figure 1).

No statistically significant variation were noticed between groups as regards to demographics, anesthetic time, operation time, or operative side (Table 1).

Postoperative HR, MAP, and oxygen saturation measurements immediately postoperative, 3 h, 6 h, 12 h, and 24 h were comparable between the groups (Figure 2).

VAS measurements at rest and movement immediately after surgery and at 3 h were insignificantly different among the three groups. VAS during rest values of groups B and C were substantially decreased than those of group A ($p < 0.05$) at 6 h, 12 h, and 24 h and in group B than in group C at 12 h and 24 h ($p < 0.05$) and comparable between Groups B and C at 6 h. VAS measurements during movement in groups B and C were markedly lower than Group A ($p < 0.05$) and in group B than in group C at 6 h, 12 h, and 24 h ($p < 0.05$) (Table 2).

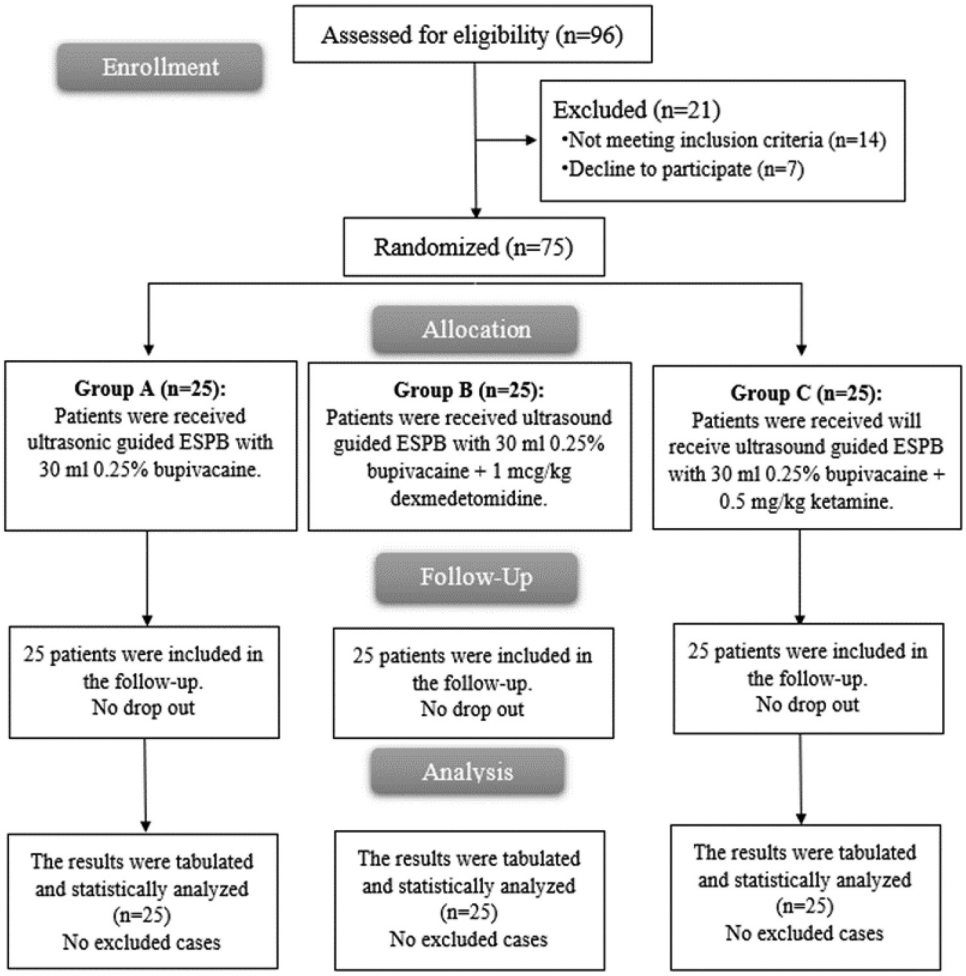

Figure 1. CONSORT flowchart of the enrolled patients.

Table 1. Demographic data, duration of anesthesia, duration of surgery, and side of surgery of the studied groups.

		Group A ($n = 25$)	Group B ($n = 25$)	Group C ($n = 25$)	P value
Age (years)		46.3 ± 12.23	49.7 ± 9.35	46.5 ± 11.38	0.483
Weight (kg)		97 ± 15.17	95.1 ± 12.7	96.3 ± 11.55	0.882
ASA physical status	II	11 (44%)	16 (64%)	11 (44%)	0.264
	III	14 (56%)	9 (36%)	14 (56%)	
Prothrombin concentration		95.8 ± 3.89	97.6 ± 2.55	96.2 ± 4.03	0.183
Duration of anaesthesia (min)		194 ± 34.16	187.2 ± 22.27	180.8 ± 29.32	0.280
Duration of surgery (min)		151.6 ± 33.59	138.6 ± 21.43	133 ± 26.06	0.055
Side of surgery	Right	13 (52%)	14 (56%)	14 (56%)	0.807
	Left	12 (48%)	11 (44%)	11 (44%)	

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

In comparison to Group A, Groups B and C had a delayed time to 1st rescue analgesia ($p < 0.05$) and was considerably delayed in Group B compared to Group C ($p = 0.003$). Patients in groups B and C required much less rescue analgesia than patients in group A ($p < 0.05$) and were not significantly different between B and C groups. both B and C Groups consumed considerably less opioids overall than Group A ($p < 0.001$), and group B consumed less opioids overall than Group C ($p = 0.029$) (Table 3).

No substantial variations were recorded in the incidences of bradycardia, hypotension, vomiting, or pruritus (Table 4).

8. Discussion

In BC surgery, the ESPB is recognized as a regional nerve block for postoperative analgesia. Deep injections of LA into the ESPB can block the dorsal and ventral main rami as well as sympathetic fibers [12]. Bupivacaine is more effective in blocking the motor and sensory effects and has more cardiac toxicity than lidocaine, for its temporary usage in nerve blocking and has limited analgesic impact postoperatively [13].

As LA only provides pain relief for a short period, it is often combined with other analgesics such as tramadol, epinephrine, ketamine, or DEX to increase its analgesic efficacy [11]. The addition of DEX to the LA administered during US ESPB was found to improve peripheral nerve block and delayed sensory block period [14]. Moreover, various studies had reported ketamine's analgesic effect in regional nerve block [15].

The current trial results showed that postoperative HR, MAP, and oxygen saturation measurements were similar between groups. VAS measurements at rest were considerably lower in groups B and C than in group A at 6 h, 12 h, and 24 h and in group B than in group C at 12 h and 24 h. VAS measurements during movement were considerably lower in groups B and C than in groups A and B at 6 h, 12 h, and 24 h. The time to first rescue analgesia was considerably delayed in groups B and C than in group A and was significantly delayed in group B than in group C. Patients who required rescue analgesia and total opioid consumption were markedly decreased in groups B and C than in group A. The consumption of total opioid was notably lower in group B than in group C. Adverse effects were similar between groups.

In accordance with these results, Neethirajan et al., [16] found that patients in the TAP with DEX group required the longest time to 1st request for analgesia compared to TAP block alone. As a result of prolonged analgesic action, patients who received DEX with bupivacaine showed less pain intensity both at rest and at movement of the shoulder after 8,12,24 hours in the form of lower VAS values.

ESPB is a secure technique that uses TP as an anteromedial barrier preventing the risk of needle injury to the pleura, decrease the probability of pleural damage and postoperative opioid consumption, and enhance analgesic effect [17].

The effectiveness of ESPB is based on the ability of the LA to reach neighboring target nerves and propagate throughout the affected compartments. The thoracic paravertebral (PV) area can be accessed via the intertransverse connective tissue and the LA can spread anteriorly to the ventral and dorsal rami of the spinal nerves [17,18].

Owing to the extensive length of the ES fascia, which begins at the nuchal fascia and ends at the sacrum, LA agents can penetrate deep into the tissue and produce a wide-ranging block [19].

After Forero et al., [20] Fang et al. [17] & Ibrahim and Elnabtity [21] utilized ESPB in several trials to introduce postoperative analgesia in breast, thoracic, and percutaneous nephrolithotomy procedures, with good outcomes. Researchers have discovered that ESPB is efficient for managing postoperative pain. The use of effective analgesia produced by ESPB was found to minimize opioid use and pain scores after surgery.

The enhancement of the analgesic profile of ESPB seen in group B may be due to the cumulative effects induced by multiple mechanisms of action. LA causes analgesia by blocking the sodium channels, whereas DEX causes analgesia by acting as a selective α-2 agonist. The inhibition of presynaptic α-2 adrenoreceptors

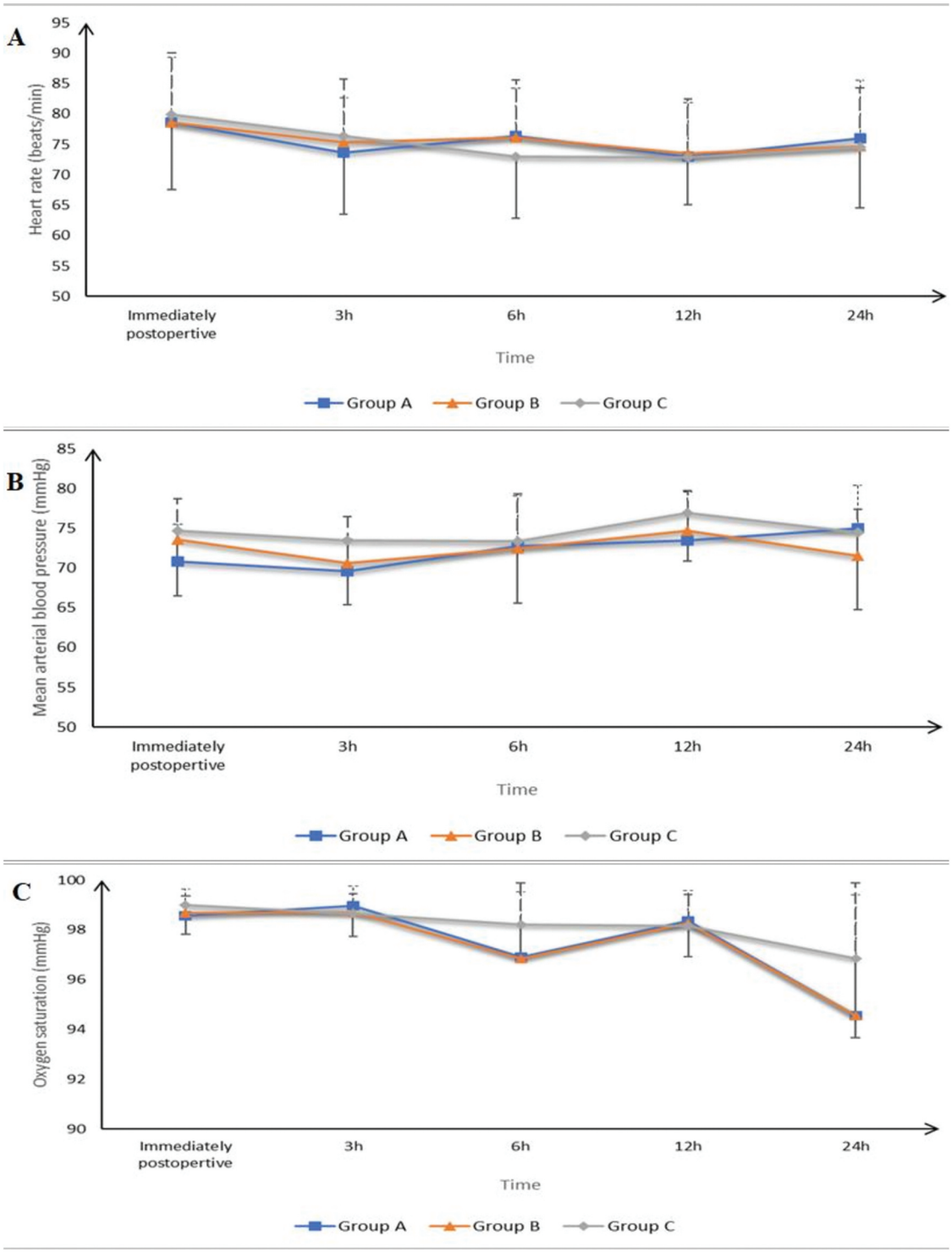

Figure 2. Comparison of the different study populations regarding postoperative measurements of A) HR, B) MAP, and C) oxygen saturation.

mediates the analgesic effect of α-2 agonists in the peripheral nervous system [6,7].

Hamed et al., [22] observed high analgesic effect with US-guided ESPB and DEX, as evidenced by the decreased consumption of intraoperative fentanyl and postoperative morphine, increased duration of analgesia, and decreased VAS in the presence of stable hemodynamics following shoulder arthroscopy.

In a study by Mohta et al., [23] DEX shown to have a central action; the nociceptive pathway is inhibited by the activation of −2 adrenoreceptors in the locus coeruleus, which in turn decreases substance P release in dorsal horn neurons.

In accordance with the current results, Wang et al., [24] found that the addition of DEX (1µcg/kg) to 0.33% ropivacaine produced a better analgesic profile with

Table 2. VAS measurements at rest and movement of the studied groups.

	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)	P value	Post hoc
VAS at rest					
Immediately postoperative	2 (1–3)	2 (1–2)	2 (1–3)	0.406	
3h	3 (2–3)	3 (2–3)	3 (2–3)	0.759	
6h	4 (2–5)	2 (2–3)	2 (2–3)	0.004*	P1=0.011* P2=0.002* P3=0.532
12h	6 (5–6)	3 (3–3)	4 (3–5)	<0.001*	P1<0.001* P2<0.001* P3=0.024*
24h	5 (5–6)	3 (2–4)	5 (2–5)	<0.001*	P1<0.001* P2=0.004* P3=0.004*
VAS at movement					
Immediately postoperative	3 (2–3)	2 (2–3)	2 (2–3)	0.439	
3h	3 (2–4)	3 (2–3)	3 (2–3)	0.163	
6h	3 (3–5)	2 (2–2)	3 (2–3)	<0.001*	P1<0.001* P2=0.007* P3=0.025*
12h	7 (6–7)	3 (2–3)	3 (3–3)	<0.001*	P1<0.001* P2<0.001* P3=0.010*
24h	7 (6–8)	3 (3–5)	6 (3–7)	<0.001*	P1=<0.001* P2=0.027* P3=0.002*

Data are presented as the median (IQR). P1: significance between A and B groups; P2: significance between A and C groups; P3: significance between B and C groups. *: p value ≤ 0.05 is significant.

Table 3. Analgesic measurements between the studied groups.

	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)	P value	Post hoc
Time to first rescue analgesia (h)	7.3 ± 5.06	19.6 ± 6.05	12.7 ± 4.69	<0.001*	P1<0.001* P2<0.005* P3=0.003*
Patients required rescue analgesia (%)	25 (100%)	11 (44%)	17 (68%)	<0.001*	P1<0.001* P2=0.002* P3=0.087
Total opioid consumption (mg)	7.6 ± 2.62	1.2 ± 1.73	2.9 ± 2.37	<0.001*	P1<0.001* P2<0.001* P3=0.029*

Data are presented as the mean ± SD or frequency (percentage). P1: significance between A and B groups; P2: significance between A and C groups; P3: significance between B and C groups. *: $p \leq 0.05$ is significant.

Table 4. Side effects of studied groups.

	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)	P value
Bradycardia	2 (8%)	5 (20%)	1 (4%)	0.162
Hypotension	7 (28%)	10 (40%)	6 (24%)	0.443
Vomiting	6 (24%)	1 (4%)	4 (16%)	0.132
Pruritis	0 (0%)	0 (0%)	0 (0%)	—

Data are presented as frequency (%).

lower postoperative VAS scores and decreased flurbiprofen use in the 1st 48 h postoperatively in MRM surgeries, but found a less intraoperative opioid consumption in patients receiving DEX as well as ropivacaine in ESPB.

A recent study by Wu et al., [25] found that adding DEX as an adjuvant to ropivacaine for different blocks (US deep serratus anterior Plane Block (SAPB)) reduced postoperative cumulative opioid consumption, relieved pain in the early postoperative period, increased patient satisfaction, and did not produce adverse effects in patients undergoing MRM surgery.

Abdelhamid et al., [26] discovered that female patients with MRM who were administered ketamine and bupivacaine during preoperative US-guided SAPB required less morphine and fentanyl.

Ketamine's analgesic effects arise from the drug's ability to stimulate the aminergic (serotonergic and noradrenergic) systems while also inhibiting its reuptake, blocking N-methyl-d-aspartate receptors, and increasing the sensitivity of the opioid system. Additionally, the analgesic effects of ketamine are linked to direct inhibition of nitric oxide synthase [27].

Moreover, Hassan and Abdelgalil [28] showed a statistically significant increase ($p < 0.001$) in analgesia duration between the ESPB and Dex groups compared to the control group and the ESPB group alone. Compared to the control group, patients in the ESPB and Dex groups used considerably less intraoperative fentanyl and postoperative morphine.

DEX considerably enhanced the time to first request of rescue analgesia, decreased the number of PCIA presses, and decreased the rate of rescue analgesia, as revealed in a recent meta-analysis. In addition, the combined effect lowered the potential for PONV [29].

There have been promising studies on the addition of ketamine to LA for epidural analgesia, compared to its analgesic effect when used in peripheral nerve blocks which has been inconsistent [27]. Ketamine was found to interact with the sodium channel of myocytes, resulting in an LA-like effect. Additionally, ketamine blocks the pain-signaling N-methyl-D-aspartate receptors [30].

Ketamine's analgesic effectiveness as an adjunct to bupivacaine has been investigated previously by Omar et al. [31] during a (0.5 mg/kg) thoracic paravertebral block for breast surgery. Comparing the tramadol group to the opioid group, they observed no difference in 24-hour opioid use or duration of analgesia. These findings were attributed by the authors to the rapid absorption and distribution of the hydrophilic ketamine throughout the body.

A study by Othman et al., [32] reported that 1 mg/kg ketamine added to 30 mL of 0.25% bupivacaine increased the time to first request for analgesia and decreased total morphine consumption compared to the controls in patients receiving MRM who received an ultrasound-guided modified pectoral block. El Mourad and Amer [11], discovered that compared to controls, MRM patients who received ketamine for thoracic paravertebral block had a substantially longer delay to initial analgesic need and lower pain levels.

Supporting the current results, El Sherif et al. [33] findings suggest that ketamine is an effective adjunct to levobupivacaine in ESPB for postoperative analgesia in patients undergoing MRM (the total amount of morphine was considerably reduced with a longer period to first request of analgesia in the ketamine than in the control group during the first 48 h postoperatively).

In contrast to the current trial, the use of ketamine as an adjuvant to LA yielded no noticeable benefits over the controls during femoral nerve block patient-controlled analgesia [34]. Hefni et al., [5] showed that adding DEX to bupivacaine in Pecs-II blocks for BC surgery offered more effective postoperative pain management than the addition of ketamine.

This study had certain limitations. It was a single-center study with a modest sample size and short postoperative assessment duration. Further studies using different blocks, additives, concentrations, and volumes are required.

9. Conclusion

In MRM surgery, adding DEX or ketamine as adjuvant to bupivacaine enhances the analgesic profile and prolong the duration of action of ESPB with significant reduction in opioid consumption and VAS value compared to ESPB alone compared to ESPB alone with superiority of DEX than ketamine.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study did not receive external funding.

ORCID

Ehab Hanafy Shaker http://orcid.org/0000-0003-4292-6103

Data availability statement

Data supporting the results reported in this manuscript can be found on request from the corresponding author.

References

[1] Łukasiewicz S, Czeczelewski M, Forma A, et al. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and Current treatment strategies—an updated review. Cancers (Basel). 2021;13. 17 4287 10.3390/cancers13174287

[2] López M, Padilla ML, García B, et al. Prevention of acute postoperative pain in breast cancer: a comparison between opioids versus ketamine in the intraoperatory analgesia. Pain Res Manag. 2021;2021:3290289. doi: 10.1155/2021/3290289

[3] Clary Z, Nazir N, Butterworth J Transversus Abdominis Plane Block With Liposomal Bupivacaine Versus Thoracic Epidural for Postoperative Analgesia After Deep Inferior Epigastric Artery Perforator Flap–Based Breast Reconstruction. Ann Plast Surg. 2020;85:e24–e6. 6 10.1097/SAP.0000000000002423

[4] Koo CH, Lee HT, Na HS, et al. Efficacy of erector spinae plane block for analgesia in thoracic surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2022;36(5):1387–95. doi: 10.1053/j.jvca.2021.06.029

[5] Hefni AF, Eldeek AM, Ismael SA, et al. Comparing effect of adding ketamine versus dexmedetomidine to bupivacaine in pecs-II block on postoperative pain control in patients undergoing breast surgery. Clin J Pain. 2022;38(9):568–74. doi: 10.1097/AJP.0000000000001055

[6] Krishna Prasad GV, Khanna S, Jaishree SV. Review of adjuvants to local anesthetics in peripheral nerve blocks: Current and future trends. Saudi J Anaesth. 2020;14(1):77–84. doi: 10.4103/sja.SJA_423_19

[7] Wang K, Wang LJ, Yang TJ, et al. Dexmedetomidine combined with local anesthetics in thoracic paravertebral block: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97 (46):e13164. doi: 10.1097/MD.0000000000013164
[8] Allen CA, Ivester JR Jr. Low-dose ketamine for postoperative pain management. J Perianesth Nurs. 2018;33:389–398. 4 10.1016/j.jopan.2016.12.009
[9] Schnabel A, Poepping DM, Kranke P, et al. Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. Br J Anaesth. 2011;107(4):601–11. doi: 10.1093/bja/aer258
[10] Lashgarinia M, Naghibi K, Honarmand A, et al. Effect of ketamine as an adjuvant in ultrasound-guided supraclavicular brachial plexus block: a double-blind randomized clinical trial study. Adv Biomed Res. 2014;3 (1):232. doi: 10.4103/2277-9175.145730
[11] 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. doi: 10.4103/ija.IJA_791_17
[12] Zhang J, He Y, Wang S, et al. The erector spinae plane block causes only cutaneous sensory loss on ipsilateral posterior thorax: a prospective observational volunteer study. BMC Anesthesiol. 2020;20(1):88. doi: 10.1186/s12871-020-01002-0
[13] Gousheh M, Akhondzadeh R, Rashidi M, et al. Comparison of Dexmedetomidine and morphine as adjuvants to bupivacaine for epidural anesthesia in leg fracture surgery: a randomized clinical trial. Anesth Pain Med. 2019;9(4):e91480. doi: 10.5812/aapm.91480
[14] Rao J, Gao Z, Qiu G, et al. Nalbuphine and dexmedetomidine as adjuvants to ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: a randomized, double-blind, placebo-controlled trial. Medicine (Baltimore). 2021;100(32):e26962. doi: 10.1097/MD.0000000000026962
[15] Abdel-Ghaffar HS, Kalefa MA, Imbaby AS Efficacy of ketamine as an adjunct to lidocaine in intravenous regional anesthesia. Reg Anesth Pain Med. 2014;39:418–422. 5 10.1097/AAP.0000000000000128
[16] Neethirajan SGR, Kurada S, Parameswari A Efficacy of Dexmedetomidine as an adjuvant to Bupivacaine in ultrasound-guided Transverse Abdominis plane block for laparoscopic appendicectomy: a randomised controlled study. Turk J Anaesthesiol Reanim. 2020;48:364–370. 5 10.5152/TJAR.2019.67689
[17] Fang B, Wang Z, Huang X Ultrasound-guided preoperative single-dose erector spinae plane block provides comparable analgesia to thoracic paravertebral block following thoracotomy: a single center randomized controlled double-blind study. Ann Transl Med. 2019;7:174. 8 10.21037/atm.2019.03.53
[18] Pourkashanian A, Narayanan M, Venkataraju A The erector spinae plane block: a review of current evidence. Update In Anaesthesia. 2020;35:27–33.
[19] Forero M, Rajarathinam M, Adhikary S, et al. Erector spinae plane (ESP) block in the management of post thoracotomy pain syndrome: a case series. Scand J Pain. 2017;17(1):325–9. doi: 10.1016/j.sjpain.2017.08.013
[20] Forero M, Adhikary SD, Lopez H, et al. The erector spinae plane block: a novel analgesic technique in thoracic Neuropathic Pain. Reg Anesth Pain Med. 2016;41 (5):621–7. doi: 10.1097/AAP.0000000000000451
[21] Ibrahim M, Elnabtity AM Analgesic efficacy of erector spinae plane block in percutaneous nephrolithotomy: a randomized controlled trial. Anaesthesist. 2019;68:755–761. 11 10.1007/s00101-019-00673-w
[22] Hamed MA, Fargaly OS, Abdelghaffar RA, et al. The role of dexmedetomidine as an adjuvant for high-thoracic erector spinae plane block for analgesia in shoulder arthroscopy; a randomized controlled study. BMC Anesthesiol. 2023;23(1):53. doi: 10.1186/s12871-023-02014-2
[23] Mohta M, Kalra B, Sethi AK, et al. Efficacy of dexmedetomidine as an adjuvant in paravertebral block in breast cancer surgery. J Anesth. 2016;30 (2):252–60. doi: 10.1007/s00540-015-2123-8
[24] Wang X, Ran G, Chen X, et al. The effect of ultrasound-guided erector spinae plane block combined with dexmedetomidine on postoperative analgesia in patients undergoing modified radical mastectomy: a randomized controlled trial. Pain Ther. 2021;10(1):475–84. doi: 10.1007/s40122-020-00234-9
[25] Wu Y, Kang Y, Li Y, et al. Impact of ultrasound-guided deep serratus anterior plane block combined with Dexmedetomidine as an adjuvant to ropivacaine inpatient quality of recovery scores undergoing modified radical mastectomy: a randomized controlled trial. Front Oncol. 2022;12:858030. doi: 10.3389/fonc.2022.858030
[26] Abdelhamid BM, Samy S, Abdalla A, et al. 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(1):356–63. doi: 10.1080/11101849.2021.1959257
[27] Taraneh R, Alireza K, Bijan Y, et al. Efficacy of dexmedetomidine and ketamine addition to bupivacaine 0.25% by epidural method in reducing postoperative pain in patients undergoing femur fracture surgery. J Family Med Prim Care. 2021; 10 (2): 832–837. 10.4103/jfmpc.jfmpc_1506_20
[28] Hassan ME, Abdelgalil AS Efficacy of dexmedetomidine as an adjuvant in erector spinae plane block in breast cancer surgery: a randomized controlled trial. Anaesth Pain Intensive Care. 2023;27:16–22. 1 10.35975/apic.v27i1.2109
[29] Yu L, Shen X, Liu H. The effect and safety of dexmedetomidine as an adjuvant to local anesthetics in erector spinae plane block: a systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiol. 2023;23(1):61. doi: 10.1186/s12871-023-02019-x
[30] Mamta S, Nitin S, Pradeep J, et al. Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. Indian J Anaesth. 2011 Mar-Apr;55(2):141–145. doi: 10.4103/0019-5049.79894
[31] Omar AM, Mansour MA, Abdelwahab HH, et al. Role of ketamine and tramadol as adjuncts to bupivacaine 0.5% in paravertebral block for breast surgery: a randomized double-blind study. Egypt J Anaesth. 2011;27(2):101–5. doi: 10.1016/j.egja.2011.04.002
[32] Othman AH, AM E-R, 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;19:485–494. 7;9 10.36076/ppj/2016.19.485

[33] El Sherif FA, Youssef HA, Fares KM, et al. Efficacy of ketamine versus Magnesium Sulphate as adjuvants to levobupivacaine in ultrasound bilevel erector spinae block in breast cancer surgery (a Double-Blinded Randomized Controlled Study). Local Reg Anesth. 2022;15:87–96. doi: 10.2147/LRA.S379194

[34] Rahimzadeh P, Faiz SH, Ziyaeifard M, et al. Effectiveness of adding ketamine to ropivacaine infusion via femoral nerve catheter after knee anterior cruciate ligament repair. J Res Med Sci. 2013;18:632–636. 8