Original Article

A randomised comparative study of erector spinae plane block versus low-dose ketamine-dexmedetomidine intravenous infusion as intraoperative opioid-free analgesia for modified radical mastectomy

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Submitted: 04-Dec-2023
Revised: 13-May-2024
Accepted: 14-May-2024
Published: 07-Jun-2024

Access this article online
Website: https://journals.lww.com/ijaweb
DOI: 10.4103/ija.ija_1167_23
Quick response code

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ABSTRACT

Background and Aims: Opioid-sparing analgesia for acute postoperative pain after breast cancer surgery is crucial due to opioid-related side effects. The utilisation of erector spinae plane block and low-dose intravenous ketamine-dexmedetomidine are widely recognised as non-opioid analgesic methodologies. The objective of this study was to conduct a randomised trial to examine the analgesic efficacy of both approaches while minimising the use of opioids. **Methods:** Seventy-two female patients scheduled for unilateral modified radical mastectomy were recruited. They were allocated randomly to Group ESPB, which received ipsilateral ultrasound-guided erector spinae plane block by 20 mL bupivacaine 0.5% at the level of T5 after induction of general anaesthesia, and Group Ket-Dex, which received intravenous (IV) bolus 0.25 mg/kg of ketamine and 0.5 μg/kg of dexmedetomidine, followed by an IV infusion of 0.25 mg/kg of ketamine and 0.3 μg/kg of dexmedetomidine per hour. Total postoperative morphine consumption (24 h) was the primary outcome. The secondary outcomes were pain scores over 24 hours during rest, duration of analgesia, isoflurane consumption, time to awakening, postoperative nausea and vomiting (PONV), and postoperative serum cortisol level. **Results:** The postoperative morphine consumption over 24-hour in Group ESPB was 3.26 mg (0–6.74) versus 2.35 mg (2.08–4.88) in Group Ket-Dex (P = 0.046). Group Ket-Dex had lower pain scores at rest, longer analgesia duration, longer awakening time, and lower postoperative serum cortisol levels. **Conclusion:** Intravenous low-dose ketamine-dexmedetomidine infusion intraoperatively with inhalational-based general anaesthesia provides superior opioid-sparing analgesia to that of ESPB in patients undergoing unilateral non-reconstructive modified radical mastectomy, with less postoperative opioid consumption and stress response.

Keywords: Analgesics, dexmedetomidine, ketamine, lidocaine, mastectomy, modified radical, nerve block, non-narcotic, opioid, opioid sparing

INTRODUCTION

Modified radical mastectomy is a common surgery that is followed by moderate-to-severe pain.[1] This pain should be adequately managed to attenuate stress response and decrease the incidence of chronic pain.[2] Opioids are known to produce nausea, vomiting, respiratory depression, and ileus. Furthermore, recent literature suggests that opioids may negatively impact outcomes following cancer

How to cite this article: Mohasseb AM, Elebiedy MG, Mohammed MN. A randomised comparative study of erector spinae plane block versus low-dose ketamine-dexmedetomidine intravenous infusion as intraoperative opioid-free analgesia for modified radical mastectomy. Indian J Anaesth 2024;68:651-7.

surgery.[3] Therefore, it is better to have opioid-free analgesia during the perioperative care of cancer patients. It is a technique where opioids are avoided during surgery in association with enhanced recovery without compromising patient comfort.[4]

Erector spinae plane block (ESPB) is an optimal analgesic technique because it is easy, effective, and safe. It involves local anaesthetic administration between the erector spinae muscle (ESM) and vertebral transverse processes (TPs), effectively blocking nociceptive transmission in ventral and dorsal spinal nerves' rami. This anatomical positioning is a clear barrier preventing the needle from advancing further.[2] Ketamine is an anaesthetic with sympathomimetic and analgesic effects, especially in subanaesthetic doses with multimodal approaches.[5] Dexmedetomidine stimulates alpha-2 receptors with sympatholytic, sedative, and analgesic properties.[6] Both combination provides analgesia and sedation with minimal side effects.[7] Intravenous (IV) lidocaine has analgesic, antihyperalgesic, antiinflammatory, and haemodynamic stabilising effects.[8] The objective is to compare the analgesic efficacy of locoregional and intravenous non-opioid analgesics as two different modalities of multimodal opioid-free anaesthesia for modified radical mastectomy.

METHODS

This research was performed from 1 June 2022 to 30 April 2023 after ethical approval of the institutional research board (vide approval code R.22.07.1762, dated 16 August 2022). The trial was registered in the Pan African Clinical Trial Registry (vide registration code PACTR202209505436358). The study was carried out using the principles of the Declaration of Helsinki, 2013, and good clinical practice. Eighty patients scheduled for modified radical mastectomy were screened, and those willing to participate were recruited and consented to the statement that written informed consent was obtained for participation in the study and the use of the patient data for research and educational purposes. Inclusion criteria were female gender, aged between 20 and 60 years, and American Society of Anesthesiologists (ASA) physical status I–II. Exclusion criteria were mental illness, drug abuse, patient refusal, local infection, coagulopathy, bilateral mastectomy, or additional surgical reconstructive procedures.

Seventy-two patients were included in the study and assigned to two groups of equal size using a computer-generated random number. The group allocation process involved using sequentially numbered, sealed opaque envelopes, which the lead investigator opened. The allocation of patients to their respective groups occurred exclusively upon their transfer to the preanaesthesia room. The study group was concealed from the patient and the outcome assessor to ensure blinding. The participants were randomised to Group ESPB (n = 36), which had ipsilateral ultrasound-guided ESPB using a 20 mL solution of bupivacaine 0.5%, and Group Ket-Dex (n = 36), which received a gradual IV loading dose of 0.25 mg/kg of ketamine and 0.5 μg/kg of dexmedetomidine, followed by an IV infusion of 0.25 mg/kg of ketamine and 0.3 μg/kg of dexmedetomidine per hour via two syringe pumps.

An IV cannula and standard monitoring, including electrocardiogram, non-invasive blood pressure, and peripheral oxygen saturation, were settled in the preanaesthetic room. IV antibiotic prophylaxis (3 g sulbactam-ampicillin) was given after a negative intradermal hypersensitivity test. Subsequently, in the operating room, following the acquisition of standard monitors and preoxygenation, general anaesthesia was initiated through the IV administration of lidocaine 1 mg/kg, IV propofol 2 mg/kg, and IV atracurium 0.5 mg/kg for endotracheal intubation. The maintenance of general anaesthesia was first achieved through the inhalation of isoflurane (1%–2%) in a combination of oxygen 40% and air 60% at a flow rate of 3 L/min to maintain haemodynamics within a tolerance of ±20% relative to the baseline values. The haemodynamic stress response to either intubation or surgical stimulation was controlled by increasing the depth of inhalational anaesthesia (isoflurane 3%–4%) and incremental IV propranolol (1 mg). When necessary, the surgeon was asked to stop surgical manipulation till control.

For Group ESPB, patients were turned laterally with the operative side upward. Under aseptic precautions, an experienced anaesthesiologist performed the block under ultrasound guidance. The spine of T5 was identified by counting down from the spine of C7. Then, a linear probe (3–15 MHz) (Mindray ultrasound machine, Shenzhen Biomedical Electronics, China) was placed in the long axis lateral to the T5 spinous process with lateral scanning searching for the T5 TP. The anechoic shadow of the TP with three muscles (trapezius, rhomboid major, and ESM, from outside inwards) was identified. Quincke spinal

needle (18 G) was inserted in the plane in a craniocaudal direction till it contacted the TP deep to the ESM. After injecting 5 mL of normal saline to confirm needle position, 20 mL of 0.5% bupivacaine was injected, with a frequent aspiration to exclude vascular puncture, visualising the linear hydro-dissection between the ESM and anechoic shadows of TPs.[1]

Group Ket-Dex was given a gradual IV loading dose of 0.25 mg/kg ketamine and 0.5 μg/kg dexmedetomidine, followed by an IV infusion of 0.25 mg/kg ketamine and 0.3 μg/kg dexmedetomidine per hour via two syringe pumps.[9] Thirty minutes before the end of the procedure, infusions were stopped as the skin was closed.

Unintentional occurrences such as bradycardia, hypotension, or hypoxemia were tracked and treated. Bradycardia was defined as heart rate (HR) below 50 bpm and treated with IV atropine 0.01 mg/kg. Hypotension was defined as mean arterial blood pressure (MBP) below 60 mmHg and treated with IV 5 mg ephedrine increments. Hypoxemia was defined as oxygen saturation (SpO_2 < 94% and treated with lung recruitment and increasing inspired oxygen fraction.

At the end of the procedure, the administration of isoflurane was ceased, and the amount consumed was documented. Isoflurane consumption was measured by an anaesthetic gas analyser (GE Healthcare, Finland OY). The residual neuromuscular blockade was reversed with IV neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. Subsequently, after tracheal extubation, the patient was shifted to the PACU. The time to awakening was noted as the duration between the completion of surgery and the occurrence of eye-opening spontaneously or in response to a spoken order. Once the Aldrete score reached 10, venous blood samples were collected to measure the serum cortisol level.[10] Then, the patients were transferred to the surgical ward.

Pain scores were assessed by a numerical rating scale (NRS) at rest (0 for no pain and 100 for the worst pain imaginable), starting from regaining full consciousness, then after 2, 4, 6, 12, and 24 hours postoperatively. Once the pain score was ≥40, the duration of analgesia was recorded, and morphine rescue analgesia was given. It was IV morphine (1 mg/mL) at a dose of 0.05 mg/kg lean body weight till a maximum of 4 mg per dose to be repeated if the pain score persisted to be ≥40. The postoperative analgesia regimen included IV ketorolac 30 mg/12 h and 1 g paracetamol/8 h.

The primary outcome was total postoperative 24-hour morphine consumption. The secondary outcomes were pain scores during rest assessed by NRS at 0-, 2-, 4-, 6-, 12-, and 24-hour postoperative time points, isoflurane consumption, duration of analgesia, and time to awakening. In addition, postoperative nausea and vomiting (PONV) severity was assessed by a 4-point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) at 30-minute, 1-hour, and 24-hour postoperative time points. When vomiting occurred or nausea became moderate or severe, IV metoclopramide (10 mg) was given. In addition, postoperative serum cortisol levels were detected. Any adverse events were recorded.

The sample size was determined using the PASS software version 2021 for Windows, based on data from a pilot trial involving 12 patients. The primary outcome was the total morphine consumption 24 hours following the surgery. The null hypothesis revealed that there was no difference in total morphine consumption between treatment modes. No previous research has compared both modalities in terms of post-procedure total morphine use, as far as we know. The pilot study found that the total morphine consumption following the surgery was 2.2 (1.28) mg for Group ESPB and 3.4 (1.31) mg for Group Ket-Dex. A sample size of 32 patients in each group was required with 95% statistical power using a two-sided, two-sample *t*-test with a significance level of 5%. Thus, 36 patients needed to be enrolled in each group, accounting for a 10% drop-out rate.

The data were analysed using Statistical Package for the Social Sciences (SPSS) software, version 25 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Qualitative measures, such as numbers and percentages, were employed to depict the characteristics of the qualitative data, including ASA physical status, comorbidities, and severity of PONV. Descriptive statistics such as the median (25,75 quartiles) were employed to define quantitative data that do not follow a normal distribution, including morphine consumption, pain scores, isoflurane consumption, duration of analgesia, time to awakening, and awakening serum cortisol level. To define those that follow a normal distribution, including age and BMI, the mean (standard deviation) was used. The

Kolmogorov-Smirnov test determined the normality of distribution. The qualitative data, including the severity of PONV, were compared using Monte Carlo. The Mann-Whitney U test was utilised to compare non-normally distributed data, including morphine consumption, pain scores, isoflurane consumption, duration of analgesia, time to awakening, and awakening serum cortisol level. The statistical significance of the results was evaluated at the level of $P < 0.05$.

RESULTS

After the assessment of eligibility for 80 patients, eight patients were excluded because they did not meet the inclusion criteria. Therefore, 72 patients were included and analysed: Group ESPB (n = 36) and Group Ket-Dex (n = 36). No case was lost to follow-up [Figure 1].

Demographic data were comparable in the two studied groups [Table 1]. Group ESPB exhibited a statistically significant increase in postoperative 24-hour morphine use ($P = 0.046$) [Table 2]. Furthermore, data showed a statistically significant increase in pain scores at rest in Group ESPB across all time points except awakening ($P = 0.087$). Group ESPB exhibited a statistically significant increase in isoflurane intake ($P = 0.016$), a decrease in the duration of analgesia ($P < 0.001$), and a decrease in the time to awakening ($P = 0.024$). There was no statistically significant distinction between the two groups regarding PONV at any given time. Moreover, Group ESPB exhibited a statistically significant increase in postoperative blood cortisol levels ($P = 0.003$).

DISCUSSION

In this randomised, double-blinded, comparative study, we observed that Group ESPB had inferior analgesic properties to Group Ket-Dex in terms of more postoperative morphine consumption, higher pain scores, and shorter duration of analgesia.

Our results agreed somewhat with those of Leong *et al.*,[11] who found that ESPB was similar to paravertebral block but inferior to pectoralis nerve block. The sensory nerve supply of the mastectomy surgical site can explain this. It includes the supraclavicular nerve, T3–T5 intercostal nerves,

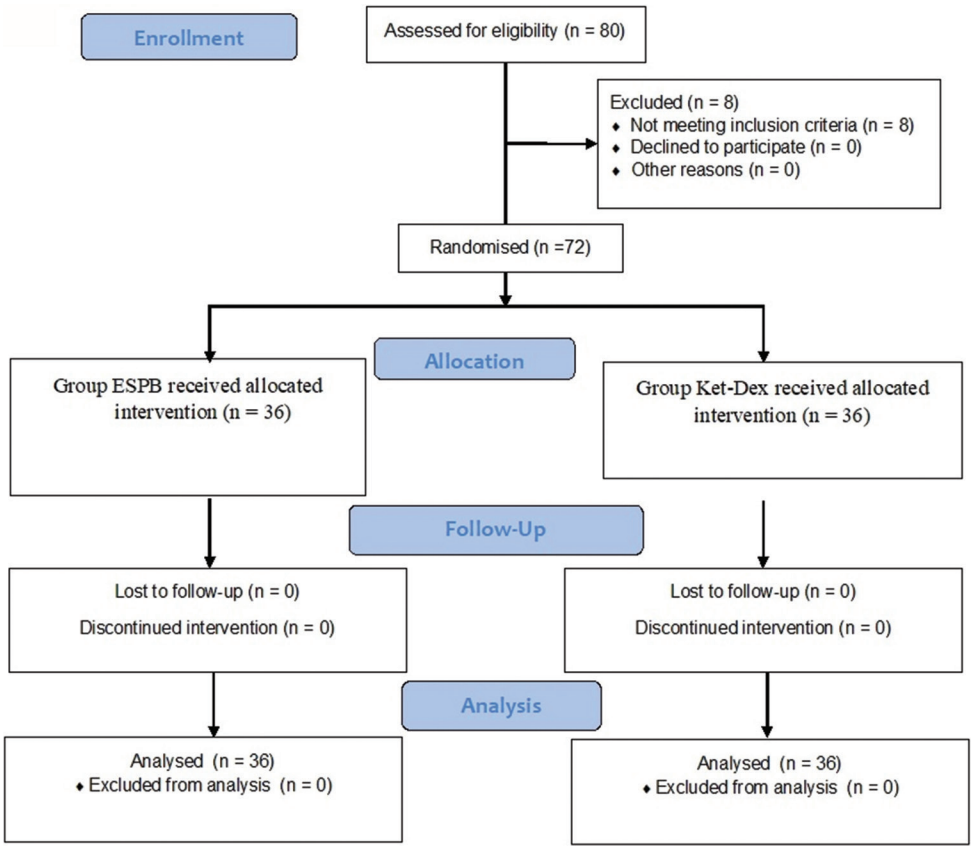

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow chart depicting trial phases

intercostobrachial nerve, pectoral nerves, and the postganglionic fibres from the cervical and thoracic ganglia. The ESPB likely covers only the intercostal nerves.[11]

Patients in Group ESPB sought rescue analgesia immediately after recovery. In contrast, patients in Group Ket-Dex showed a slowly rising trend in pain intensity during the first 2 postoperative hours, reflecting the waning of their systemic effects due to elimination, whose half-life is approximately 2 hours for both drugs.[6,12] Therefore, morphine consumption was significantly higher in group ESPB as they required two doses of morphine rescue analgesia during the first 2 postoperative hours in comparison to only a single dose for Group Ket-Dex.

Table 1: Demographic characteristics

	Group ESPB (*n*=36)	Group Ket-Dex (*n*=36)
Age (years), mean (SD)	48.42 (6.81)	49.56 (8.75)
BMI (kg/m^2), mean (SD)	35.53 (6.39)	34.03 (5.84)
ASA: I/II, *n*	12/24	18/18
Diabetes Mellitus, *n*	3	9
Hypertension, *n*	7	6

Data expressed as mean (standard deviation), or number. BMI=Body mass index; ASA=American Society of Anesthesiologists, SD=Standard deviation, *n*=Number of patients

Pain scores in Group ESPB expressed severe burning pain, especially in the axilla and, to some extent, in the surgical site; meanwhile, Group Ket-Dex expressed less severe pain with a more delayed onset. Lower pain scores in Group Ket-Dex can be explained by the analgesic and anti-inflammatory properties of ketamine and dexmedetomidine, as inflammation is one of the leading causes of postoperative pain and hyperalgesia.[13,14] Subsequently, Group Ket-Dex had a longer duration of analgesia.

Isoflurane consumption was significantly higher in Group ESPB because we had to increase the depth of inhalational anaesthesia by increasing the inspired fraction of isoflurane to control the haemodynamic response to intubation and surgical manipulation. In contrast, we did not do so in Group Ket-Dex due to the additive effects of both drugs, stress attenuating and systemic analgesic effects. This agrees with Shah SB *et al*.,[15] who noted their propofol-sparing effect. In addition, the time to awakening was significantly shorter in Group ESPB than in Group Ket-Dex due to the sedative effects of both drugs. This agrees with Alshaimaa AF *et al*.,[4] who noted shorter extubation time in the locoregional group.

Table 2: Comparison of outcomes among the studied groups

Outcome	Group ESPB (*n*=36)	Group Ket-Dex (*n*=36)	Test of significance	Mean difference (95% CI)
Morphine consumption (mg)	3.26 (0–6.74)	2.35 (2.08–4.88)	*Z*=1.99, *P*=0.046	0.72 (0.029, 1.43)
NRS 0	80 (0–80)	50 (0–80)	*Z*=1.71, *P*=0.087	14.3 (0.200, 28.41)
NRS 2	40 (10–50)	10 (0–50)	*Z*=1.98, *P*=0.048	10.82 (2.27, 19.38)
NRS 4	10 (0–20)	0 (0–20)	*Z*=5.49, *P*<0.001	9.58 (6.60, 12.56)
NRS 6	10 (0–20)	0 (0–70)	*Z*=3.80, *P*<0.001	1.81 (−5.95, 9.57)
NRS 12	10 (0–20)	0 (0–50)	*Z*=3.06, *P*=0.002	2.92 (−2.54, 8.38)
NRS 24	10 (0–30)	0 (0–20)	*Z*=3.21, *P*=0.001	6.53 (2.51, 10.55)
Isoflurane consumption (mL)	10.7 (6–23)	9 (6.2–17.5)	*Z*=2.46, *P*=0.016	2.7 (0.515, 4.90)
Duration of analgesia (hours)	0.0	1.25 (0.35–2.0)	*Z*=10.39, *P*<0.001	−1.22 (−1.46, −0.988)
Time to awakening (hours)	8 (4–25)	12 (5–26)	*Z*=2.26, *P*=0.024	−2.99 (−6.13, 0.134)
PONV 0.5 h				
None	24	25	MC=3.24	-
Mild	3	4	*P*=0.356	
Moderate	3	0		
Severe	6	7		
PONV 1 h				
None	27	25	MC=4.55	-
Mild	3	0	*P*=0.103	
Moderate	0	0		
Severe	6	11		
PONV 24 h				
None	36	36	*P*=1.0	-
Awakening Serum cortisol (µg/dL)	27.6 (12.9–34.2)	23.1 (14.3–28.5)	*Z*=2.94, *P*=0.003	3.38 (0.986, 5.79)

Morphine consumption, NRS, isoflurane consumption, duration of analgesia, time to awakening, and awakening serum cortisol level are shown as median (25,75 quartiles), while PONV is shown as number. NRS=Numerical rating score at rest; PONV=Postoperative nausea and vomiting; *Z*=Mann Whitney *U*-test; MC=Monte Carlo test; 95% CI=95% confidence interval, *n*=Number of patients

Postoperative morphine was limited to the first 2 hours in the PACU, while postoperative analgesia was maintained by multimodal non-opioid analgesics, which protected the patients in both groups from extra doses of morphine and its nauseating effect. This agrees with Shah SB *et al*.,[15] who observed the protective effect of opioid-free anaesthesia against PONV in modified radical mastectomy.

Postoperative serum cortisol level provided an objective indicator for stress response to surgery. In Group ESPB, it was significantly higher than in Group Ket-Dex due to the attenuating effect of both drugs on the perioperative stress response.[7,14] The importance of this finding is that surgical stress, together with opioid consumption, is associated with immunosuppression and cancer progression.[16]

None of our patients developed any complication related to either the ESPB or IV infusion, such as neurotoxicity, systemic toxicity, hypoxemia, bradycardia, xerostomia, hypersalivation, or hallucination, confirming the safety of both techniques and the symbiotic relationship between dexmedetomidine and ketamine. However, Group Ket-Dex experienced hypotension by the end of surgery and the start of skin closure. Ephedrine was given to raise blood pressure and detect bleeding spots and haemostasis.

In this study, we compared two safe opioid-free anaesthetic techniques for common surgery in fragile cancer patients where acute postoperative pain control and immunocompetence are crucial. Aiming to determine the optimal technique, we used bupivacaine at a concentration of 0.5% to exclude the negative effect of lower concentrations on the analgesic efficacy of the block. Moreover, we used low infusion doses for ketamine and dexmedetomidine, which potentiated their desired effects and offset the undesired ones. We sought a uniform delivery of other drugs out of the spot of comparison in both groups. On the contrary, the limitation was the possibility that bupivacaine needed more contact time to intensify the block as the surgery was started within 15–20 minutes after the institution of the block.

CONCLUSION

We conclude that intravenous low-dose infusion of ketamine and dexmedetomidine intraoperatively with inhalational-based general anaesthesia provides superior pre-emptive opioid-sparing analgesia to that of ESPB in patients undergoing unilateral non-reconstructive modified radical mastectomy in association with less opioid consumption and stress response.

Study data availability

Authors confirm that De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

Acknowledgement

We acknowledge the anaesthesia residents' participation in the follow-up of the cases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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