




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)

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Purpose: Breast surgeons seek simple, safe, effective, and novel regional anesthesia techniques for postoperative analgesia. Erector spinae plane (ESP) block is a new ultrasound-guided technique. We aimed to explore the analgesic effect of adding ketamine and magnesium sulfate as adjuvants to levobupivacaine in ESP.

Patients and Methods: Sixty female patients (aged 18–60 years) with breast cancer, weighing 50–90 kg who were scheduled for modified radical mastectomy (MRM) were randomly allocated into three groups (20 patients each) to receive an ESP block with 20 mL 0.25% levobupivacaine with adjuvants according to the following groups: group C: levobupivacaine; group K: levobupivacaine + 2 mg/kg ketamine; and group M: levobupivacaine + 2 mg/kg magnesium sulfate. The block was administered preoperatively before anesthesia induction. Postoperatively, hemodynamics, visual analog scale scores, the first request for analgesia, total analgesic consumption, and side effects were observed for 48 hours.

Results: The total amount of Morphine rescue analgesia was significantly lower in groups M (7.00 ± 0.61 mg) and K (7.50 ± 0.58 mg) than in group C (14.40 ± 3.47 mg) during the first 48 h postoperatively. Nine (45%) patients in group M and 13 (65%) patients in K, compared with 20 (100%) patients in group C, requested analgesia. The time to first request of analgesia was significantly longer in groups M (30 h) and K (24 h) than in group C (7 h). No hemodynamic changes or serious side effects were observed.

Conclusion: Magnesium sulphate and ketamine seem to be both effective adjuvants to levobupivacaine in ESP blocks for postoperative analgesia in patients undergoing MRM, with slightly better analgesia provided by magnesium sulphate.

Keywords: acute pain, breast cancer, ketamine, levobupivacaine, ultrasound, modified radical mastectomy, erector spinae plane block

Introduction

Breast cancer is the most common cancer globally among women and the leading cause of death due to cancer worldwide.¹ Modified radical mastectomy (MRM) is the standard surgical procedure for these patients.² Acute pain is a major concern for most MRM patients and influences patient recovery and overall experience. If poorly treated, pain can lead to poor outcomes and patient dissatisfaction.

Therefore, understanding, assessing, and treating acute pain effectively is crucial.³

Opioid administration remains the mainstay of postoperative pain relief; however, it can have significant adverse effects.⁴ Regional analgesia may be considered superior to opioid analgesia during and after surgery for cancer.⁵ An erector spinae block (ESP) can offer effective postoperative analgesia to patients undergoing T4–5 level breast cancer

and thoracic surgery, whereas T7-level upper abdominal surgery requires complex analgesia protocols for pain management.⁶ Currently, various adjuvants, such as tramadol, morphine, fentanyl, epinephrine, and alpha-2 agonists, have been used alongside local anesthetics.⁷

Magnesium sulfate ($MgSO_4$) may be helpful as an analgesic adjuvant in regional anesthesia because it improves and prolongs the analgesic effect of local anesthetics; moreover, $MgSO_4$ alone modulates the transmission of nociceptive stimuli and pain perception by blocking the N-methyl-D-aspartate (NMDA) receptor.⁸

In addition, central, regional, and local anesthetic and analgesic properties have been reported for ketamine.⁹ Peri-incisional use of 0.3–0.5% ketamine combined with a local anesthetic in surgical wounds has been shown to enhance analgesia by a peripheral mechanism.¹⁰

Our aim was to find out how effective is and compare the use of ketamine and $MgSO_4$ as adjuvants to levobupivacaine using ultrasound-guided ESP in patients undergoing MRM.

Patients and Methods

Enrollment and Eligibility

This randomized prospective double-blinded clinical trial was based on a thesis titled: “Efficacy and safety of ketamine versus magnesium sulphate as adjuvants to levobupivacaine in Ultrasound (US) bilevel erector spinae block in breast cancer surgery” submitted for fulfillment of master’s degree in Anesthesia. The study was obtained by the Institutional Medical Ethics Committee, Faculty of Medicine, Assiut University, on 15 June 2020 (IRB no. 17101099), and was recorded on the Egyptian Universities Libraries Consortium (<http://www.eulc.edu.eg>).¹¹ It was prospectively registered at www.clinicaltrials.gov under No: NCT04275661, and strictly followed the regulations and amendments of the Helsinki Declaration. It was conducted in patients in the surgical oncology department and postoperative anesthesia care unit (PACU). Written informed consent was obtained from 60 female American Society of Anesthesiology (ASA) I–II patients with breast cancer aged 18–60 years, weighing 50–90 kg, who were scheduled for MRM with axillary dissection. Patient enrollment commenced on August 1, 2020.

Patients were excluded from the study if they had a known allergy to the study drugs, a skin infection at the site of the needle puncture, significant organ dysfunction, coagulopathy, drug or alcohol abuse, epilepsy, or a psychiatric illness that would interfere with the perception and assessment of pain.

Randomization and Blindness

Patients were randomly allocated into one of three groups using a computer-generated randomizer program (<http://www.randomizer.org>).

Computer-generated software of randomization was used to generate a random sequences with each code enclosed in a sealed opaque envelop. An assistant who was not included in the study and had no rule in the assessment of outcomes was responsible for envelope opening. Patients were randomly allocated to one of the three studied groups;

Group C: 20 Patients (Control Group)

Patients received 20 mL of 0.25% levobupivacaine into the interfascial plane below the erector spinae muscle at the T5 and T7 levels.

Group K: 20 Patients (Ketamine Group)

Patients received 20 mL of 0.25% levobupivacaine as above + 2 mg/kg of ketamine (Ketamin[®] Sigma-Tec, Egypt).

Group M: 20 Patients ($MgSO_4$ Group)

Patients received 20 mL of 0.25% levobupivacaine as above + 2 mg/kg of $MgSO_4$

All clinical staff, including surgeons, anesthetists, ICU-trained nurses, investigators, and observers, and patients were blinded to the treatment group assignment.

Preoperative Protocol

Before the surgery, all patients were instructed on how to evaluate their acute postoperative pain using the visual analog scale (VAS), which was scored from 0 to 10, where 0 = no pain and 10 = the worst pain imaginable. All patients were also instructed on how to use the patient-controlled analgesia (PCA) device. Premedication in the form of midazolam oral tablet (1mg tab.) was given the night before surgery.

Anesthetic Procedure

Standard monitoring (noninvasive blood pressure, pulse oximetry, electrocardiography ECG, and capnography) was applied, and an intravenous cannula was placed and secured onto the side opposite the surgery site.

The ultrasound (US)-guided ESP block was provided while the patient was in a seated position according to the surgical site (right or left). Using a high-frequency linear US transducer, a probe was placed in the longitudinal orientation lateral to the thoracic fifth and seventh spinous processes, then the trapezius, rhomboid major, and erector spinae muscles were identified from the surface, and 20 mL of 0.25% levobupivacaine was injected into the interfascial plane below the erector spinae muscle.

General anesthesia was induced with intravenous fentanyl 2 µg/kg, propofol 1–2 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by atracurium 0.5 mg/kg and was maintained with isoflurane 1.5–1.7 minial alveolar concentration MAC in 50% oxygen/air mixture, atracurium in 0.1 mg/kg increments, and controlled ventilation using ventilation parameters to maintain normocapnia (35–45 mmHg). Intravenous fluids were administered. All patients received 1 g of paracetamol half an hour before wound closure. At skin closure, the neuromuscular block was antagonized by neostigmine 50 µg/kg and atropine 20 µg/kg. Patients were extubated and transferred to the post-anesthesia care unit (PACU).

Post-Operative Monitoring

In the PACU, heart rate (HR), mean blood pressure, respiratory rate, oxygen saturation, and VAS scores (R, at rest; M, during movement in the form of abduction of the ipsilateral arm) were obtained at baseline and 2, 4, 6, 12, 24, 36, and 48 h postoperatively to evaluate acute pain.

If the VAS score was ≥ 3 , rescue postoperative analgesia in the form of PCA morphine with an initial bolus of 0.1 mg/kg was administered once the patient exhibited pain, followed by a 1 mg bolus with a locked period of 15 minutes when no background infusion was permitted. The time to first request of analgesia and total analgesic consumption in the first 48 h were recorded.

Postoperative adverse effects, such as nausea, vomiting, respiratory depression, and itching, were recorded and treated.

Statistical Analysis

Power of the Study

Our primary end-point was total postoperative morphine consumption in the first 48 h. The secondary end-points were time to first request of rescue analgesia, VAS score, hemodynamic changes, and side effects (nausea, vomiting, vascular puncture, nerve injury, local anesthetic toxicity and pneumothorax).

There was no previous studies that compare the effects of ketamine to magnesium sulphate as adjuvants to local anesthetics in peripheral nerve blocks but based on other literatures that study the effect of ketamine to local anesthetics in peripheral nerve blocks and other studies for magnesium with an expected background standard deviation of 1.0, an alpha error not exceeding 0.05, and a power of 80%, we estimated that 20 patients in each group would be required. The sample size was calculated using the G*power software version 3.1.9.2,¹² and based on previous similar studies.^{13,14}

Statistical Tests

Data entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). The normality of the quantitative variables were tested with Shapiro–Wilk test. Parametric variables were presented as mean and standard deviation. Non-parametric variables were presented as median and range. Chi-square test was used to compare between

qualitative variables. Fisher's exact test was used if more than 20% of the cells have expected frequency less than five. ANOVA/post-hoc (LSD) test was used to compare quantitative variables among groups in case of parametric data. Mann–Whitney test was used to compare quantitative variables between two groups and Kruskal–Wallis test for more than two groups in case of non-parametric data. P-value considered statistically significant when $P < 0.05$.

Results

Participant Flow

Sixty female patients with breast cancer who underwent MRM were assessed for eligibility for our study. The flow chart of the study participants is provided in Figure 1.

Baseline Data

No significant differences were found among the three groups in regard to demographic and operative data (Age, weight, height, BMI, ASA, duration of surgery, and anesthesia; $p > 0.05$) (Table 1).

Primary Outcome

The mean total dose of morphine consumption was significantly lower in groups M (7.00 ± 0.61 mg) and K (7.50 ± 0.58 mg) than in group C (14.40 ± 3.47 mg; $p < 0.001$) (Table 2).

Secondary Outcomes

The time to first request was significantly longer in groups M (30.67 ± 10.58 minutes) and K (24.92 ± 10.35 minutes) than in group C (7.50 ± 1.82 minutes; $p < 0.001$). Twenty patients (100.0%) in group C requested analgesia compared with only nine (45.0%) and 13 patients (65.0%) in groups M and K, respectively, which was significantly different ($p < 0.001$). No significant differences were found between groups M and K in the number of requested patients or total morphine consumption (Table 2).

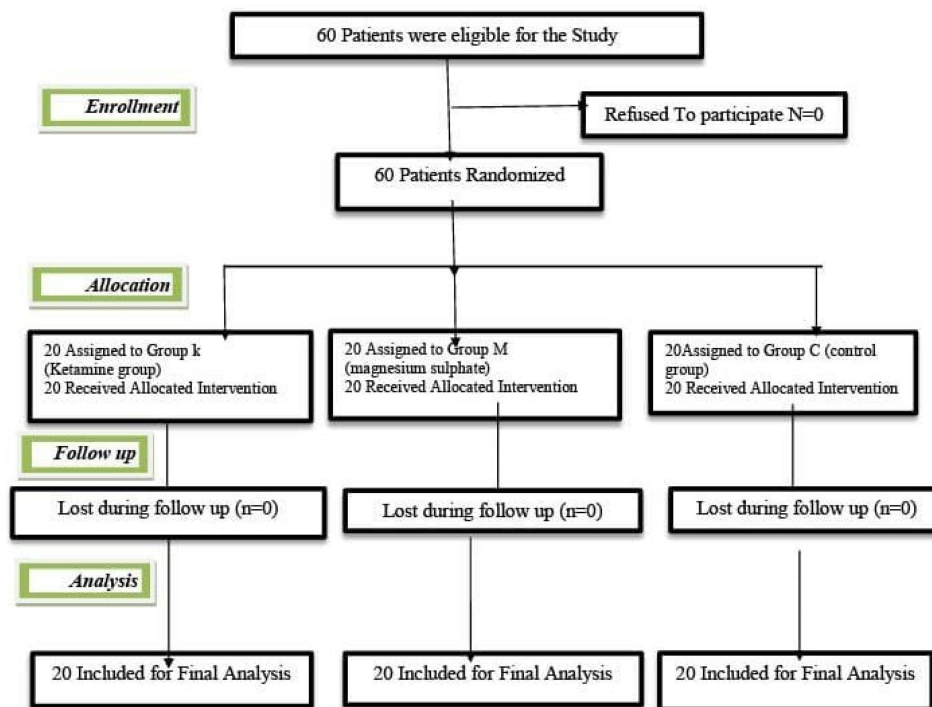


Figure 1 Participant flow chart of 60 female patients with breast cancer who underwent modified radical mastectomy were assessed for eligibility for our study. Twenty-patients in each group with no patient rolled out. Group (C): Control group (N=20) Group (M): magnesium sulphate group (N=20). Group (K): Ketamine group (N=20).

Table 1 Demographic and Clinical Data of the Three Studied Groups

Baseline data	Group C (n= 20)	Group M (n= 20)	Group K (n= 20)	P-value ¹	P-value ²	P-value ³	P-value ⁴
	Mean ± SD	Mean ± SD	Mean ± SD				
Age	46.10 ± 11.12	46.00 ± 8.04	43.10 ± 7.95	0.504	0.974	0.333	0.259
Weight (kg)	74.65 ± 8.21	71.70 ± 5.73	74.80 ± 5.30	0.248	0.196	0.946	0.084
Height (cm)	166.95 ± 2.87	168.10 ± 2.51	168.20 ± 1.67	0.198	0.136	0.106	0.896
BMI (kg/m ²)	26.82 ± 3.19	25.39 ± 2.09	26.44 ± 1.80	0.165	0.068	0.626	0.176
ASA							
I	10 (50.0%)	11 (55.0%)	9 (45.0%)	0.819	0.752	0.752	0.527
II	10 (50.0%)	9 (45.0%)	11 (55.0%)				
Side							
Right	11 (55.0%)	10 (50.0%)	10 (50.0%)	0.935	0.752	0.752	1.000
Left	9 (45.0%)	10 (50.0%)	10 (50.0%)				
Anesthesia duration (min)	105.00 ± 7.61	106.50 ± 7.45	106.50 ± 8.13	0.779	0.533	0.550	1.000
Surgery duration (min)	98.65 ± 8.07	99.75 ± 7.25	99.50 ± 8.71	0.902	0.653	0.751	0.922

Notes: Data expressed as (Mean ± SD) and number and percentage P-value is significant if <0.05. ANOVA test was used to compare quantitative variables among groups. Chi-square test was used to compare between qualitative variables. P1: P value between the three studied groups. P2: P value between C and M groups. P3: P value between C and K groups P4: P value between M and K groups.

Abbreviations: Group (C), control group; Group (M), magnesium sulphate group; Group (K), Ketamine group; ASA, American Society of Anesthesiologists.

Table 2 Number of Patients Requested Rescue Analgesia, Time of First Request of Analgesia, Total Morphine Amount Requested Among the Three Studied Groups During the Study Period (48 h)

	Group C (n= 20)	Group M (n= 20)	Group K (n= 20)	P-value ¹	P-value ²	P-value ³	P-value ⁴
	Mean ± SD	Mean ± SD	Mean ± SD				
Need for analgesia	20 (100.0%)	9 (45.0%)	13 (65.0%)	0.001*	0.000*	0.004*	0.204
First time analgesia (h)	7.50 ± 1.82	30.67 ± 10.58	24.92 ± 10.35	0.000*	0.000*	0.000*	0.089
Total morphine (mg)	14.40 ± 3.47	7.00 ± 0.61	7.50 ± 0.58	0.000*	0.000*	0.000*	0.642

Notes: Data expressed as (Mean ± SD) and number and percentage P-value is significant if <0.05. ANOVA test was used to compare quantitative variables among groups. Chi-square test was used to compare between qualitative variables. P1: P value between the three studied groups. P2: P value between C and M groups. P3: P value between C and K groups. P4: P value between M and K groups. * Significant difference between groups.

Abbreviations: Group (C), control group; Group (M), magnesium sulphate group; Group (K), Ketamine group.

The median VASR and VASM scores did not differ between group C and groups M and K at any time point except for 36 h post-surgery ($p > 0.05$). Also, when comparing M to K group at any time point (Figures 2 and 3).

For the intra-operative and postoperative hemodynamic variables, there were no significant differences among the three studied groups or between each pair of groups at any time point ($p > 0.05$).

Eight patients (40%) in group C, three patients (15%) in group M, and five patients (25%) in group K had nausea and vomiting. There were no significant differences in the number or percentage of patients that experienced nausea and vomiting among the three groups or between each pair of groups. No other serious side effects or complications were observed in any of the three groups (Table 3).

Discussion

To the best of our knowledge, no clinical trial has studied the effects of MgSO₄ or ketamine as adjuvants to local anesthetics in ESP blocks in patients undergoing MRM. We explored the effect of adding MgSO₄ or ketamine as

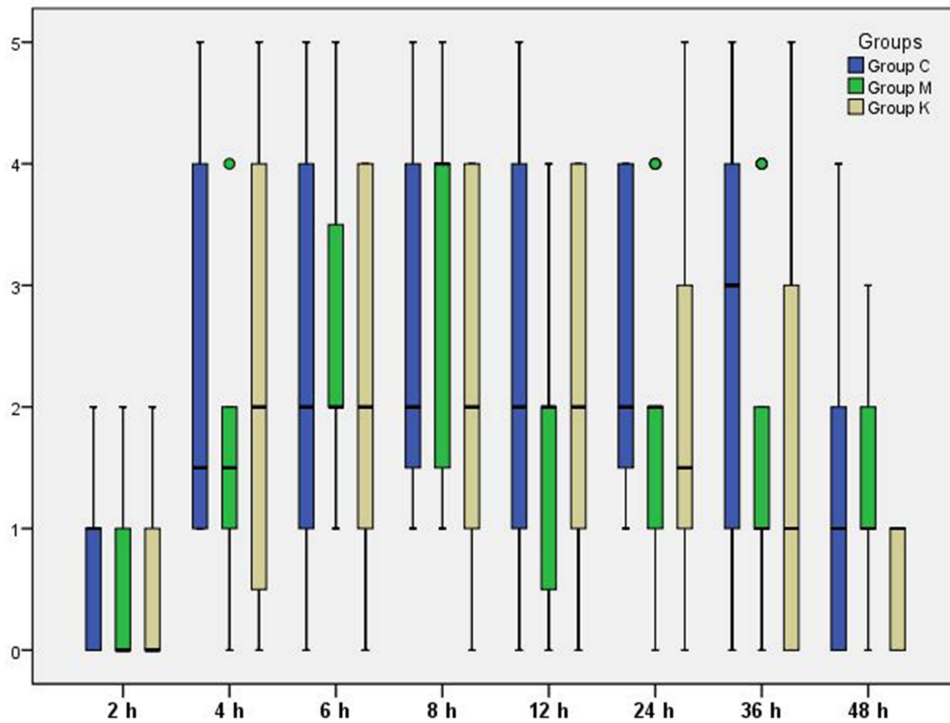


Figure 2 Visual analogue scale changes at rest (VASR) of the three studied groups during the study period (48 h). Data presented as median (range); Group (C): control group. Group (M): magnesium sulphate group. Group (K): Ketamine group. Mild outliers are marked with a circle (O) on the boxplot.

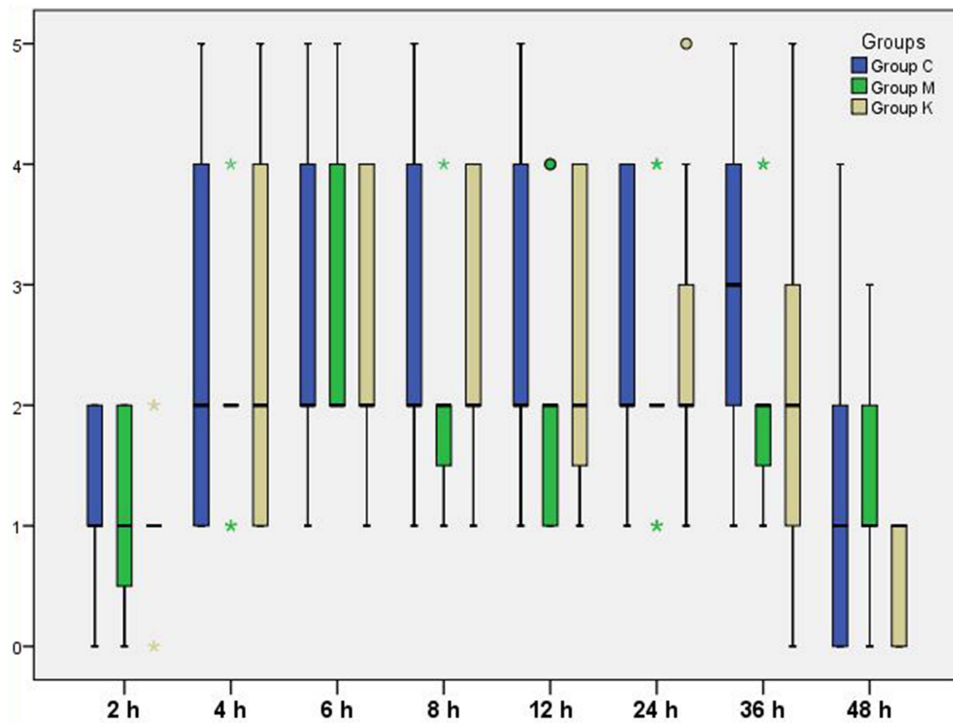


Figure 3 Visual analogue scale changes at movement (VASM) of the three studied groups during the study period (48 h). Data presented as median (range); Group (C): control group. Group (M): magnesium sulphate group. Group (K): Ketamine group. Mild outliers are marked with a circle (O) on the boxplot. Extreme outliers are marked with an asterisk (*) on the boxplot.

Table 3 Incidence of Side Effects in the Three Studied Groups

Side Effects	Group C (n= 20)	Group M (n= 20)	Group K (n= 20)	P-value ¹	P-value ²	P-value ³	P-value ⁴
	No. (%)	No. (%)	No. (%)				
Nausea	8 (40.0%)	3 (15.0%)	5 (25.0%)	0.198	0.077	0.311	0.695
Vomiting	8 (40.0%)	3 (15.0%)	5 (25.0%)	0.198	0.077	0.311	0.695
Vascular puncture	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–
Nerve injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–
LA toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–
Pneumothorax	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–

Notes: Data expressed as number (percentage). P-value is significant if <0.05. Chi-square test was used to compare between qualitative variables. Fisher's exact test was used if more than 20% of cells have expected frequency less than five. P1: P value between the three studied groups. P2: P value between C and M groups. P3: P value between C and K groups. P4: P value between M and K groups.

adjuvants to levobupivacaine in ESP blocks on acute pain for 48 h postoperatively in 60 female patients who underwent MRM.

We found that both the MgSO₄ and ketamine groups showed satisfactory pain relief without serious side effects with a prolonged time of first request of rescue analgesia and lower total morphine consumption than the control group. There were no significant differences in hemodynamic measures or side effects between groups, and the results of the MgSO₄ group were superior to those of the ketamine group. The total amount of rescue analgesia was lower in both the MgSO₄ and ketamine groups than in the control group during the first 48 h post-surgery. Moreover, nine and 13 patients in the MgSO₄ and ketamine groups, respectively, requested analgesia compared with all patients in the control group. Furthermore, the first request for analgesia was longer in the MgSO₄ (30 h) and ketamine groups (24 h) than in the control group (7 h).

An ESP block is a new US-guided technique that has been recently developed for the management of acute and chronic thoracic pain. An ESP block is a regional anesthetic technique in which a local anesthetic is injected between the erector spinae muscle and the transverse process under US guidance, blocking the dorsal and ventral rami of the thoracic and abdominal spinal nerves.¹⁵

A key advantage of an ESP block is that it is considered technically easier to perform than neuraxial, paravertebral, nerve plexus, and nerve blocks.¹⁶ In addition, an ESP block has a lower risk of serious complications because the injection is administered to the tissue plane that is distant from potentially problematic structures.

Because the duration of postoperative analgesia is often a limiting factor, various adjuvants, such as tramadol, morphine, fentanyl, epinephrine, alpha-2 agonists, dexamethasone, neostigmine, midazolam, ketamine, and sodium bicarbonate, have been used alongside local anesthetics.¹⁷ However, these drugs are often associated with numerous adverse effects, and results to date have been inconclusive.¹⁸

Central sensitization and NMDA-receptor activation by excitatory amino acid transmitters is considered the mechanism underlying postsurgical pain.¹⁹ MgSO₄, an NMDA-receptor antagonist in the central and peripheral nervous systems, has been used as an adjuvant for perioperative pain management and has been shown to decrease intraoperative and postoperative analgesic consumption.⁸ Ketamine is also a noncompetitive NMDA-receptor antagonist used for its analgesic and anesthetic effects.²⁰ And has been shown to possess central, regional, and local anesthetic properties. Recent clinical applications include its use as an adjuvant in caudal or Bier's block.²¹ Moreover, ketamine has been used for pectoral nerve, axillary, and supraclavicular blocks with inconsistent results.^{22,23} Both MgSO₄ and ketamine have been used in combination with different local anesthetics for perineural injections.

We showed that groups K and M had significantly longer mean times for the first request of analgesia than group C. Moreover, total morphine consumption was significantly lower in the K and MgSO₄ groups than in the control group. Similarly, Lashgarinia et al²⁴ found that compared with saline, ketamine decreased postoperative pain and the need for

analgesics, without significant adverse effects. Our findings are also in line with those of El-Mourad et al²⁵ who found that patients in the dexamethasone and ketamine groups had lower VAS scores than the control group, and pain scores were significantly lower in the ketamine group than in the dexamethasone and control groups. Moreover, our results are consistent with a study conducted by Yangtse et al,²⁶ who found that the addition of 2 mL of 10% MgSO₄ to local anesthetics prolonged the duration of analgesia following a peripheral nerve block.

A study conducted by Akhondzade et al²⁷ also similarly showed that postoperative VAS scores were significantly lower in the MgSO₄ group than in the control group. Our findings also agree with those of Gupta et al²⁸ who used MgSO₄ as an adjuvant to ropivacaine in SBP blocks and observed that postoperative VAS scores were significantly lower in the MgSO₄ group than in the control group.

Our results are in accordance with a study conducted by Lashgarinia et al²⁴ who found that the time of administration of the first dose of analgesia was prolonged in the ketamine group compared with the control group and that the total consumption of analgesics was lower in the ketamine group than in the control group. For MgSO₄, Mukherjee et al²⁹ similarly reported that the time to first request for analgesia in the MgSO₄ group was longer than that in the control group; moreover, rescue analgesia was administered less in the MgSO₄ group than in the control group.

We observed no significant differences in intraoperative or postoperative hemodynamics among the three groups. In line with this finding, Lashgarinia et al,²⁴ who evaluated the effect of ketamine added to lidocaine in SBP blocks for patients undergoing elective upper extremity surgery, found no significant differences in heart rate (HR) or mean arterial blood pressure (MAP). Similarly, Akhondzade et al²⁷ investigated the effect of MgSO₄ as an adjuvant for postoperative pain following upper limb surgery using an SBP block under US guidance and found that hemodynamic parameters remained stable with no significant changes in either group at any of the measurement intervals. Elyazed and Mogahed studied the effects of adding 150 mg MgSO₄ to 0.5% ropivacaine to an infraclavicular block and found a significant prolongation of both the sensorimotor block and duration of analgesia without any side effects.³⁰ In contrast, Choi et al³¹ reported no differences in the postoperative VAS score or opioid consumption between groups. The discrepancy in results may be attributed to differences in the methodology, such as the lower concentration (0.2%) and volume (20 mL) of ropivacaine and the site (brachial) and timing (postoperative) of the block.

The absence of selection bias and the blinding procedure at multiple levels are the strengths of this study. However, the study has several limitations worth recognizing. The serum levels of the drugs were not measured; thus, we could not determine whether the effects of the study drugs were due to systemic absorption or a local mechanism. Comparisons of the systemic administration of the study drugs with perineural administration may clarify this issue.

Conclusion

Magnesium sulphate and ketamine seem to be both effective adjuvants to levobupivacaine in ESP blocks for postoperative analgesia in patients undergoing MRM, with slightly better analgesia provided by magnesium sulphate.

Data Sharing Information

Raw data (de-identified) used in this clinical trial are available from the corresponding author Dr Fatma Elsherif. It will be available following publication up on reasonable request and for a period of 2 years.

Implication Statement

This is a randomized controlled clinical trial comparing bilevel erector spinae block with ketamine versus magnesium sulphate added to levobupivacaine for postoperative analgesia in breast cancer surgery. This study conforms with Helsinki Declaration.

Acknowledgments

We are grateful to the operating theatre and SICU staff for their co-operation in data collection. This work was based on a thesis titled: "Efficacy and safety of ketamine versus magnesium sulphate as adjuvants to levobupivacaine in Ultrasound (US) bilevel erector spinae block in breast cancer surgery". The study was obtained by the Institutional Medical Ethics Committee, Faculty of

Medicine, Assiut University, on 15 June 2020 (IRB no. 17101099), and was recorded on the Egyptian Universities Libraries Consortium (<http://www.eulc.edu.eg>). It was prospectively registered at www.clinicaltrials.gov No. NCT04275661.

Disclosure

The authors declare no conflicts of interest in this work.

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