Randomized Study

Efficacy and Safety of Ketamine Added to Local Anesthetic in Modified Pectoral Block for Management of Postoperative Pain in Patients Undergoing Modified Radical Mastectomy

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Background: Breast surgery is an exceedingly common procedure with an increased incidence of acute and chronic pain. Pectoral nerve block is a novel peripheral nerve block alternative to neuro-axial and paravertebral blocks for ambulatory breast surgeries.

Objectives: This study aims to compare the analgesic efficacy and safety of modified Pecs block with ketamine plus bupivacaine versus bupivacaine in patients undergoing breast cancer surgery.

Study Design: A randomized, double-blind, prospective study.

Setting: Academic medical center.

Methods: This study is registered at www.clinicaltrials.gov under number: (NCT02620371) after approval by the ethics committee of South Egypt Cancer Institute, Assuit University, Assuit, Egypt. Sixty patients aged 18 – 60 years scheduled for modified radical mastectomy were enrolled and randomly assigned into 2 groups (30 patients each):

Control group patients were given ultrasound-guided, Pecs block with 30 mL of 0.25% bupivacaine only. Ketamine group patients were given ultrasound-guided, Pecs block with 30 mL of 0.25% bupivacaine plus ketamine hydrochloride (1 mg/kg). Patients were followed up for 48 hours postoperatively for vital signs, VAS score, first request of rescue analgesia and total morphine consumption, sedation score, and side effects.

Results: Ketamine plus bupivacaine in Pecs block compared to bupivacaine alone prolonged the mean time of first request of analgesia (18.25 ± 1.98), (12.56 ± 2.64), respectively ($P < 0.001$), reduced total morphine consumption (12.50 ± 4.63), (18.86 ± 6.28), respectively ($P = 0.016$). With no significant difference in hemodynamics, respiratory rate, oxygen saturation, VAS and sedation scores, and side effects observed between the 2 groups ($P > 0.05$).

Limitations: This study is limited by its sample size.

Conclusion: The addition of ketamine to modified Pecs block prolonged the time to first request of analgesia and reduced total opioid consumption without serious side effects in patients who underwent a modified radical mastectomy.

Key words: Ketamine, bupivacaine, pecs block, postoperative, pain, breast cancer

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Breast surgery is one of the most common forms of surgery conducted in hospitals; even relatively minor breast surgery can be associated with significant postoperative pain (1). Poorly controlled postoperative pain has negative physiological and psychological consequences. Furthermore, effective acute pain control preserves immune function, both by suppressing the surgical stress response and by decreasing the need for general anesthetics and opioids. Acute postoperative pain is an integral risk factor in the development of chronic post mastectomy pain. Regional anesthesia techniques have provided better quality of acute pain control and subsequently less chronic pain (2,3).

The Pecs block aims to place local anesthetic into the interfascial plane between pectoralis major and minor muscles. A second version of the Pecs block is called modified Pecs block' or Pecs block type II. It aims at blocking the pectoral nerves, the intercostobrachial, intercostals (III, IV, V, and VI), and the long thoracic nerve. These nerves need to be blocked to provide complete analgesia during breast surgery. The Pecs II aims to block the serratus muscle area, together with the lateral branches of the intercostal nerves that exit at the level of the mid-axillary line to innervate the mammary gland and the skin from T2 to T6 (4,5).

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptors. It is used for premedication, sedation, induction, and maintenance of general anesthesia. Central, regional, and local anesthetic and analgesic properties have been reported for ketamine (6).

Ketamine decreases postoperative pain intensity up to 48 hours, decreases cumulative 24-hour morphine consumption, and delays the time to first request of rescue analgesic therapy (7,8). It also improves analgesia in cancer pain that is refractory to opioid therapy, but there is a high incidence of dysphoria and sedation (9). The specific role of ketamine in preventing opioid induced hyperalgesia (OIH) is also of interest: whether its site of action is in the spinal cord (where central sensitization involving the NMDA receptor occurs) or in higher centers does require further study (10).

In a chronic pain, low-dose intravenous (IV) ketamine seems to reduce peripheral neuropathic and spinal cord injury pain, fibromyalgia symptoms, lower limb ischemic rest pain, and chronic phantom limb pain (10). In addition, there are case reports and pilot studies suggesting beneficial effects of the S(+) isomer in complex regional pain syndromes (CRPS) (11,12).

This study aims to compare the analgesic efficacy and safety of ultrasound-guided modified Pecs block with local bupivacaine alone versus bupivacaine plus ketamine in patients undergoing breast cancer surgery.

Methods

This prospective randomized clinical trial was approved by the ethics committee of South Egypt Cancer Institute, Assuit University, Assuit, Egypt. Sixty patients aged 18 – 60 years, American Society of Anesthesiologists (ASA) class I – II, with body weight of 50 – 90 kg scheduled for modified radical mastectomy were enrolled in this study. Patients with a history of bleeding diathesis; relevant drug allergy; opioid dependence; sepsis; prior surgery in the supraclavicular, infraclavicular or axillary regions; alcohol or drug abuse;; patients with advanced cardiovascular disease; and those with psychiatric illnesses that would interfere with perception and assessment of pain were excluded from the study.

Preoperatively, patients were taught how to evaluate their own pain intensity using the Visual Analog Scale (VAS), scored from 0 – 10 (where 0 = no pain and 10 = worst pain imaginable). All patients were premedicated with 10 mg of oral diazepam on the night of surgery.

On arrival to the operating room, an intravenous line was inserted in the contralateral upper limb to the side of surgery. Monitoring included electrocardiography (ECG), non-invasive blood pressure (NIBP), arterial oxygen saturation (Sao2), and end-tidal carbon dioxide (EtCo2).

Anesthesia was induced for all participating patients with 2 µg/kg fentanyl, 2 – 3 mg/kg propofol and 1.5 mg/kg lidocaine. Endotracheal intubation was facilitated by 0.15 mg/kg cis-atracurium.

The 60 patients were randomly assigned into 2 groups (30 patients each) using a randomization-computer program.

Control group: Patients were given ultrasound-guided, modified Pecs block with 30 mL of 0.25% bupivacaine hydrochloride (Markyrene®Sigma-Tec, Egypt) divided into 10 mL injected between the 2 pectoral muscles on the interfascial plane, and 20 mL injected between the pectoralis minor and the serratus anterior muscles.

Ketamine group: Patients were given ultrasound-guided, modified Pecs block with 30 mL of 0.25% bupivacaine hydrochloride (Markyrene®Sigma-

Tec, Egypt) plus ketamine hydrochloride (1 mg/kg) (Ketamine®Sigma-Tec, Egypt) divided into 10 mL injected between the 2 pectoral muscles on the interfascial plane, and 20 mL injected between the pectoralis minor and the serratus anterior muscles.

The Pecs block was performed using a 2 needle approach instead of one while the patient was in the supine position with the ipsilateral upper limb abducted 90 degree with an 80 mm 21 G needle (Pajunk®SonoPlex Stim cannula U.S.A) using linear array ultrasound probe of high frequency (Sonosite®, Inc. U.S.A) starting from the lateral third of the clavicle and moving distally and laterally to the mid axillary line. The first needle was inserted in plane with ultrasound probe to the fascial plane between 2 pectoralis muscles and 10 mL of bupivacaine 0.25% was injected between the 2 pectoral muscles, and then the ultrasound probe was moved towards axilla until the serratus anterior was identified above the second, third, and fourth ribs then the second needle was inserted into the fascial plane between pectoralis minor and serratus anterior muscles and 20 mL of bupivacaine 0.25% was injected after negative aspiration. This breaks through the axillary door and will reach the long thoracic nerve and reliably at least 2 intercostal nerves. Skin incision was performed 15 minutes after the block was given. Anesthesia was maintained by 1 – 1.5 MAC isoflurane in 50% oxygen/air mixture and 0.03 mg/kg cisatrcurium, respectively, in ventilation parameters that maintain normocapnia.

At the end of surgery, a reversal of the muscle relaxant was done using neostigmine (0.04 mg/kg) and atropine (0.01 mg/kg). After extubation, all patients were transmitted to the post anesthesia care unit (PACU). Postoperative analgesia comprised patient controlled anesthesia (PCA) with an initial morphine bolus of 0.1 mg/kg once pain was expressed by the patient or if the VAS was ≥ 3 followed by 1 mg bolus with a lockout period of 15 minutes with no background infusion allowed.

All patients were followed up and assessed at baseline, one hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, and 48 hours postoperatively for vital signs (patients' heart rate, non-invasive arterial blood pressure, respiratory rate, and oxygen saturation), VAS score, the time to first request of rescue analgesia, and total morphine consumption in the 48 hours.

Potential side effects including sedation by sedation score of 0 – 4 (0 = patient fully awake; 1 = patient somnolent and responsive to verbal commands; 2 = patient somnolent and responsive to tactile stimulation; and 3 = patient asleep and responsive to painful stimulation; 4 = not arousable) (13), chest pain, nausea, vomiting (treated by IV bolus of metochlopromide 10 mg), and psychological complications (hallucination, delirium, dreams, nystagmus, dissociative effects) were also recorded.

Statistical Analysis

Our sample size calculations were based on data from previous work on pectoral nerve block. To detect a difference of one SD between the mean of the total amount of postoperative morphine consumption in the 24 hours of 2 study groups, it was calculated that 26 patients per group were required for the study to have a power of 80% and type I error of 0.05; using a confidence interval of 95%. We intended to recruit at least 30 per group to account for random errors, patient drop out, and additional comparisons.

Date entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean, and standard deviation. Chi-square test was used to compare between qualitative variables. Mann-Whitney test was used to compare between 2 quantitative variables in case of non-parametric data. Wilcoxon signed rank test was done to compare quantitative variables between baseline and each time in each group. *P*-value considered statistically significant when $P < 0.05$.

Results

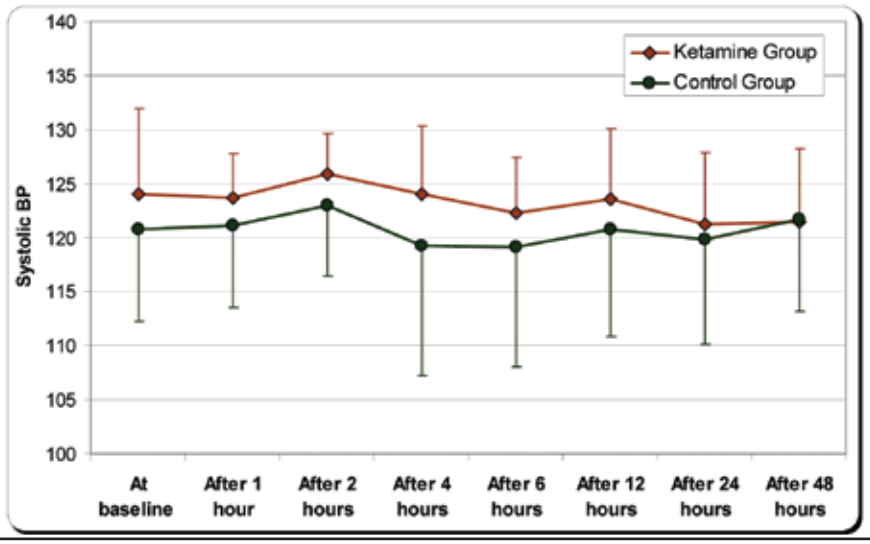
Sixty patients with breast cancer scheduled for modified radical mastectomy were recruited in this study with no patient drop out. No significant difference was found among the 2 groups regarding demographic data (age and weight), American Society of Anesthesiologists score (ASA), and duration of surgery ($P > 0.05$) (Table 1).

As regard to the mean postoperative hemodynamic variables (systolic and diastolic blood pressure and heart rate), respiratory rate, and oxygen saturation, there was no significant difference between the control and ketamine groups or within the same group comparing each time point with the baseline over the entire study period ($P > 0.05$) (Figs. 1, 2, 3, 4, and 5).

The mean postoperative VAS score values showed no statistically significant difference between the 2 groups at all time points and in the same group comparing each time point with the baseline ($P > 0.05$), but VAS values were lower in the ketamine group compared to the control group at the 12, 24, and 48 hour time points (1.20 ± 0.48, 1.18 ± 0.33, 1.17 ± 0.37) and

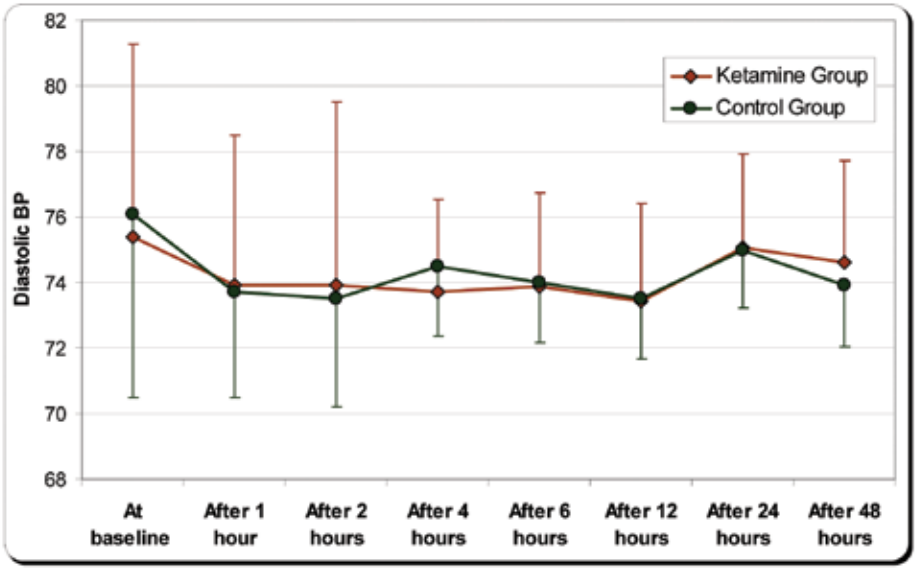
Table 1. *Demographic and clinical data.*

	Ketamine Group (n = 30)	Control Group (n = 30)	*P*-value
	Mean ± SD	Mean ± SD	
Age (yrs)	48.27 ± 8.53	45.90 ± 9.93	0.293
Weight (kg)	69.17 ± 9.42	67.50 ± 6.92	0.448
Duration of surgery (min)	92.16 ± 31.18	98.45 ± 37.22	0.491
ASA score: No. (%)			
ASA I	25 (83.3%)	22 (73.3%)	0.347
ASA II	5 (16.7%)	8 (26.7%)	



Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

Fig. 1. *Systolic blood pressure (mmHg).*



Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

Fig. 2. *Diastolic blood pressure (mmHg).*

Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

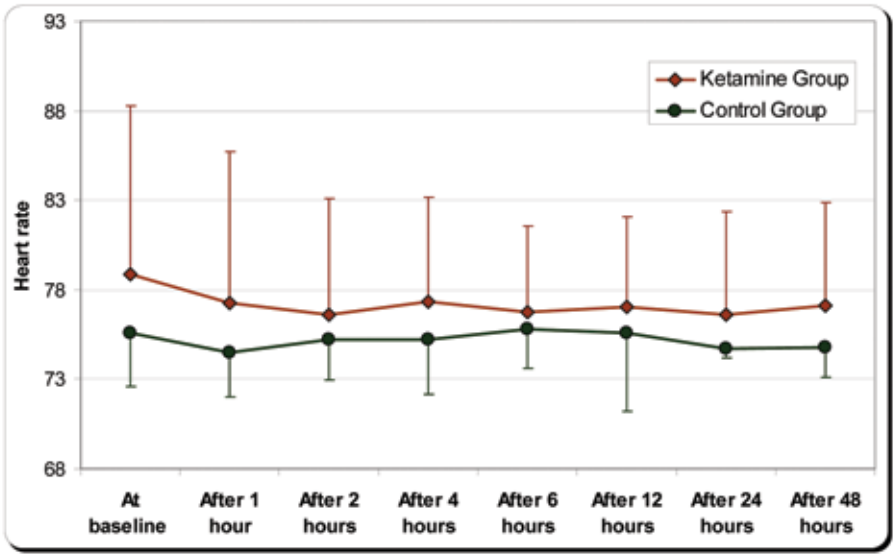


Fig. 3. *Heart rate (beat/min)*.

Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

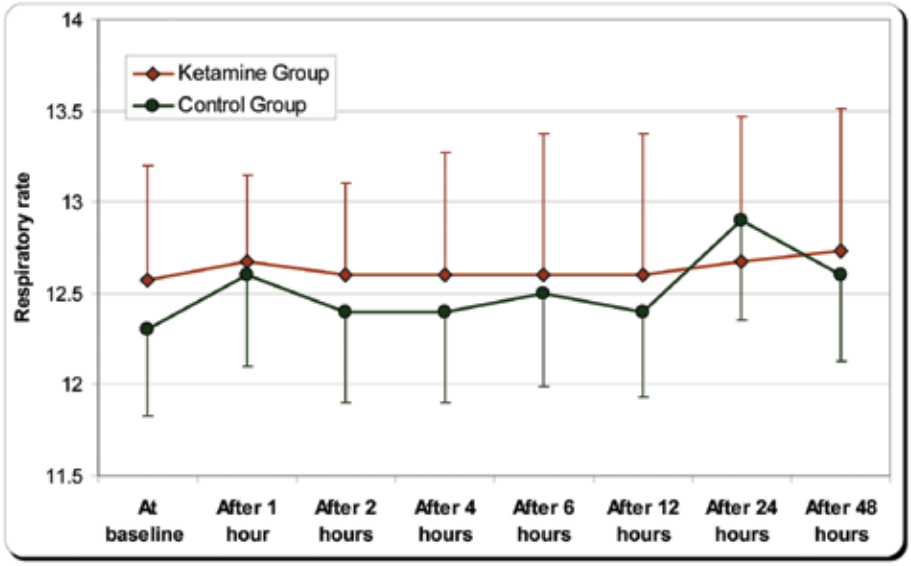
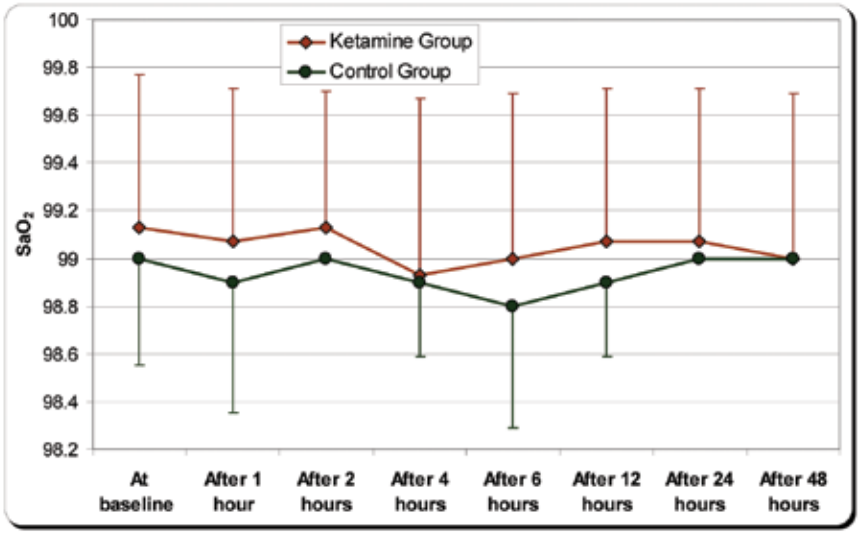


Fig. 4. *Respiratory rate (breath/min)*.

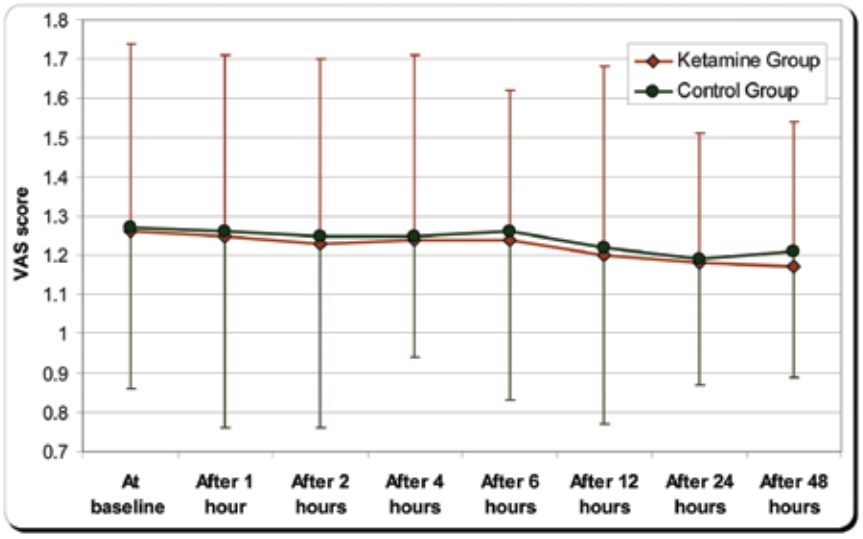
(1.22 ± 0.45, 1.19 ± 0.32, 1.21 ± 0.32), respectively, but were not statistically significant ($P > 0.05$) (Fig. 6).

Only 8 of 30 patients in the ketamine group required morphine based on the protocol of the study; in comparison, 18 of 30 patients in the control group required morphine administration to keep VAS < 3. As regard to analysis of the first request, it was prolonged in the ketamine group in comparison to the control group (18.25 ± 1.98), (12.56 ± 2.64), respectively, and the difference was found to be statistically significant ($P < 0.001$). Moreover, there was a significant decrease in the total amount of morphine consumption in the ketamine group (12.50 ± 4.63) compared to the control group (18.86 ± 6.28) ($P = 0.016$) (Table 2).



Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

Fig. 5. *Oxygen saturation (%).*



Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

Fig. 6. *VAS in the studied groups (cm).*

No significant difference in sedation score between the 2 groups was observed ($P > 0.05$). But there was a significant decrease in sedation score values in each group throughout the 48 hours of the study compared to the baseline ($P < 0.001$) (Fig. 7).

Three patients had nausea and 2 patients developed vomiting in the ketamine group with no one in the control group ($P > 0.05$). No other side effects such as chest pain, arrhythmia, and psychological complications (hallucination, delirium, dreams, nystagmus, and dissociative effects) were observed (Table 3).

Table 2. *First request analgesia and total morphine dose.*

	Ketamine Group (n = 30)	Control Group (n = 30)	*P*-value
	Mean ± SD	Mean ± SD	
First request analgesia (hr)	18.25 ± 1.98	12.56 ± 2.64	0.000*
Total morphine dose (mg)	12.50 ± 4.63	18.86 ± 6.28	0.016*

* Significant *P* value
Data expressed as (Mean ± SD).

Baseline (immediately postoperative after extubation); After 1, 2, 4, 6, 12, 24, 48 hours (postoperative).

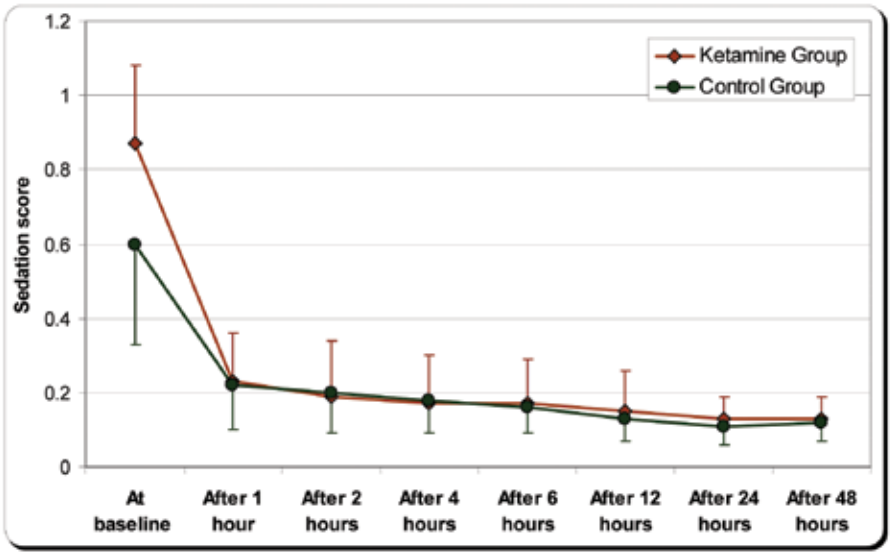


Fig. 7. *Sedation score.*

Table 3. *Side effects.*

	Ketamine Group (n = 30)		Control Group (n = 30)		*P*-value
	No.	%	No.	%	
Nausea	3	10.0	0	0.0	0.236
Vomiting	2	6.7	0	0.0	0.472
Chest pain	0	0.0	0	0.0	--
hallucination	0	0.0	0	0.0	--
Delirium	0	0.0	0	0.0	--
Arrhythmia	0	0.0	0	0.0	--
Others	0	0.0	0	0.0	--

Data expressed as number (%).

Discussion

Breast cancer is the most common cancer diagnosed in Egyptian women (14), and it is considered to be the most common in women worldwide. Several forms of regional techniques like local anesthetic infiltration (15), intercostals nerve block (16), epidural block (17), and paravertebral nerve block (PVB) have been used for management of pain after breast surgery.

To our knowledge, no previous studies have been carried out exploring the analgesic efficacy of ketamine added to local anesthetic in modified Pecs block for management of postoperative pain following modified radical mastectomy.

In our study, ketamine added to bupivacaine in modified Pecs block prolonged the time to first request of analgesia and reduced the total amount of morphine consumption in comparison to bupivacaine alone. On the other hand, no significant difference in hemodynamic variables (systolic and diastolic blood pressure and heart rate), respiratory rate, oxygen saturation, VAS and sedation scores, and side effects was observed between the 2 groups.

Pectoral nerve block is a novel interfacial block technique first described by Blanco in 2011 (18). One year later, Blanco et al (19) described a second version of the block (modified Pecs block or Pecs II), aiming to block the axilla and the intercostal nerves necessary for axillary node dissection and wider excisions. Initial technique descriptions and case series described decreased opioid utilization with the Pecs block techniques.

Recently, Bashandy and Abbas (20) found that patients receiving Pecs block showed lower postoperative pain scores at all time points (up to 24 hours) and significantly decreased opioid consumption for 12 hours in comparison to control group patients. Additionally, Wahba and Kamal (21) found that Pecs block reduced postoperative morphine consumption in the first 24 hours and pain scores in the first 12 hours postoperatively following modified radical mastectomy in comparison to PVB. This agrees with our findings, where the VAS values in both groups after receiving Pecs block were less than 3 for the whole follow-up period of 48 hours. However, in our study adding ketamine to local anesthetic in Pecs block increased the time to first request of analgesic requirement and reduced the total morphine consumption in comparison to plain Pecs block.

The addition of ketamine to a local anesthetic in peripheral or neuraxial anesthetic and analgesic techniques improves or prolongs pain relief (22,23) with a decrease in drug-related side effects (sedation, pruritus, or adverse psychological reactions) mainly because the required drug doses are reduced (24,25).These effects may be explained by blockade of central and peripheral NMDA receptors and/or an antinociceptive action complementary to that of the other drugs used.

Gantenbein et al (26), in a study conducted to address effects of ketamine on local bupivacaine activity, found that ketamine increased the total anesthetic effect of bupivacaine; they explained this by a possible inhibiting effect of ketamine on the metabolism of bupivacaine.

Other possible peripheral mechanisms of action of ketamine include binding to multiple opioid receptors (ORs) (27); binding to monoamine transporters (28); binding to muscarinic and nicotinic cholinergic receptors and inhibition of function (29); binding to D2 and 5-HT2 receptors (30); inhibition of ion channels (Na+, Ca2+, K+) (31,32); decreased activation and migration of microglia (32); and finally, inhibition of production of inflammatory mediators (33).

Many studies have so far investigated the effect of adding local ketamine to local anesthetics. For instance, Dal et al (34) showed that local injection of ketamine in children undergoing adenotonsillectomy significantly reduced pain score, dose of rescue analgesia, and increased time interval to the first dose of opiate compared to the group receiving IV normal saline. Tverskoy et al (35) used local injection of 0.5 mg/kg ketamine after herniorrhaphy to reduce pain and showed that ketamine improved the quality of anesthesia and analgesia created by local anesthetics (0.5 % bupivacaine) used in these patients.

Lashgarinia et al (36) concluded that adding ketamine in a dose of 2 mg/kg to lidocaine 5 mg/kg 1.5 % in ultrasound-guided brachial plexus block could decrease the postoperative pain and need for analgesia most probably due to the local anesthetic effect of ketamine at the level of surgical trauma.

Further, Kazemeini et al (37) found that local wound injection with 50 mg of ketamine plus 2 mL of bupivacaine 0.5% provided superior postoperative analgesia compared to bupivacaine 0.5% alone following anal surgery. Abdel-Ghaffar et al (38) concluded that 30 mg epidural ketamine reduced post hysterectomy pain, prolonged the time to first analgesia request, and reduced postoperative epidural PCA consumption.

On the contrary, multiple studies have revealed negative results. For example, 30 mg ketamine did not enhance the onset time and duration of sensory and motor blockade when added to 30 mL of 0.5% ropivacaine for interscalene brachial plexus block (39). Moreover, the addition of 1 mg/kg ketamine to 0.1% ropivacaine infusion via the femoral nerve catheter after repairing an anterior cruciate ligament (ACL) injury/tear could not improve postoperative pain control (40). In addition, Senel et al (41) compared the analgesic efficacy of 50 mg tramadol and 50 mg ketamine added

to 40 mL 0.375% ropivacaine in axillary brachial plexus block and found that tramadol extended the onset and duration of the block and improved the quality of postoperative analgesia more than did ketamine.

The variable effects of ketamine probably come from the different ketamine concentrations used in different clinical trials. In addition, it has been observed that the effect of ketamine might be different when injected at the level of inflamed tissue compared with the normal tissue site (39). Ketamine has demonstrated an anti-inflammatory effect that significantly inhibits the early postoperative inflammatory response. It can act at different levels of inflammation, interacting with inflammatory cell recruitment, cytokine production, and inflammatory mediator regulation (42,43).

The effect of ketamine is more likely to occur locally in an inflamed tissue, but not at the level of a nerve plexus distant from the surgical site (42,43). Its effects are not specific to a certain type or dose of local anesthetic agents.

We believe that our results strongly highlight the value of adding ketamine to local anesthetic in peripheral nerve block, especially in this relatively new technique of modified Pecs block, where postoperative analgesia lasted for a long period and only 8 patients requested rescue morphine in the ketamine group. We think this drug combination in Pecs block needs to be further investigated including larger number of patients, using different higher or lower doses of ketamine and local anesthetic, and extending to a long-term follow-up period to explore its effect on chronic post mastectomy pain.

Conclusion

In conclusion, the addition of ketamine to modified Pecs block prolonged the time to first request of analgesia and reduced total opioid consumption without serious side effects in patients undergoing modified radical mastectomy.

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