Effect of different doses of topical ketamine on hemodynamics in patients undergoing modified radical mastectomy

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Background
Ketamine has been administered by many routes with different adverse effects according to the selected route of administration and the given doses.
Objectives
We investigated the effect of three different doses of topical ketamine on hemodynamics and adverse effects. We aimed to find the most effective dose with the least hemodynamic derangements and minimal adverse effects.
Study design
A prospective, double-blind randomized dose finding study was conducted.
Setting
The study was done at the Cancer Institute.
Patients and methods
Patients scheduled for modified radical mastectomy were enrolled into three groups (n=30) to receive ketamine hydrochloride topical instillation. The study drug was diluted by 20-ml normal saline (0.9%) and instilled before wound closure by anesthesia assistant as follows: groups A, B, and C: in which patients received 1 mg, 2 mg, and 3 mg/kg ketamine, respectively. Hemodynamic assessments included the mean arterial blood pressure, heart rate, and respiratory rate recorded at baseline and 2, 4, 6, 12, 24, 36, and 48 h postoperatively.
Results
Intergroup comparison showed that the three doses of ketamine instillation (1, 2, and 3 mg/kg), showed no difference in the mean arterial blood pressure, either in the heart rate or respiratory rate at any time point during the study (P>0.05). Five patients versus 2 and 4 experienced postoperative nausea and two patients versus 6 and 6 vomited in groups A, B, and C, respectively.
Limitations
Small sample size was a limitation.
Conclusion
Topical instillation of ketamine in patients undergoing modified radical mastectomy is a safe technique. The three doses investigated were comparable regarding the hemodynamics with no significant adverse effects.

Keywords:
breast cancer, hemodynamics, instillation, ketamine, modified radical mastectomy

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Introduction

Breast cancer is one of the most serious and leading causes of death among women. It has high incidence, with a 5-year survival reaching 90% of women diagnosed with breast cancer in developed countries. Younger women are considered at high risk in comparison with older age groups despite the early detection and treatment of diagnosed cases [1].

The incidence of new cases with invasive breast cancer in the USA reached approximately 11 000 women annually with age less than 40 years, representing 4.7–4.9% of all patients diagnosed with breast cancer [2–4]. The stage and type of the tumor is considered the main guide for wise surgical management, so either lumpectomy or surgical removal of the entire breast is performed. Standard practice states that clear margins should be obtained from the tissue removed during surgery to ensure complete excision of the tumor [2–4].

Good management of postoperative pain within the first 72 h hastens the recovery and hospital discharge and decreases the risk of chronic pain afterward [5]. Opioids are considered the mainstay of postoperative pain relief. However, opioids have significant adverse

effects like sedation, nausea, vomiting, bradycardia, urinary retention, respiratory depression, and prolonged postoperative ileus [6].

Ketamine is an anesthetic and analgesic drug. Its mechanism of action is through a noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptors. Ketamine has been administered through many routes such as intravenous, intramuscular, oral, rectal, nasal, epidural, or intrathecal.

Ketamine used in parenteral routes is known to cause systemic effects as tachycardia, hypertension, increased intraocular tension, and hallucination [7]. Local ketamine instillation in surgical wounds may provide effective postoperative analgesia, reduce postoperative opioid consumption, and reduce adverse effects of systemic ketamine and opioids [8].

Aim

We hypothesized that topical ketamine is associated with less hemodynamic changes and adverse effects compared with systemic ketamine. We aimed to find the most effective dose of topical ketamine instillation with the least hemodynamic derangements and minimal adverse effects.

Patients and methods

Ninety female patients, who were scheduled for modified radical mastectomy (MRM), were included in this randomized prospective double-blinded clinical trial on patients with breast cancer in South Egypt Cancer Institute, Assiut University, Egypt. The study was prospectively registered at clinicaltrial.gov (identifier: NCT03165149).

Ethical consideration

An informed written consent was obtained from the patients before surgery. The participants could not be identified by name in any report or publication concerning this study. Before the participants were admitted in this study, the purpose and instructions of the study as well as the risks–benefit assessment were explained to them.

Inclusion criteria

ASA I–II patients, from 18 to 60 years, and scheduled for MRM for breast cancer were included.

Exclusion criteria

Patients allergic to ketamine or with significant systemic diseases like cardiac, respiratory, renal or hepatic disease, drug addiction or alcohol abuse, uncooperative patients, or patients with psychiatric disorders that would interfere with perception of the research instructions were excluded.

Study protocol

Oral diazepam 5 mg was given to all participants the night before surgery to decrease stress of surgery. At the operative theater, monitoring included electrocardiography, noninvasive blood pressure, and pulse oximetry. General anesthesia was started with 5 min preoperative oxygenation followed by intravenous fentanyl 2 μg/kg, lidocaine 1.5 mg/kg, and propofol 1–2 mg/kg. Muscle relaxation to facilitate endotracheal intubation was done by cisatracurium 0.15 mg/kg.

Isoflurane 1.5 MAC in 50% oxygen/air mixture and cisatracurium 0.03 mg/kg were used for maintenance of anesthesia and muscle relaxation, respectively.

Patients were randomly distributed into three groups by the online randomizer program (*http://www.randomizer.org*). Each group has 30 patients who received ketamine hydrochloride (Rotexmedica, Trittau, Germany) instillation where the drug is diluted by 20 ml normal saline (0.9%) and instilled over the wound before skin closure by a blinded physician. The suction drain was closed for 30 min after ketamine instillation in the following doses:

(1) Group A: received 1 mg/kg of ketamine.
(2) Group B: received 2 mg/kg of ketamine.
(3) Group C: received 3 mg/kg of ketamine.

After skin closure and before extubation, muscular relaxation was antagonized by neostigmine 50 μg/kg with atropine 20 μg/kg. All the patients received 1 g paracetamol (Perfalgan; Bristol Myers Squibb, Egypt) before the end of surgery; patients were then transferred to the postanesthesia care unit after extubation.

At the postanesthesia care unit, hemodynamic data such as the mean arterial pressure, heart rate, respiratory rate, oxygen saturation, and visual analog scale (VAS) at baseline, and at 2, 4, 6, 12, 24, 36, and 48 h postoperatively were recorded. Then 1-g intravenous paracetamol was given every 6 h to keep VAS less than 3; if pain was not controlled or VAS was more than or equal to 3, ketorolac 30 mg intravenous was given. All clinical staff including surgeons, anesthetists, trained nurses, investigators, observers, and the patients was masked to treatment-group assignment.

Statistical analysis

Based on previous similar studies, with an expected SD of 1.0, an alpha error less than 0.05 and power of study

of 80%, we estimated that 28 patients in each group would be required.

Data entry and analysis were done using Statistical Package for the Social Science, version 19 (An American multinational information technology company headquartered in Armonk, New York). χ^2 test was used to compare between qualitative variables. Independent samples *t* test was used to compare quantitative variables between two groups and analysis of variance test to compare three group at once in case of parametric data. Mann–Whitney test was used to compare between each two groups and Kruskal–Wallis test between three groups in case of nonparametric quantitative variables. *P* value was considered statistically significant when *P* value was less than 0.05.

Results

A total of 96 female patients with surgical decision of MRM were enrolled in this study; six of them were excluded owing to refusal (Fig. 1). Ninety patients were subjected to statistical analysis and were equally distributed in the three groups ($n = 30$). Their age ranged from 34 to 56 years and their weight ranged from 60 to 78 kg. There were no significant differences between groups in the demographic and baseline characteristics.

Regarding the mean arterial blood pressure changes postoperatively, there were no significant differences among the three studied groups when compared all together or between each two groups at any recorded time point during the study ($P > 0.05$), except when comparing between group A and group C at 6 h ($P = 0.029$) and 48 h ($P = 0.036$) postoperatively (Fig. 2).

In comparing the mean heart rate changes among the three studied groups, there were no significant differences when comparing all groups together or between each two groups, at any recorded time point during the study ($P > 0.05$), as shown in Fig. 3.

In comparing the changes in the median respiratory rate postoperatively, there were no significant differences among the three groups or when comparing between each two groups at any recorded time point during the study ($P > 0.05$), as shown in Fig. 4.

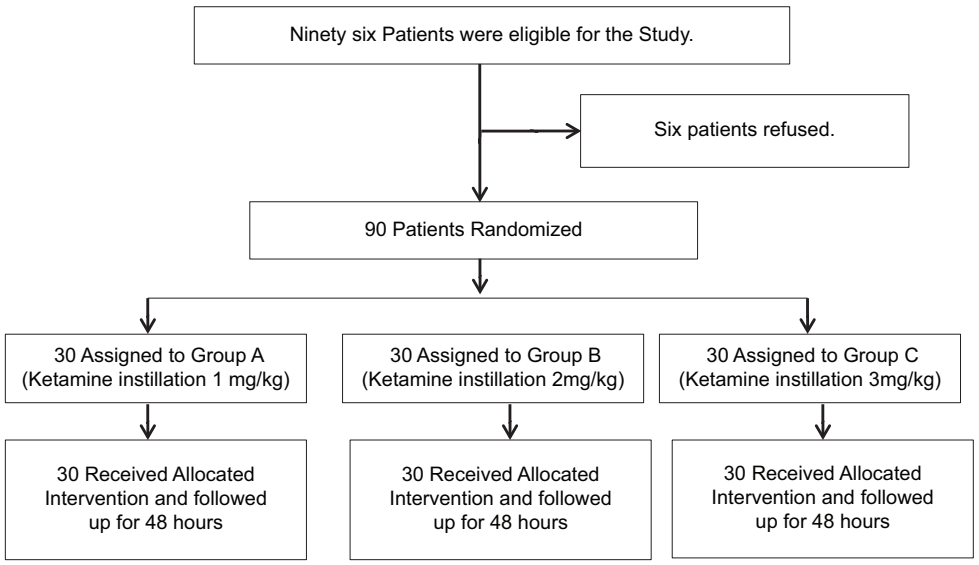
Five patients versus 2 and 4 experienced postoperative nausea and two patients versus 6 and 6 vomited in groups A, B, and C, respectively. No other adverse effects were recorded in this study, and no patient showed hallucination, delirium, nystagmus, or respiratory depression.

Discussion

Many receptors are the main site of action of peripheral ketamine usage such as multiple opioid receptors, monoamine transporters, muscarinic and nicotinic cholinergic receptors, D2 and 5-HT2 receptors, ion channels (Na+, Ca2+, K+) blockage, inhibition and migration of microglia, and finally, deactivation of inflammatory mediator production [9–14].

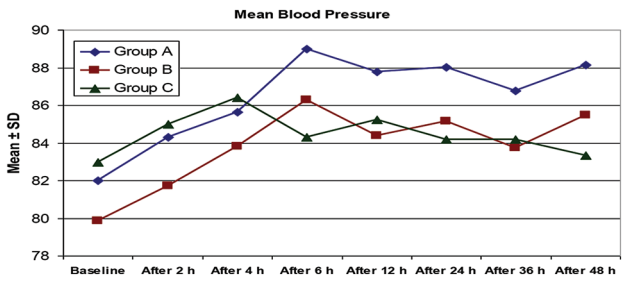
The peripheral primary afferent neurons carry NMDA receptor and ionotropic glutamate receptors in the hairy skin of humans [15]. The number of NMDA receptors is increased by inflammation on peripheral nerve fibers. Carlton and Coggeshall[16] demonstrated that inflammation increases the number of NMDA

Figure 1



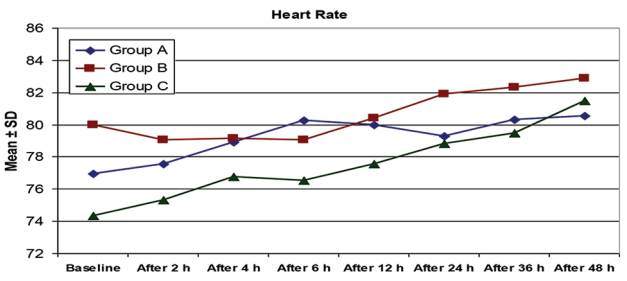
Participant flow diagram.

Figure 2



Changes in the postoperative mean arterial blood pressure with time in the three studied groups. Data are expressed as mean ± SD. Baseline: immediately postoperative. Group A, patients received 1 mg ketamine/kg; group B, patients received 2 mg ketamine/kg; and group C, patients received 3 mg ketamine/kg.

Figure 3



Changes in the mean postoperative heart rate with time in the three studied groups. Data are expressed as mean ± SD. Baseline: immediately postoperative. Group A, patients received 1 mg ketamine/kg; group B, patients received 2 mg ketamine/kg; and group C, patients received 3 mg ketamine/kg.

and non-NMDA receptors found on primary afferent axons.

In our study, minimal changes in hemodynamics were experienced after local instillation. It was found that ketamine in its local form will probably decrease the systemic absorption and consequently minimizes the adverse effects seen in other studies using ketamine either intravenous or intramuscular. Topical ketamine at 50 mg/ml was shown to elicit neither systemic nor local adverse effects, whereas intravenous ketamine showed adverse effects in hemodynamics such as tachycardia, hypertension, intraocular tension intracranial hypertension, nightmares, and hallucinations [17,18].

Othman *et al.* [19], in their study where pectoralis block with ketamine hydrochloride (1 mg/kg) was given and the patients were observed for 48 h postoperatively, concluded that there is no changes in hemodynamic variables (systolic, diastolic blood pressure, and heart rate), respiratory rate, oxygen saturation, sedation scores, and adverse effects when compared with control group. Moreover, Honarmand *et al.*[20] in their study, where the efficacy of intravenous (0.5 mg/kg) and subcutaneous infiltration of (0.5 mg/kg) ketamine was compared for postoperative pain relief after appendectomy, revealed no hemodynamic changes such as hypotension or bradycardia in the subcutaneous group.

Abd El-Rahman and El-Sherif[8] found no apparent hemodynamic changes (blood pressure and heart rate) or respiratory rate changes in the local instillation group after local ketamine instillation of 1 mg/kg in comparison with 1 mg/kg intramuscular ketamine after total thyroidectomy for the 48-h study period. Nejati *et al.*[21] found that there were no changes in the heart rate or mean arterial pressure in the two groups: one of them with intranasal ketamine (50 mg plus sterile water 2 ml added to lubricating gel) and the second with lubricating gel alone for nasogastric tube insertion.

Moreover, Kim *et al.*[22] concluded that there was a decrease in systemic adverse effects (delirium, tachycardia, hypertension, or dizziness, sedation, pruritus, or adverse psychological reactions) when they compared between ketamine by intravenous route and dexmedetomidine infusion on spinal block.

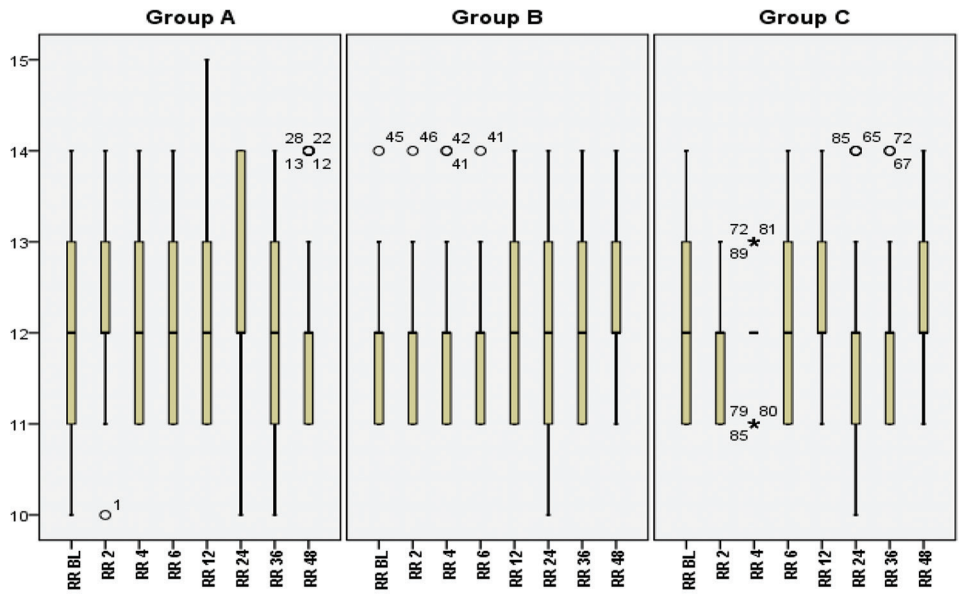
Elbaradie *et al.*[23] reported that intraperitoneal administration of ketamine 2 mg/kg for diagnostic laparoscopy elicited antinociception without undesirable central adverse effects, which occurred after systemic administration. Furthermore, a study by Javid *et al.*[24] compared the satisfaction of patients who received either subcutaneous or intravenous ketamine (0.6 mg/kg) as adjuvants to narcotics in laparoscopic peritoneal dialysis catheter implantation, and it was found that subcutaneous ketamine was effective and safer than intravenous ketamine.

As previously known, ketamine used either intravenously or intramuscularly will produce more adverse effects [24]. Mercadante and Arcuri [25] used intravenous ketamine 0.25 or 0.50 mg/kg in a trial on patients with cancer for neuropathic pain syndromes (plexopathy or spinal cord compression) management, and hallucination was found in four out of 10 patients. Buonsenso *et al.* [26] concluded that there were no serious adverse effects (such as oxygen desaturation, bradycardia, hypotension, or apnea) in their study investigating the efficacy and safety of intranasal 2 mg/kg ketamine in uncooperative children undergoing gastric aspirates. The only adverse effect registered was postsedation agitation and confusion.

Conclusion

Topical instillation of ketamine in patients undergoing MRM is a safe technique. The three doses investigated were comparable regarding the hemodynamics with no significant adverse effects.

Figure 4



Changes in the postoperative respiratory rate with time in the three studied groups. Data are expressed as median (range). Baseline: immediately postoperative. Group A, patients received 1 mg ketamine/kg; group B, patients received 2 mg ketamine/kg; and group C, patients received 3 mg ketamine/kg.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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