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Effect of Ketamine Instillation on Acute and Chronic Post Mastectomy Pain, a Dose Finding Clinical Study

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Abstract

Background: Uncontrolled acute postoperative pain is considered a risk factor for the development of chronic pain afterward. **Objectives:** To explore the most effective dose of ketamine instillation (1 of 3 doses: 1, 2, or 3 mg/kg) for acute and chronic post mastectomy pain (PMP). **Methods:** Ninety female patients with cancer breast, aged (18 - 60 yrs), weighted (50 - 90 kg), scheduled for modified radical mastectomy, randomly allocated into 3 groups to receive ketamine instillation after surgical homeostasis before wound closure (1 of 3 doses; 1, 2, or 3 mg/kg as A, B or C groups respectively) patients were followed up for 48 h for acute pain (total morphine consumption, the first request of analgesia and visual analog scale at rest and movement (VASR/M), chronic pain by Leeds assessment of neuropathic signs and symptoms (LANSS) for six-months, hemodynamics, and side effects. **Results**: Median total dose of morphine consumption was 8 mg (5 - 10) versus 6 mg (6 - 7) in A and B groups respectively in the first 48 h postoperatively. Lowest VASR/M was recorded in C then B and lastly A group ($P = 0.037$). No patients in the C group requested analgesia versus thirty (100%) and nine (30%) patients in the A and B groups respectively with the first request of analgesia was 12 h (5 - 36) in the A group versus 30 h (12 - 36) in the B group respectively ($P < 0.001$). In the three studied groups, no patients in the C group had neuropathic pain versus 2 and 9 patients in B and A groups respectively ($P \leq 0.001$) without serious side effects. **Conclusion**: Ketamine instillation effectively controlled acute post mastectomy pain (PMP) in a dose-dependent manner and reduced the incidence and severity of chronic pain in patients who undergoing a modified radical mastectomy.

Keywords

Acute Pain, Breast Cancer, Chronic Pain, Ketamine Instillation, Modified Radical Mastectomy

1. Introduction

Modified radical mastectomy (MRM) is the standard surgical procedure of choice for breast cancer patients [1]. Acute pain is a major concern for most of those patients and influences their recovery and overall experience.

Poorly controlled acute postoperative pain is considered an independent risk factor for the development of chronic pain afterward [2]. Hence, it is important to understand, assess, and treat acute pain effectively.

Chronic post mastectomy pain syndrome is a common sequel of breast cancer surgery that has been known to be present in 20% to 47% of patients [3].

Opioid administration remains the mainstay of postoperative pain relief but can result in significant adverse effects [4]. Other techniques such as paravertebral, modified pectoral nerve, and thoracic epidural blocks could be used.

However, these techniques are technically complicated and associated with complications (eg, neural damage), although rare but might be dangerous [5].

Topical application of local anesthetics or analgesic drugs into the post mastectomy wound is a simple, yet effective technique that has been recently investigated [6].

Ketamine may be used for postoperative pain management. Central, regional, local anesthetic, and analgesic properties have been reported for ketamine [7]. It also crossed through most tissue membranes, which leads to easy absorption. It also had an early onset and a short duration of action [8].

Local wound instillation with 1 mg/kg ketamine provided superior postoperative analgesia with a lower incidence of side effects in comparison with IM ketamine [9].

Because of the different sizes and sites of the wound after surgery, we hypothesized that the effect of different doses of ketamine instillation had to be explored on acute and chronic post mastectomy pain.

Our aim was to explore the most effective dose of ketamine instillation (1 of 3 doses: 1, 2, or 3 mg/kg ketamine) for acute and chronic post mastectomy pain (PMP).

2. Methods

2.1. Enrollment and Eligibility

This randomized prospective double-blinded clinical trial was conducted in South Egypt Cancer Institute, Assuit University, Egypt, after obtaining local ethical committee approval with IRB number (17100205) and written informed consent from ninety female patients with cancer breast with ASA I-II, aged 18 -

60 yrs, weighted from 50 - 90 kg and scheduled for MRM. Excluded from the study, were patients with known allergies to the studied drugs, significant cardiac, respiratory, renal, or hepatic diseases, drug or alcohol abuse, and psychiatric illness that would interfere with the perception and assessment of pain.

2.2. Randomization and Blindness

Patients were randomly allocated using an online research randomizer computer program (http://www.randomizer.org) into three groups (30 patients each) to receive three doses of ketamine hydrochloride (Ketamin Sigma-Tec, Egypt) at the end of surgery (after surgical hemostasis before wound closure) where the drug is diluted by 20 ml 0.9% saline and irrigated onto the surgical field as follow:

Group (A): Patients had received 1 mg/kg ketamine hydrochloride diluted by 20 ml 0.9% saline and irrigated onto the surgical field (Ketamin Sigma-Tec, Egypt) at the end of surgery (after surgical hemostasis before wound closure).

Group (B): Patients had received 2 mg/kg of ketamine diluted by 20 ml 0.9% saline and irrigated onto the surgical field (Ketamin Sigma-Tec, Egypt) at the end of surgery (after surgical hemostasis before wound closure).

Group (C): Patients had received 3 mg/kg of ketamine diluted by 20 ml 0.9% saline and irrigated onto the surgical field (Ketamin Sigma-Tec, Egypt) at the end of surgery (after surgical hemostasis before wound closure). Then the suction drain was closed for 30 minutes in the three groups after the studied drugs had been instilled and irrigated. The study medications were prepared in sterile color-coded syringes by a blinded hospital clinical pharmacy. All attending physicians (anesthesiologists, surgeons, and observers) and the patients were masked to the treatment group assignment (double-blinded). Randomization codes hadn't been decoded until the end of data collection for all patients.

2.3. Preoperative Protocol

All patients preoperatively were taught how to evaluate their acute pain intensity using a visual analog scale (VAS) scored from 0 to 10 where 0 = no pain and 10 = the worst pain imaginable, how to use the patient-controlled analgesia device (PCA), and LANSS pain scale for chronic post mastectomy pain [10]. Patients received 5 mg of oral diazepam the night before surgery.

2.4. Anesthetic Procedure

Monitoring included electrocardiography (ECG), non-invasive blood pressure (NIBP), and oxygen saturation (Sao_2). After five minutes of pre-oxygenation, general anesthesia was induced with intravenous (IV) 2 μg/kg fentanyl, 1 - 2 mg/kg propofol, and 1.5 mg/kg lidocaine. Endotracheal intubation was facilitated by cisatracurium 0.15 mg/kg and anesthesia was maintained with isoflurane 1.5 - 1.7 MAC in 50% oxygen/air mixture, cis-atracurium 0.03 mg/kg increments, and controlled ventilation to maintain normocapnia (35 - 45 mmHg).

It was planned to give 1 μg/kg fentanyl to the patients if there was a 20% increase in the mean arterial blood pressure (MAP) or heart rate (HR) from baseline values intraoperative. IV 1 g/100mL paracetamol infusion (Perfalgan, Bristol-Myers Squibb, and the UK) was given towards the end of surgery. After surgical hemostasis before wound closure, patients were randomly assigned into three groups (A, B, or C) to receive the studied drug doses with the surgical drains were clamped for 30 minutes after their irrigation. Isoflurane was discontinued and 0.05 mg/kg IV neostigmine with 0.02 mg/kg atropine was administered for reversal of neuromuscular blockade. Patients were extubated in the operating room and transferred to the post-anesthesia care unit (PACU), where they were assessed for acute pain intensity by VASR/M scores, time to the first request of analgesia, and total analgesic consumption, hemodynamics, and side effects in the 1st 48 h, then chronic neuropathic pain in the pain clinic for the first six months postoperatively.

2.5. Surgical Technique

All patients underwent modified radical mastectomy by total mastectomy and axillary lymph node dissection which was including level I and II lymph nodes and sentenil lymph node technique for non-clinical palpable nodes through a transverse elliptical incision. Interpectoral lymph nodes were removed by retraction of pectoralis minor muscle. Preservation of intercostobrachial nerve has been done. Drains were removed when the output was less than 30 mL on two successive days. Two-thirds of cases closure of deltopectoral fascia to chest wall had been done to close axillary space to decrease seroma formation. Patients had been encouraged to ambulate early and begin arm movements.

Acute pain had been followed for 48 h postoperatively in the post-aneshesia care unit (PACU):

Patients had been followed up and assessed in 48h postoperatively in PACU for the following:

- Total morphine consumption.
- Time to the first request of analgesia.
- VASR/M scores at baseline, 2, 4, 6, 12, 24, 36, and 48 h postoperatively. If VAS score ≥ 3, rescue analgesia in the form of PCA with an initial bolus of 0.1 mg/kg morphine once the pain had been expressed followed by 1 mg bolus with a locked out period of 15 minutes with no background infusion had been allowed.
- Heart rate (HR), mean arterial blood pressure (MBP), respiratory rate (RR), arterial oxygen saturation (SaO_2) at the same previous time points.
- The patient's sedation level had been assessed at the same previous time points using a sedation score of (0 - 4) in which 0 = patient is fully awake, 1 = patient is somnolent and responsive to verbal command, 2 = patient is somnolent and responsive to tactile stimulation, 3 = patient is asleep and responsive to painful stimulation and 4 = patient isn't arousable.

- Postoperative adverse effects such as nausea, vomiting, respiratory depression, itching, nystagmus, dreams, hallucinations, delirium, and dissociative effects had been observed, treated, and recorded.

Chronic pain had been followed up for six-month postoperatively.

Chronic pain assessments have been conducted during patient visits in the pain clinic at the 1st, 3rd and 6th months by a blinded physician and data collectors includeding the following; the location, intensity, nature, and duration of pain as well as any aggravating or mitigating factors and analgesic medication used. Chronic neuropathic pain had been assessed using the LANSS pain scale (appendix) [10].

2.6. Statistical Analysis

Our primary outcome was the total amount of morphine consumption and the secondary outcome was the first request of analgesia, pain scores (VASR/M and LANSS), hemodynamic variables, sedation score, and side effects.

Based on previous research on ketamine instillation [9], with an expected background standard deviation of 1.0, an alpha error not exceeding 0.05 and power of 80%, we estimated that 28 patients in each group would be required. To compensate for dropouts, we recruited 30 patients in each group to account for random errors and additional comparisons.

Data entry and analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, and mean ± standard deviation (SD), and median (range).

A Chi-square test was used to compare qualitative variables. Independent samples t-test was used to compare quantitative variables between two groups and ANOVA tests to compare three groups at once in case of parametric data. Mann-Whitney test was used to compare every two groups and the Kruskal-Wallis test between three groups in case of non-parametric quantitative variables. P-value considered statistically significant when $P < 0.05$.

3. Results

One hundred female patients with breast cancer who underwent modified radical mastectomy (MRM) have been assessed for eligibility in our study. Ninety-five patients were successfully enrolled. Five patients have been dropped out from the study during the acute postoperative phase of follow-up (because of surgical complications such as bleeding from the surgical wound, hematoma, and splitting of the surgical drain) and one patient dropped out during the chronic phase of follow up. Ninety patients had completed the acute postoperative phase of the study and eighty-nine patients had completed the chronic phase of the study. The flow chart of the study participants was illustrated in **Figure 1**.

No significant difference had found among the three studied groups as regards the demographic and operative data (Age, weight, ASA, and duration of surgery) ($P > 0.05$) (**Table 1**).

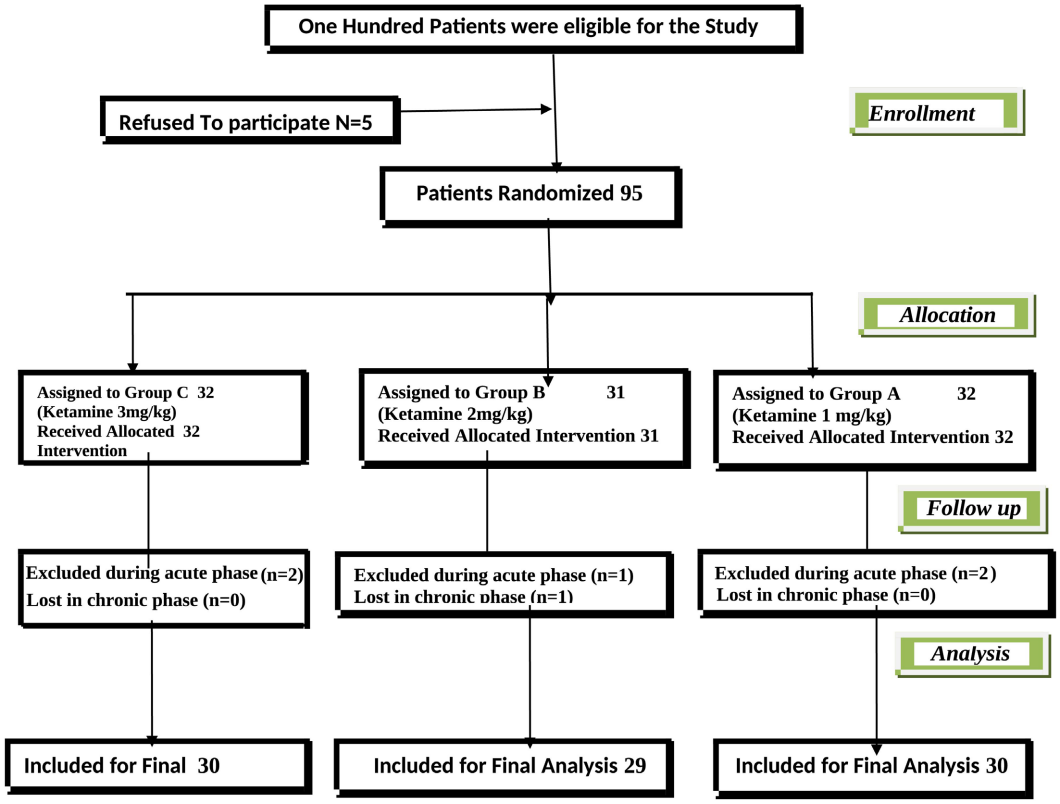

Figure 1. Flow chart of the enrolled cases. One hundred female patients with breast cancer who underwent modified radical mastectomy (MRM) have been assessed for eligibility in our study. Ninety five patients were successfully enrolled. Five patients have been dropped out from the study during the acute postoperative phase of follow up and one patient dropped out during the chronic phase of follow up.

Table 1. Demographic and clinical data of patients in the three studied group.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P-value[1]
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (yrs)	43.83 ± 11.31	44.10 ± 11.21	45.87 ± 10.86	0.745
Weight (kg)	69.17 ± 9.12	68.67 ± 9.33	67.50 ± 9.10	0.772
ASA score:				
I	20 (66.7%)	22 (73.3%)	19 (63.3%)	0.700
II	10 (33.3%)	8 (26.7%)	11 (36.7%)	
Duration of surgery (mins)	113.5 ± 6.04	113.33 ± 5.92	113.43 ± 6.15	0.368

Data expressed as (Mean ± SD) and number and percentage. Group (A): Patients received 1 mg Ketamine/kg. P1: P value between the three studied groups. Group (B): Patients received 2 mg Ketamine/kg. Group (C): Patients received 3 mg ketamine/kg. Baseline: immediately postoperative. ASA: American Society of Anesthesiologists.

The median (range) total dose of morphine consumption was 8 mg (5 - 10) in group A versus 6 mg (6 - 7) in B group respectively (P = 0.006) with thirty patients (100%) in A versus nine patients (30%) in B group requested rescue analgesia and no one requested analgesia in C group during the first 48 h with the

first request of analgesia was 12 h (5 - 36) in A group versus 30 h (12 - 36) in B group (P = 0.001) (Table 2).

A significant decreased in the median VASR had been observed when comparing both B and C groups to the A group at baseline, 2, 4, 6, 12, 24, and 36 h. Moreover when comparing the C to B group at 12 h postoperatively (P ≤ 0.05) (Figure 2).

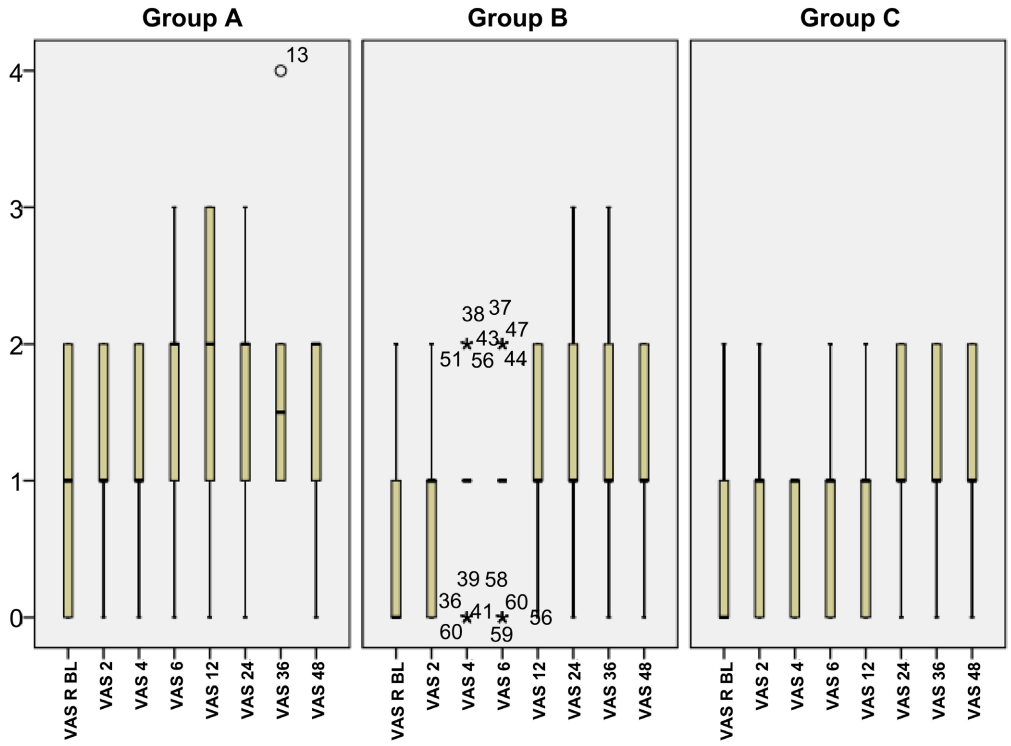

Figure 2. Visual analgesic scale at rest (VASR) of the studied three groups during 48h postoperatively. Data expressed as median (range). Group (A): Patients received 1 mg ketamine/kg; Group (B): Patients received 2 mg ketamine/kg; Group (C): Patients received 3 mg ketamine/kg. Baseline: Immediately postoperative. VAS: Visual analog scale. VAS R BL: Visual Analgesic Scale at rest immediately postoperative (baseline). * = significant decreased in the VASR scores when comparing the three studied groups.

Table 2. Number (%) of the patients requested analgesia and time of first request of analgesia and total amount of morphine consumption among the three studied groups during the first 48 h postoperatively.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P-value[1]	P-value[2]	P-value[3]	P-value[4]
	Median (Range)	Median (Range)	Median (Rang)				
Patients need analgesia No. (%)	30 (100.0)	9 (30.0%)	0 (0.0%)	0.000*	0.000*	0.000*	0.002*
Time to first request (h)	12 (5 - 36)	30 (12 - 36)	--	0.000*	0.000*	--	--
Total analgesic consumption (mg) in 48 h	8 (5 - 10)	6 (6 - 7)	--	0.006*	0.006*	--	--

Data expressed as (Median ± Range) and No. %. Group (A): Patients received 1mg Ketamine/kg. P1: P value between the three studied groups. Group (B): Patients received 2 mg Ketamine/kg. P2: P value between A and B groups. Group (C): Patients received 3 mg ketamine/kg. P3: P value between A and C groups. P4: P value between B and C groups. *Significant P value (<0.05). Baseline: immediately postoperative.

Looking to the median VASR/M, there was a significant decreased when comparing both (B and C) groups to (A) group at the baseline, 2, 4, 6, 12, 24, and 36 h postoperatively ($P \leq 0.05$). Also when comparing C to B groups at 4 and 12 h ($P = 0.012$ and 0.025) respectively (Figure 3).

As regards to heart and respiratory rates and sedation scores; there was no significant difference between the three studied groups or between every two groups at the following time points (baseline, after 2, 4, 6, 12, 24, 36 and 48 h postoperatively) ($P > 0.05$). Also mean arterial blood pressure significantly increased in A compared to C group at 6 and 48 h respectively ($P = 0.029$ and 0.036).

Only five patients (16.7%) had nausea in group A versus two (6.7%) and four patients (13.3%) in B and C groups respectively. Two (6.7%) patients had vomiting in (A) group versus six (20%) and eight (26.7%) patients in B and C groups respectively.

There was a significant difference between A and C groups in the incidence of vomiting ($P \leq 0.038$). No other adverse side effects like (respiratory depression, hallucination, delirium, nystagmus, or dissociation) had been observed.

In the first month of follow up the median LANSS score of all patients was 13 (7 - 17) in A group and 9 (2 - 15) in B group versus 2.5 (0 - 7) in C group. In the

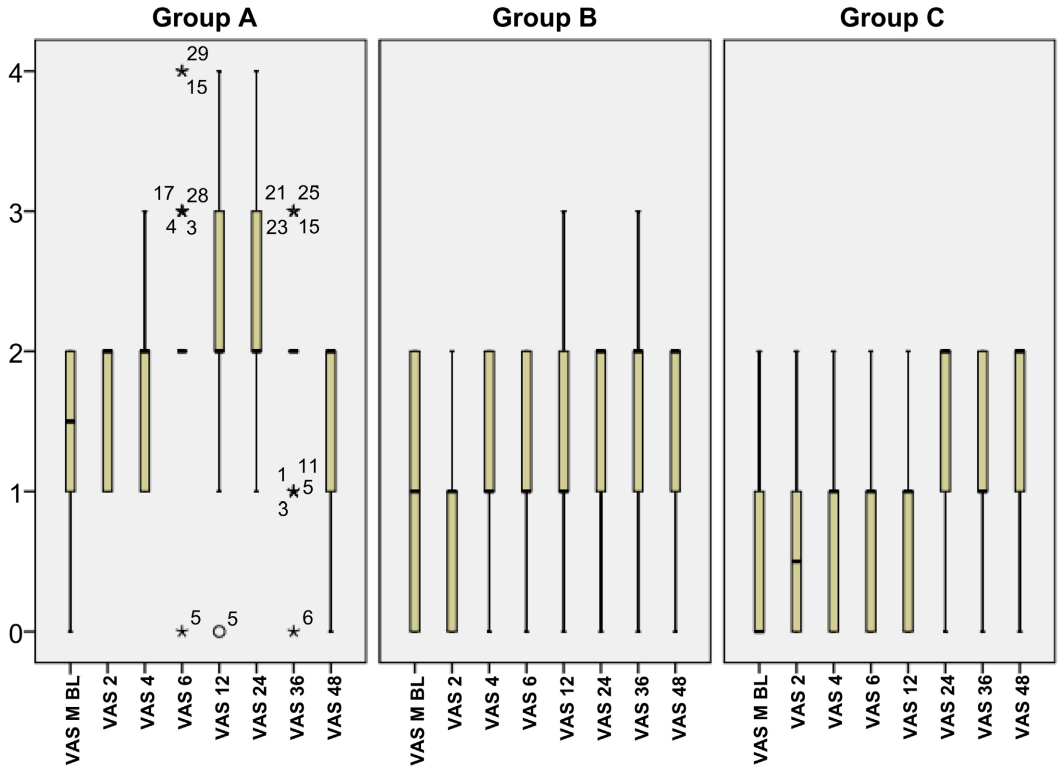

Figure 3. Visual analogue scale at movement (VASM) of the three studied groups 48 h postoperatively. Data expressed as median (range). Group (A): Patients received 1 mg ketamine/kg; Group (B): Patients received 2 mg ketamine/kg. Group; (C): Patients received 3 mg ketamine/kg. Baseline: Immediately postoperative. VAS: Visual analogue scale. VAS M BL: Visual Analgesic Scale at movement immediately postoperative (baseline). * = significant decreased in the VASR scores when comparing the three studied groups.

third month of follow up, the median score of patients was 10 (4 - 14) in A group and 6 (2 - 13) in B group versus 2 (0 - 5) in C group. At the sixth month of follow up the median LANSS score in A group was 9 (3 - 18) and 4 (0 - 13) in B group versus 2 (0 - 5) in C group (P = 0.001).

There was a significant difference in the LANSS score when comparing the three groups together at 1, 3, and 6 months postoperatively (P ≤ 0.001). Among the three studied groups, no patient in C group had neuropathic pain (LANSS score ≥ 12) in the first and third or sixth postoperative month versus 2 and 9 patients only in B and A groups respectively had neuropathic pain at sixth month postoperatively (P = 0.001) (Table 3).

4. Discussion

Using local instillation of ketamine for postoperative analgesia has been tried in varies studies as Abd EL-Rahman and El Sherif [9], who concluded that local wound instillation of ketamine reduced total postoperative morphine consumption and delayed the first request of rescue analgesia with lower sedation score in the local ketamine group compared to that of intramuscular.

Ketamine may be used for postoperative pain management. Since postoperative pain is mainly caused by tissue inflammation and C-fiber activation, also cytokines can influence the development of postoperative hyperalgesia. Thus reduced cytokine production might limit the inflammatory response after surgery and the severity of postoperative pain [11].

Table 3. Median of Leeds assessment of neuropathic symptoms and signs score (LANSS) among the three studied groups during1st, 3rd and 6th months postoperatively.

LANSS	Group A (n = 30)		Group B (n = 30)		Group C (n = 30)		P-value[1]	P-value[2]	P-value[3]	P-value[4]
1st month:	**(n = 30)**		**(n = 30)**		**(n = 30)**					
Median (range)	13 (7 - 17)		9 (2 - 15)		2.5 (0 - 7)		0.000*	0.001*	0.000*	0.000*
<12 NO. (%)	11	36.7	23	76.7	30	100.0	0.000*	0.002*	0.000*	0.011*
≥12 NO. (%)	19	63.3	7	23.3	0	0.0				
3rd month:	**(n = 30)**		**(n = 29)**		**(n = 30)**					
Median (range)	10 (4 - 14)		6 (2 - 13)		2 (0 - 5)		0.000*	0.000*	0.000*	0.000*
<12 NO. (%)	19	63.3	27	93.1	30	100.0	0.000*	0.006*	0.000*	0.237
≥12 NO. (%)	11	36.7	2	6.9	0	0.0				
6th month:	**(n = 30)**		**(n = 29)**		**(n = 30)**					
Median (range)	9 (3 - 18)		4 (0 - 13)		2 (0 - 5)		0.000*	0.000*	0.000*	0.000*
<12 NO. (%)	21	70.0	27	93.1	30	100.0	0.001*	0.023*	0.001*	0.237
≥12 NO. (%)	9	30.0	2	6.9	0	0.0				

Data expressed as (Median ± Range) and NO (%). Group (A): Patients received 1mg Ketamine/kg. P1: P value between the three studied groups. Group (B): Patients received 2 mg Ketamine/kg. P2: P value between A and B groups. Group (C): Patients received 3 mg ketamine/kg. P3: P value between A and C groups. P4: P value between B and C groups. *Significant P value (<0.05). Baseline: immediately postoperative.

We had been investigated analgesic effect of three doses of ketamine instillation (1, 2 and 3 mg/kg ketamine) on acute post mastectomy pain for 48 h postoperatively and the development of chronic pain 6 months afterward, our study resulted in that, the three doses were effective and acceptable to the patients with minimal detectable systemic side effects without affecting hemodynamic variables. Moreover patients who received 3 mg/kg ketamine showed the lowest median VASR/M and LANSS scores during the 1st, 3rd and 6th months and no patient in this group asked for PCA morphine for the first 48 h postoperative or developed chronic PMPS afterward for 6 months postoperatively.

Central, regional, local anesthetic, and analgesic properties have been reported for ketamine [7]. Peripheral mechanisms of action of ketamine include binding to multiple opioid receptors (ORs); binding to monoamine transporters; binding to muscarinic and nicotinic cholinergic receptors binding to monoamine inhibition of function, binding to D_2 and 5-HT_2 receptors, inhibition of ion channels (Na^+, Ca_2^+, K^+) decreased activation and migration of microglia and finally, inhibition of production of inflammatory mediators [12]. The N-methyl-D-Aspartate Receptors (NMDAR) and related ionotropic glutamate receptors are present on peripheral primary afferent neurons in the hairy skin of humans [13].

Ketamine, in sub anesthetic doses, produces systemic analgesia in chronic pain settings, an action largely attributed to block of N-methyl-d-Aspartate receptors in the spinal cord and inhibition of central sensitization processes. N-methyl-d-aspartate receptors also are located peripherally on sensory afferent nerve endings, and this provided the initial impetus for exploring peripheral applications of ketamine [12]. Peripheral administration of ketamine by localized injection produced some alterations in sensory thresholds in experimental trials in volunteers and in complex regional pain syndrome subjects in experimental settings, but many variables were unaltered [12].

Moharari *et al.* [14] concluded that 100 mg ketamine instillation added to lidocaine gel in the urethra decreased pain of outpatient rigid cystoscopy. Also, Nejati *et al.* [15] also found that local intranasal ketamine added to lubricating gel reduced nasogastric tube insertion pain significantly. Moreover Elbaradie *et al.* [16] reported that intraperitoneal administration of 2 mg/kg ketamine after diagnostic laparoscopy elicited antinociception without producing the undesirable central side effects observed following the systemic administration.

Many studies approved the efficacy of subcutaneous (SC) ketamine infiltration in acute pain control as Mohamed *et al.* [17] concluded that local wound infiltration with 2 mg/kg ketamine added to bupivacaine had an opioid-sparing effect, delayed the first request of rescue analgesia, and attenuated postoperative stress response. Also Safavi *et al.* [18] reported that SC ketamine infiltration at a dose of 2 mg/kg given approximately 15 minutes before surgical incision provided adjunctive analgesia for 24 h after surgery and related that to the local effect of ketamine.

Javid *et al.* [19] compared the efficacy of SC or IV ketamine added to narcotics and results showed that SC ketamine was as effective as IV ketamine but safer in avoiding systemic side effects. Also Othman *et al.* [20] who added 1mg/kg ketamine

to modified pectoral block, increased time to the first request of analgesic requirement in the 1st 48 hrs postoperatively and reduced the total morphine consumption.

Increasing doses of ketamine instillation are thought to be most probably effective in prolonging the pain-free time postoperative (48 h) which was observed in our study especially with the 3 mg group or C group. It was supposed that SC ketamine was absorbed more slowly and acts as a depot reservoir for the drug allowing the longer duration of analgesia [18].

In our study minimal side effects were experienced, vomiting occurred with five patients in (A), two in (B), and four in (C) groups respectively. Also nausea was seen in only two patients in group (A), six in (B), and eight in (C) groups respectively. It was observed that using ketamine instillation with its local analgesic effect most probably bypasses the systemic absorption and consequently minimizes the side effects seen in other studies using IV or IM ketamine. Honarmand *et al.* [21] in his study which designed to evaluate the clinical efficacy of pre-incisional, IV, and SC infiltration of ketamine for postoperative pain relief that revealed no significant hypotension or bradycardia was noted in the SC group.

Pain persists for months after thoracotomy, amputation, or breast surgery in every second patient [22] [23]. Mild chronic pain can significantly impact function and quality of life [22].

Whereas severe chronic intractable pain is devastating, prevention is a major concern even for surgeries with a low risk of persistent pain [23]. By these facts; we concluded that by controlling the acute pain there is a significant control of chronic pain as observed in the LANSS score especially in C group where no one developed neuropathic pain, then B and A groups respectively.

Persistent pain after a mastectomy is typically neuropathic. The intensity of early postoperative pain has been identified as the most important determinant of chronic pain [24]. So, in our study, we found that the good control of acute pain affected the development of chronic pain as there is a difference in LANSS score in C, B and A groups respectively, where the number of patients with score ≥ 12 was zero patient in C group among the whole study period, two patients in B group and nine in A group. We noticed that increasing the analgesic dose of ketamine from 1 mg/kg to 2 mg/kg or 3 mg/kg had better acute postoperative pain control and consequently development of chronic pain.

Supporting our results on the effect of topical ketamine in controlling the development of chronic pain afterward, Gammaitoni *et al.* [25] who recommended the use of ketamine gel for treating refractory cases of neuropathic pain, at lower doses, the patient described alterations in temperature sensation.

Also Crowley *et al.* [26] proved the clinical efficacy of topical ketamine in relieving sympathetically maintained pain, including complex regional pain syndrome types I and II, involving the upper and/or lower extremities. Also Mercadante*et al.* [27] treated neuropathic cancer pain by SC continuous ketamine infusion. Starting dose of 150 mg/day provided good pain relief and a dramatic reduction of the oral morphine dose.

On the other hand, Mahoney *et al.* [28] revealed that 5% topical ketamine cream was no more effective than comparison with placebo in relieving pain caused by diabetic neuropathy. And O'Brien *et al.* [29] found that topical administration of ketamine at any concentration has not shown any significant benefit in the reduction of neuropathic pain in lower concentrations.

Also Jendoubi *et al.* [30] reported that ketamine and lidocaine are safe and effective adjuvants to decrease opioid consumption and control early pain and they also suggest that lidocaine infusion prevent chronic neuropathic pain at three months after open nephrectomy but ketamine failed to prevent neuropathic pain.

The limitation to our study was the small sample size, shorter duration of acute pain follow-up in 3 mg/kg and continuous follow until the development of chronic post mastectomy pain after word and assessment of serum ketamine level to exclude its systemic absorption and exclude fairly extent its systemic effect.

5. Conclusion

Ketamine instillation was effectively controlled acute post mastectomy pain in a dose-dependent manner and reduced the incidence and severity of chronic PMPS without serious side effects in patients underwent modified radical mastectomy.

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Data Sharing Statement

We are not planning to share any of the data with anyone.

Conflicts of Interest

The authors declare no conflicts of interest.

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