The effect of Ketamine infusion on post mastectomy pain syndrome: a randomized controlled study

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Received 16 April 2014; Accepted 27 April 2014

Abstract

Background: Acute postoperative pain after breast surgery is one of the major factors contributing to prolonged hospital stay. In addition persistent post mastectomy pain (PPMP) is rated as the most important cause of suffering in those patients.

Objectives: The objectives of this study are to investigate the efficacy and safety of ketamine infusion on the incidence of acute postoperative and chronic post-mastectomy pain in female patients undergoing modified radical mastectomy.

Patients and methods: 40 Patients were included in this study, divided into 2 groups (20 patients for each): Group 1 (G1): Control group in which patients received I.V. saline infusion before skin incision and for 24 hours after surgery. Group 2 (G2): In which patients received pre-emptive I.V bolus 0.5 mg / kg ketamine before skin incision followed by a continuous infusion of 0.25 mg / kg per hour for 24 hours post-operative. We measured hemodynamic variables, Visual Analogue Score at rest and movement of the limb or cough (VAS-R and VAS-M respectively) at zero line, 2, 4, 8, 12, 16, 24 hours postoperatively, time to the first request of analgesia, total morphine consumption, sedation score and development of side effects. LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) score was assessed at 1, 2, 3, 6 months postoperatively.

Results: There was a significant reduction in VAS-R and VAS-M (p<0.05), total morphine consumption (p<0.01) with significant delay in the 1st analgesic request (p<0.001) at all time points in ketamine group. LANSS score was significant reduced (p<0.05) in ketamine group compared to control group at all time points.

Conclusion: Perioperative use of ketamine in patients undergoing modified radical mastectomy, reduced acute postoperative pain, morphine consumption and the development of chronic post mastectomy pain with no serious side effects.

Introduction

Post mastectomy pain syndrome (PMPS) is the chronic neuropathic pain after surgery for cancer breast. PMPS has been known to develop in 20-68% of patients [1,2]. Post mastectomy pain syndrome is somewhat a misleading terminology, as the syndrome has been described after breast conserving surgery as well. The exact mechanisms are not known but neuropathic pain has been documented to be a major mechanism of PMPS. Damage to the nerves in the axilla and or the chest wall during surgery has been found in many cases [1,2].

Like other neuropathic pain, the treatment is often difficult. A study from 1994 and a later study suggest that the prognosis of PMPS is better than expected, with a decline in prevalence over years [3,4]. Previous studies have identified following risk factors: young age [5] sectioning of the inter costo-brachial nerve [6] and axillary dissection [7]. Dissection of the axillary lymph nodes has been shown to be a critical component in the
etiology of chronic pain after surgery for breast cancer. The frequency of this procedure has been reduced over the last decade, due to the introduction of the sentinel node biopsy [8]. The need for opioid to control such chronic pain syndromes, though it shows efficacy, it has been associated with multiple concerns.

Use of the N-methyl-D-aspartate receptor antagonist ketamine to control pain refractory to high-dose of opioids is well described in a number of clinical trials [9]. Such use is supported by preclinical data demonstrating an important role for the NMDA receptor in opioid-induced hyperalgesia [10]. Persistent pain from inflammation [11], nerve injury [12] and cancer [13]. The noncompetitive NMDA antagonist ketamine has also been shown in clinical studies to attenuate pain hypersensitivity [14]. This effect of ketamine on neuropathic pain seems to be more potent than that of dextromethorphan [15].

The objectives of this study were to investigate the efficacy and safety of ketamine infusion on the incidence of acute postoperative and chronic post-mastectomy pain in female patients undergoing modified radical mastectomy.

Patients and Methods

This study was approved by the local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut, Egypt. After written informed consent, forty female patients, ASA physical status I and II age group 25-55 years old, body weight from 50-85 kg scheduled for elective modified radical mastectomy under general anesthesia were enrolled in this study.

Exclusion criteria include patients on opioid therapy for chronic pain, a history of allergic reactions to the study medications, preexisting hypertension, ischemic heart disease, congestive heart failure, glaucoma, hepatic impairment, renal impairment, drug or alcohol abuse and psychiatric disease or therapy.

Preoperatively, patients were taught how to evaluate their own pain intensity using the visual analogue scale (VAS) scored from 0-10 (where 0 = no pain and 10= the worst pain imaginable). Patients were allocated into 2 groups of 20 patients each:

- Group 1 (G1): Control group in which patients received I.V. saline infusion before skin incision and for 24 hours after surgery.
- Group 2 (G2): In which patients received preemptive I.V bolus of 0.5 mg / kg ketamine before skin incision followed by a continuous infusion (immediate post-operative) of 0.25 mg / kg per hour for 24 hours.

All patients received 2mg of Midazolam at induction of anesthesia and before ketamine infusion, to avoid hypertensive response and muscle pain. The general anesthesia was induced by IV propofole 2mg/Kg ,fentanyl 1-2µ/kg and tracheal intubation was facilitated using atracurium 0.5mg/Kg. Anesthesia was maintained with isoflurane in a mixture of oxygen, atracurium 0.25 mg Kg-1 as a muscle relaxant. Ventilation was controlled to maintain PaCO2 between 35 and 45 mmHg.

Standard monitoring included pulse oximetry, electrocardiograph, and non-invasive blood pressure measurement were done. Residual neuromuscular block was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg after surgery was completed. After extubation patients were transferred to post- anesthesia care unit. Continuous monitoring by ECG, non-invasive blood pressure, oxygen saturation, respiratory rate at zero line (immediately post-operative), at 2, 4, 8, 12, 16, 24 hours postoperative were done.

The respiratory depression was defined as a respiratory rate <10/min, Hypotension is defined as a 20% decrease in systolic blood pressure from base line, Bradycardia is defined as heart rate less than 50 beats per minutes.

All patients in the two groups received morphine via PCA for post-operative analgesia. The PCA bolus dose was set at 1.5mg, with a lockout interval 6min and a maximal 4-hourly dose of 20 mg was given (Using Abbott® Pain Management provider Chicago USA).

Pain intensity was evaluated by using a 10 cm VAS score (VAS-R and VAS-M) at zero line, 2, 4, 8, 12, 16, 24 hours post-operatively. Sedation score also was evaluated. The degree of sedation was rated on a 4-point scale with 0 = a wake, 1=drowsy, 2 = a sleep but respond to verbal commands, or 3 = unarousable. The incidence of adverse effects such as nausea, vomiting, dizziness, anxiety and purities were evaluated with (yes or no) survey. Also morphine consumption by PCA was also recorded for 24 hours after operation. Then patients will be assessed after 1, 2, 3 and 6 months by Leeds Assessment of Neuropathic Symptoms and Signs (LANSS).

Statistical analysis:

Data collected and analysis by computer program “SPSS ver. 17” Chicago USA (Statistical package for social science). The sample size was 20 patients with the power of 80% and a 5% risk of type1 error. Data expressed as mean ±SD and number, percentage Using T. test to determine significant for numeric variables, using Chi. square to determine significant for non-parametric variables. Using person’s correlation for numeric variables in the same group <0.05 significant.

Results

Forty female patients were randomly allocated into 2 groups. There was no statistically significant difference between the two groups as regards demographic data: age, weight, height, sex and body mass index (p>0.05). There was no statistically significant difference between the two groups in the duration of the operation, site of surgery or the adjuvant therapy (chemotherapy, radiotherapy and hormonal therapy) (p>0.05). Table (1)

The hemodynamic parameters measured during the postoperative period (24 hours); heart rate, systolic and diastolic blood pressure showed no statistically significant difference between the two groups (p>0.05). Also no statistically significant difference were seen in the respiratory rate and oxygen saturation between the two groups or when comparing the follow up readings with zero line (p>0.05). Figures (1-5).
**Table (1): Demographic data in the two groups**

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>20(100%)</td>
<td>20(100%)</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>44.80±3.00</td>
<td>43.80±7.36</td>
<td>P=0.385, n.s</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73.40±7.23</td>
<td>75.35±8.33</td>
<td>P=0.573, n.s</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.0±4.86</td>
<td>164.5±5.87</td>
<td>P=0.256, n.s</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.26±2.03</td>
<td>27.78±1.82</td>
<td>P=0.472, n.s</td>
</tr>
<tr>
<td>Time of operation (min)</td>
<td>74.56±8.32</td>
<td>69.56±3.51</td>
<td>P=0.873, n.s</td>
</tr>
<tr>
<td>Treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chemotherapy</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td></td>
</tr>
<tr>
<td>- Radiotherapy</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>P=1.000, n.s</td>
</tr>
<tr>
<td>- Hormonal</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>Site:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Right</td>
<td>11 (55%)</td>
<td>10 (50%)</td>
<td>P=1.000, n.s</td>
</tr>
<tr>
<td>- Left</td>
<td>9 (45%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD and number (%)

n.s: non significance P>0.05

BMI: Body mass index

G1: Control group

G2: Ketamine group

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**Table (2): Sedation score in the two groups in postoperative period**

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation: 0 line</td>
<td>1.10±0.00</td>
<td>2.80±0.58</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Sedation: 2 hrs.</td>
<td>0.98±0.23</td>
<td>1.04±0.10</td>
<td>P=0.892, n.s</td>
</tr>
<tr>
<td>Sedation: 4 hrs.</td>
<td>0.00±0.00</td>
<td>0.80±0.10</td>
<td>P=0.497, n.s</td>
</tr>
<tr>
<td>Sedation: 8 hrs.</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>P=1, n.s</td>
</tr>
<tr>
<td>Sedation: 12 hrs.</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>P=1, n.s</td>
</tr>
<tr>
<td>Sedation: 16 hrs.</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>P=1, n.s</td>
</tr>
<tr>
<td>Sedation: 20 hrs.</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>P=1, n.s</td>
</tr>
<tr>
<td>Sedation: 24 hrs.</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>P=1, n.s</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD, n.s: non significance P>0.05.
P<0.05: significant

G1: Control group

G2: Ketamine group
As regards mean VAS score at rest (VAS-R), there was statistically significant decrease in the mean VAS-R in G2, in comparison to G1 (p<0.05). Table (3) and figure (6).

Table (3): VASR mean±SD in the two groups in postoperative period

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASR: 0 line</td>
<td>5.50±0.00</td>
<td>3.91±0.60</td>
<td>P&lt;0.03</td>
</tr>
<tr>
<td>VASR: 2 hrs.</td>
<td>5.41±0.23</td>
<td>3.10±0.43</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>VASR: 4 hrs.</td>
<td>5.20±0.50</td>
<td>3.05±0.08</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASR: 8 hrs.</td>
<td>4.98±0.50</td>
<td>3.11±0.10</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASR: 12 hrs.</td>
<td>4.92±0.50</td>
<td>3.09±0.22</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASR: 16 hrs.</td>
<td>4.00±0.34</td>
<td>3.07±0.04</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>VASR: 24 hrs.</td>
<td>4.12±0.16</td>
<td>3.00±0.00</td>
<td>P&lt;0.04</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. n.s: non significance P>0.05. P<0.05: significant

VASR: VAS measurements during rest.
G1: Control group. G2: Ketamine group.

As regards mean VAS score with movement (VAS-M) in 24 hours follow up; there was statistically significant decrease in the mean VAS-M in G2, in comparison to G1 (p<0.05) . When comparing the mean of VAS-M at zero time with later readings in the 24 hours postoperatively, there was statistically significant decrease in mean of VAS-M in G2, starting after 8 hours and it continued to the end to the 24 hours (p<0.05). Table (4) and figure (7).

Table (4): VASM mean±SD in the two groups in postoperative period

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASM: 0 line</td>
<td>7.79±1.51</td>
<td>4.95±1.91</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>VASM: 2 hrs.</td>
<td>6.70±0.73</td>
<td>4.07±0.80</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASM: 4 hrs.</td>
<td>6.56±0.40</td>
<td>4.33±0.63</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASM: 8 hrs.</td>
<td>6.05±0.00</td>
<td>3.81±0.31</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>VASM: 12 hrs.</td>
<td>5.90±0.90</td>
<td>3.23±0.22</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>VASM: 16 hrs.</td>
<td>5.87±0.00</td>
<td>3.99±0.12</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>VASM: 24 hrs.</td>
<td>5.84±0.21</td>
<td>3.88±0.11</td>
<td>P&lt;0.04</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. n.s: non significance P>0.05. P<0.05: significant

* is a significance between readings and zero line: P<0.05
VASM: VAS measurements during movement.
G1: Control group. G2: Ketamine group.

As regard the time to first request for rescue analgesic; the time was significantly longer in Ketamine group (G2) 72.60±2.45 minutes in comparison with (G1) 8.65±1.63 minutes (p<0.05) Table (5).

Table (5): First request of Morphine in the two groups

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine first req. (minutes)</td>
<td>8.65±1.63</td>
<td>72.60±2.45</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. n.s: non significance P>0.05. P<0.05: significant
G1: Control group. G2: Ketamine group.

The PCA morphine consumption in the 1st 24 hours postoperatively was significantly decreased in the ketamine group (G2) (10.30±2.58 mg) in comparison to the control group (16.70±12.01) (p<0.05) Table(6).

Table (6): Morphine consumption in mg in the two groups in postoperative period

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine 24 hrs.</td>
<td>18.70±12.01</td>
<td>10.30±2.58</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. n.s: non significance P>0.05. P<0.05: significant
G1: Control group. G2: Ketamine group.

There was no significant differences between G1 and G2 in the mean of LANSS score measured at the end of 1st postoperative month (p>0.05).
At the 2nd, 3rd and 6th months the mean of LANSS score was significantly decreased in G2 in comparison to G1 (p<0.000). Table (7) and figure (8).
Table (7): LANSS in the two groups

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LANSS 1 (At 1st month)</strong></td>
<td>7.20±2.64</td>
<td>6.80±1.28</td>
<td>P=n.s</td>
</tr>
<tr>
<td><strong>LANSS 2 (At 2nd month)</strong></td>
<td>7.85±4.65</td>
<td>5.15±2.43</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td><strong>LANSS 3 (At 3rd month)</strong></td>
<td>7.30±3.89</td>
<td>7.30±3.89</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>LANSS 6 (At 6th month)</strong></td>
<td>6.90±1.41</td>
<td>4.15±0.81</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. n.s: non significance P>0.05

G1: Control group. G2: Ketamine group.

Fig (8): LANSS change in the two groups in postoperative period

The incidence of neuropathic pain (LANSS≥12) in the 1st month was significantly reduced in G2 (2 patients 10%) and G1 (7 patients 35%) respectively (p<0.05).

Regards the incidence of neuropathic pain (LANSS≥12) in the 2nd month; it was significantly reduced in G2 (2 patients 10%) in comparison to G1 (6 patients 30%) (p<0.05). At 3rd and 6th months; there were 2 patients with neuropathic pain (10%) in G2, in comparison to 5 patients (25%) in G1. Table (8) and figure (9).

Table (8): Incidence of Neuropathic pain in the two groups “LANSS≥12”

<table>
<thead>
<tr>
<th></th>
<th>G1 (35%)</th>
<th>G2 (10%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LANSS 1 (At 1st month)</strong></td>
<td>7</td>
<td>2</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>LANSS 2 (At 2nd month)</strong></td>
<td>6(30%)</td>
<td>2(10%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>LANSS 3 (At 3rd month)</strong></td>
<td>5(25%)</td>
<td>1(5%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>LANSS 6 (At 6th month)</strong></td>
<td>5(25%)</td>
<td>1(5%)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Data were expressed as number and (%)

G1: Control group. G2: Ketamine group.

As regard the adverse effects in the postoperative 24 hours there was a higher number of patients complaining of dizziness in G2. There were 9 patients (45%) in comparison to 2 patients in G1 (10%) (p<0.05). There were 6 patients (30%) complaining of nausea in G1, compared to 3 patients (15%) in G2.

Vomiting occurred in 5 patients (25%) in G1 and 2 patients (10%) in G2. Table (9) and figure (10). In our study no patients suffered from sleep disorders, hallucination, constipation, anxiety, irritability or pruritus.

Table (9): Incidence of side effect in the two groups in postoperative period

<table>
<thead>
<tr>
<th></th>
<th>G1 (35%)</th>
<th>G2 (10%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dizziness</strong></td>
<td>2(10%)</td>
<td>9(45%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>6(30%)</td>
<td>3(15%)</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>5(25%)</td>
<td>2(10%)</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

Data were expressed as number and (%)

Discussion

Postoperative pain after breast surgery is one of the major factors contributing to delay in mobilization and prolonged hospital stay. In addition, the use of opioids for analgesia contributes to post-operative nausea and vomiting (PONV). Pre-emptive analgesia is the preoperative administration of an analgesic with the aim of preventing sensitization of the central nervous...
Ketamine is also used as an adjuvant to opioids in the treatment of refractory pain in cancer patients [32], in the treatment of neuropathic pain [33], and in the treatment of acute postoperative pain [34].

Blockade of NMDA receptors has been shown in animal studies to prevent the development of increased pain sensitivity and opioid [35,15]. Ketamine is a non-competitive NMDA receptor antagonist. NMDA receptor blocking could be a fruitful therapy for improving postoperative opioid effectiveness. Ketamine could, in addition to having an opioid sparing effect, conceivably reduce the development of chronic postoperative pain through NMDA receptor blockade and reduction of wind-up and central sensitization.

In agreement with us, Michelet et al. 2007[36] used (1 mg/kg at the induction, 1 mg/kg/h during surgery, then 1 mg/kg during 24 hrs. postoperative) after thoracotomy; he found a statistically significant reduction (25%) of morphine consumption in ketamine group in comparison to placebo group.

There was a significant reduction in pain scores at rest and movement (VASR &VASM) was observed in our study. And the first analgesic requirement were significantly delayed in ketamine group (72.60± 2.45 minutes,) in comparison with control group G1 (8.65±1.63). The significantly decreased PCA morphine requirements during 24 hours postoperative period was lower in G2 10.3±2.58mg instead of 18.7±12.01 in the control group. In agreement with our findings, Christophe M, et al., 2000[37] found significant delay in the first request and decrease the morphine consumption. However in his study the VAS score was not significantly different as he used 0.15 mg ketamine / kg bolus (no infusion) preoperative in 1st group and post-operative in 2nd group and a placebo after anterior cruciate ligament repair.

Most of the studies demonstrating the analgesic effect of the Coad-ministration of small-dose ketamine during pain-provoking movement were performed in patients undergoing visceral or thoracic surgery [22,38,39]. Tverskoy et al., 1994 found a decrease in wound hyperalgesia 48 hours after anesthesia using ketamine.

Adam, et al., 1999 [40] used a preoperative Small-Dose Ketamine, he has found no preemptive analgesic effect in patients undergoing total mastectomy, which didn’t conform to our results. They compared the effects of 0.15mg /kg ketamine preoperative and at the time of skin closure which significantly reduces PCA morphine consumption, and VAS in post-operative group but this was in the 1st 2 hours only.

Our results were in agreement with Roytblat, et al., 1993[41] reported a 40% decrease in PCA morphine consumption after surgery. Barbieri, et al., 1997 [42] compared the analgesic effect of 1 mg/kg IM ketamine in patients undergoing elective laparoscopy for ovarian cysts. They documented that VAS pain scores were significantly lower until 24 hours after surgery in the group of patients given ketamine before operation. Fu E, et al., 1997[43] compared the analgesic effect of a presurgical loading dose (0.5 mg/kg), followed by a continuous infusion (10 µg /kg/ min with a single postsurgical dose (0.5 mg/kg). They found a significant
reduction in PCA morphine consumption 48 hours after surgery in the preemptive group.

A short ketamine infusion (<3 days), combined with epidural analgesia, produced interesting results in 2 randomized studies after oncologic surgery, decreasing postoperative pain up to 3 month after thoracotomy [44] and up to 6 month after rectal surgery, [45] that probably due to its antihyperalgesic effects[45].

It was found by Aveline, et al. 2009 and Adam F et al. 2005, that ketamine could be a good candidate to decrease early and chronic postoperative pain after Total Hip Arthroplasty (THA) [46,47].

Wind-up pain at 7 days was evaluated by Stubhaug et al., 1997[22] and was reduced by ketamine. De Kock et al., 2001[45] evaluated chronic persistent pain by a standardized telephone questionnaire regarding the nature and duration of pain and the analgesic requirements at 2 weeks, 1 month, 6 month, and 1 year after surgery. Patients who received IV ketamine had significantly lower long-term pain. All patients studied by De Kock, et al., 2001[45] had undergone surgery for rectal adenocarcinoma. Thus, small dose ketamine may have a role in reducing pathological pain, which is chronic and neuropathic, even without any effect on acute nociceptive pain. Surgical procedures such as thoracotomy and amputation are associated with chronic postoperative neuropathic pain [48-50].

Repeated administration of low-dose ketamine on a daily basis in patients with chronic pain syndromes was reported to induce long-term pain relief [51,52]. There are reports that demonstrate prolonged pain relief when low doses of ketamine were given repeatedly in patients who suffered from chronic pain [51,52].

Another study reported decreased residual pain and decreased need for chronic medications at 2 week, 1 and 6 month, and 1 year. [45] The same study reported decreased wound hyperalgesia and chronic residual pain [45]. The observed reduction in PONV in the studies mentioned here may be due to a morphine-sparing effect or to other as yet undetermined factors.

In agreement with our results PONV was reduced with ketamine in two studies [53,54]. Karrazma A et al., 2003[55] noted significant reduction in the incidence of nausea and itching with the addition of ketamine whereas others did not find any significant difference. Pruritus was significantly less in patients treated with ketamine in two studies [54,56].

One trial reported significantly less nausea in the ketamine treated group compared to placebo [57]. One trial reported significantly less nausea in the ketamine + morphine treated group, compared with the morphine group [54].

Despite the reassuring results of a meta-analysis [58] and reviews, [27,59] a common concern about ketamine is excessive sedation or psychedelic side effects.

Four trials [60-63] reported increased sedation in the ketamine treated groups: Ilkjaer,et al., 1998[61] reported significantly higher sedation scores for 0 to 24 hours after surgery. Guignard, et al., 2002[60] reported higher sedation scores for the first 15 minutes after extubation. Mathisen, et al., 1999[62] found that the placebo-treated group opened their eyes significantly faster and were extubated earlier than the racemic ketamine treated groups. Subramaniam 2001[63] reported high sedation scores in six patients in the ketamine group, compared to none in the control group, for the first two hours after surgery, but no difference thereafter.

In agreement with our study ketamine groups show increase sedations score than control group only in the first postoperative hour. However in one study, ketamine-treated patients were less sleepy [53] whereas other studies did not show any significant effect of ketamine on sedation. Sedation was increased in one studies with ketamine infusion [55].

Evgeny, et al., 2011 [26] used a repeated and escalating sub anesthetic doses of IM ketamine administration, the 25 mg dose was associated with sensations of dizziness for 2 minutes. These features are reassuring compared with the disturbing side effects reported decades ago when higher doses of the drug were administered in emergency surgery or in children [64].

They are similar to those reported following the administration of sub anesthetic IV doses of ketamine given to attenuate morphine tolerance [31].

**Conclusion**

Perioperative use of ketamine in patients undergoing modified radical mastectomy, reduced acute postoperative pain, morphine consumption and the development of chronic post mastectomy pain with no serious side effects.

**References:**


