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

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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

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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 (NMDA) 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 pre-emptive 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, electro cardiograph, 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 ,24hours 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).

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Table (1): Demographic data in the two groups

	G1 "n=20"	G2 "n=20"	P- value
Sex (female)	20(100%)	20(100%)	-
Age (yrs.)	44.80±3.00	43.80±7.36	P=0.385, n.s
Weight (Kg)	73.40±7.23	75.35± 8.33	P=0.573, n.s
Height (cm)	164.0±4.86	164.5±5.87	P=0.256, n.s
BMI (kg/m^2)	27.26±2.03	27.78±1.82	P=0.472, n.s
Time of operation (min)	74.56±8.32	69.56±3.51	P=0.873, n.s
Treatment:			
- Chemotherapy	20 (100%)	20 (100%)	
- Radiotherapy	20 (100%)	20 (100%)	P=1.000, n.s
- Hormonal	10 (50%)	10 (50%)	
Site:			
- Right	11 (55%)	10 (50%)	P=1.000, n.s
- Left	9 (45%)	10 (50%)	

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.

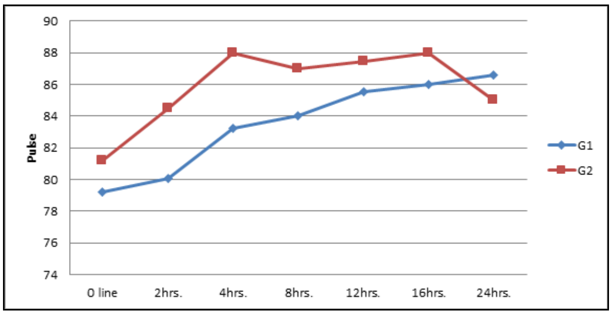

Fig (1): Pulse change in the two groups in postoperative period

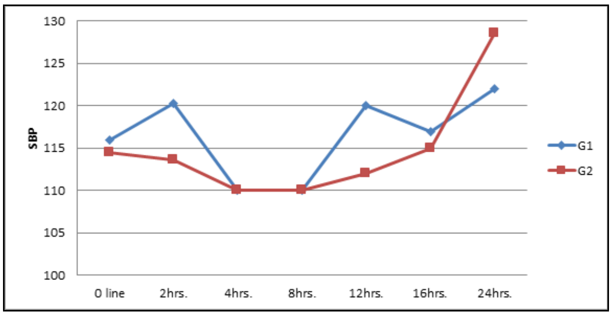

Fig (2): Systolic blood pressure change in the two groups in postoperative period

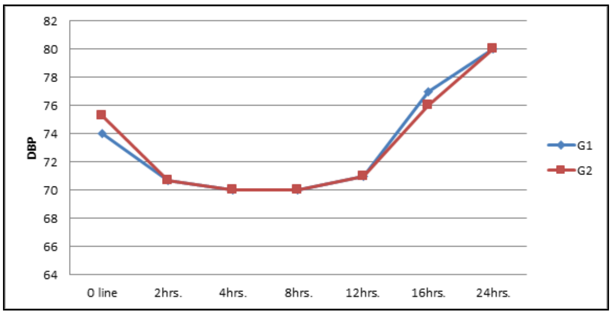

Fig (3): Diastolic blood pressure change in the two groups in postoperative period

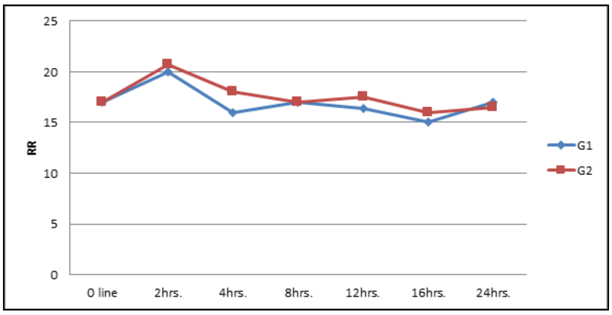

Fig (4): Respiratory rate change in the two groups in postoperative period

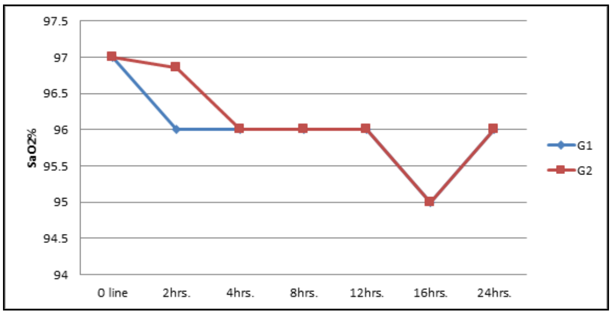

Fig (5): SaO2% change in the two groups in postoperative period

There was a statistically significant increase in the sedation score in G2 (ketamine group) as mean ±SD were (2.80±0.58) in comparison to G1 (control group) (1.1±0.0) at zero line (p<0.01). Table (2).

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

	G1	G2	P- value
Sedation: 0 line	1.10±0.00	2.80±058	P<0.02
Sedation: 2 hrs.	0.98±0.23	1.04±0.10	P=0.892, n.s
Sedation: 4 hrs.	0.00±0.00	0.80±0.10	P=0.497, n.s
Sedation: 8 hrs.	0.00±0.00	0.00±0.00	P=1, n.s
Sedation: 12 hrs.	0.00±0.00	0.00±0.00	P=1, n.s
Sedation: 16 hrs.	0.00±0.00	0.00±0.00	P=1, n.s
Sedation: 20 hrs.	0.00±0.00	0.00±0.00	P=1, n.s
Sedation: 24 hrs.	0.00±0.00	0.00±0.00	P=1, n.s

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 inG2, in comparison to G1 (p<0.05).Table (3) and figure (6)

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

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

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.

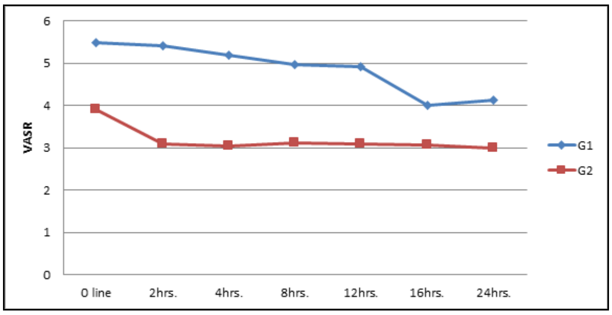

Fig (6): VASR change in the two groups in postoperative period

As regards mean of the VAS score with movement (VAS-M) in 24 hours follow up; there was statistically significant decrease in the mean VAS-M inG2, in comparison to G1(p<0.05) .

When comparing the mean of VAS-M at zero time with later readings in the 24hours postoperativel, there was statistically significant decrease in mean of VAS-M in G2, starting after 8hours and it continued to the end to the 24 hours (p<0.05). Table (4) and figure (7).

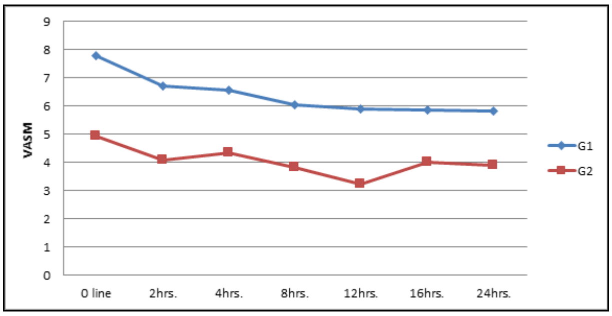

Fig (7): VASM change in the two groups in postoperative period

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

	G1	G2	P- value
VASM: 0 line	7.79±1.51	4.95±1.91	P<0.01
VASM: 2 hrs.	6.70±0.73	4.07±0.80	P<0.02
VASM: 4 hrs.	6.56±0.00	4.33±0.63	P<0.02
VASM: 8 hrs.	6.05±0.00	3.81±0.31*	P<0.01
VASM: 12 hrs.	5.90±0.90	3.23±0.22*	P<0.02
VASM: 16 hrs.	5.87±0.00	3.99±0.12*	P<0.04
VASM: 24 hrs.	5.84±0.21	3.88±0.11*	P<0.04

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±.2.45minuts in comparison with (G1) 8.65±.1.63 minutes (p<0.05) Table (5).

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

	G1	G2	P- value
Morphine first req. (minutes)	8.65±1.63	72.60±2.45	P<0.001

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

	G1	G2	P- value
Morphine 24 hrs.	18.70±12.01	10.30±2.58	P<0.01

Data were expressed as mean ±SD. n.s: non significance P>0.05
Morphin.24hrs: Morphine consumption during the 1st 24 hours
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 G2in comparison to G1 (p<0.000). Table (7) and figure (8).

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Table (7): LANSS in the two groups

	G1	G2	P- value
LANSS 1 (At 1st month)	7.20±2.64	6.80±1.28	P=n.s
LANSS 2 (At 2nd month)	7.85±4.65	5.15±2.43	P<0.04
LANSS 3 (At 3rd month)	7.30±3.89	7.30±3.89	P<0.001
LANSS 6 (At 6th month)	6.90±1.41	4.15±0.81	P<0.001

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

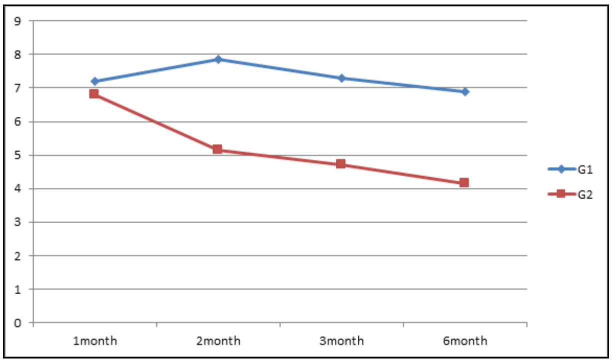

Fig (8): LANSS change in the two groups in postoperative period

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"

	G1	G2	P- value
LANSS 1 (At 1st month)	7 (35%)	2 (10%)	P<0.001
LANSS 2 (At 2nd month)	6(30%)	2(10%)	P<0.001
LANSS 3 (At 3rd month)	5(25%)	1(5%)	P<0.001
LANSS 6 (At 6th month)	5(25%)	1(5%)	P<0.001

Data were expressed as number and (%)
G1: Control group. G2: Ketamine group.

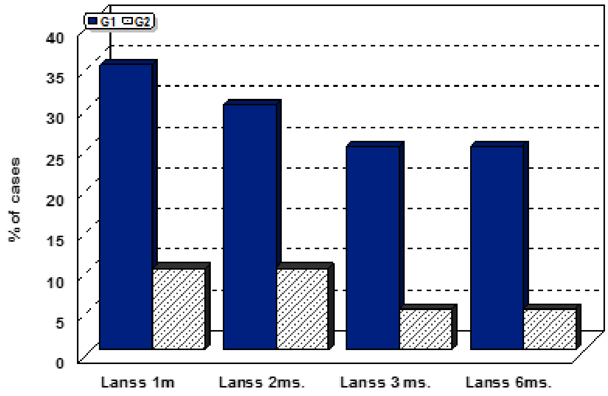

Fig (9): Neuropathic pain change in the two groups

As regard the adverse effects in the postoperative 24 hours there was a higher number of patients complaining of dizziness inG2.There were 9patients (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 G1and 2patients (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

	G1	G2	P- value
Dizziness	2(10%)	9 (45%)	P<0.001
Nausea	6(30%)	3(15%)	P<0.02
Vomiting	5(25%)	2(10%)	P<0.01

Data were expressed as number and (%)

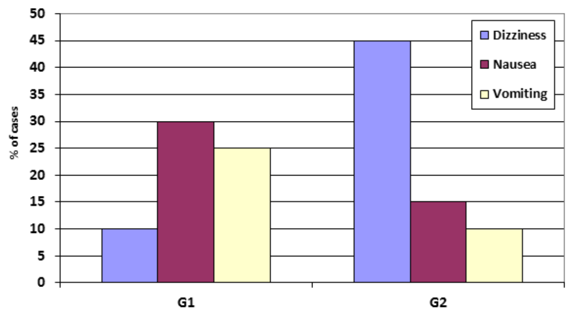

Fig (10): Incidence of side effects in the two groups in postoperative period

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

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system. This sensitization is precipitated by the original surgical insult and subsequent inflammatory conditions, and in turn leads to increased postoperative pain [16].

The reported incidence of persistent post mastectomy pain (PPMP) ranges from (25–60%) of breast cancer patients [17-19], PPMP is rated as the most troubling symptom [20], leading to disability and psychological distress, and is notably resistant to management [21]. The most established risk factor for chronic pain following breast cancer surgery, appears to be severe acute post-operative pain [5].

Stubhaug et al., 1997[22] demonstrated that perioperative ketamine plus morphine treatment reduces postoperative hyperalgesia following nephrectomy .Ketamine has analgesic properties that are mediated by a number of mechanisms. NMDA receptor noncompetitive antagonism accounts for most of its analgesic effects through a use-dependent channel blockade [23]. In experimental pain research, NMDA receptor antagonists reduced wind-up and central sensitization [24]. We found no statistically significant difference between the two groups as regard the 24hrs postoperative hemodynamic parameters (heart rate, systolic and diastolic blood pressure), the respiratory rate and oxygen saturation.

In agreement with our results Bilgen, et al., 2012 [25] tried 3 doses of preoperative IV Ketamine 0.25mg, 0.50mg and 1mg in caesarean delivery and found no significant difference in heart rate or in mean arterial blood pressure. Also no significant hemodynamic or respiratory rate changes, were associated with repeated and escalating sub anesthetic doses of IM ketamine administration [26]. Ketamine is a potent anesthetic and analgesic drug. When administered IV during anesthesia in adults, ketamine decreased postoperative pain intensity for up to 48 hours, decreased cumulative 24- hour morphine consumption, and delayed the time to first request of rescue analgesic [27].

Most of the trials reported on a statistically significant decrease in morphine consumption with ketamine; morphine- sparing ranged from 9% [28] to 47% [29], at the same time, patients had a reduction in pain intensity. Thus, the beneficial albeit moderate effect of ketamine on pain intensity should be interpreted in conjunction with the opioid- sparing effect. Some of them commented that there was no decrease in the incidence of morphine-related adverse effects although morphine consumption was clearly reduced with ketamine. One reason may be that these trials mainly concentrated on efficacy and did not systematically evaluate and report on adverse effects. This limitation on the reporting of adverse effects has been described by Edwards et al, 1999 [30].

Another reason may be that the decrease in morphine consumption was not strong enough to impact the incidence of morphine-related adverse effects; In postoperative patients who experienced only partial pain relief with morphine (i.e. VAS pain intensity O6/10 despite intravenous morphine 0.1 mg/kg), small doses of ketamine (0.25 mg/kg, up to three times) rapidly improved pain relief [31]. These observations support the role of the NMDA receptor in the acute pain setting.

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 by 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]. Kararmaz 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: Ilkjær,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:

[1] Kuehn T, Klauss W Darsow M Regele S, Flock F, Maiterth C, Dahlbender R, Wendt I, Kreienberg R: **Long-term morbidity following axillary dissection in breast cancer patients-clinical assessment, significance for life quality and impact of demographic, oncologic and therapeutic factors**. *Breast cancer Res Treat* 2000**: 64**(3):275-86.

[2] Peintinger F, Reitsamer R, Stranzl H, Ralph G: **Comparison of quality of and life arm complaints after axillary lymph node dissection vs sentinel node biopsy in breast cancer patients**. *Br J Cancer*. 2003;**89**:648–52.

[3] De Vries JE, Timmer PR, Erftemeier EJ, van der Weele LT: **Breast pain after breast conserving therapy**. *Breast.* 1994;**3**:151–54.

[4] Macdonald L, Bruce J, Scott NW, Smith WC, Chambers WA: **Long-term follow up of breast cancer survivors with post-mastectomy pain syndrome***. Br J Cancer* 2005;**92**:225–30.

[5].Poleshuck EL, Katz J, Andrus CH, Jung BF, Kalick DI, Dworkin RH: **Risk factors for chronic pain following breast cancer surgery: a prospective study**. *The Journal of Pain* 2006**;7(9**):626-34

[6] Torresan RZ, Cabello C, Conde DM, Brenelli HB.: **Impact of the preservation of the intercostobrachial nerve in axillary lymphadenectomy due to breast cancer.** *The Breast J.* 2003;**95:**389–92.

[7] Johansson S, Svensson H, Larsson LG, Denekamp J**: Brachial plexopathy after postoperative radiotherapy of breast cancer patients—a long-term follow- up**. *Acta Oncol* 2000, **39**:373-82.

[8] Shons AR, Cox CE**: Breast cancer: advances in surgical management**. *Plast Reconstr Surg*. 2001**;107** 2:541–9.

[9] Mercadante S, Arcuri E, Tirelli W, Casuccio A: **Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study**. *J. Pain Symptom. Manage*. 2000,**20,** 246–52 .

[10] Celerier E, Laulin JP, Corcuff JB, Le Moal, M, Simonnet G: **Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process**. *J Neurosci* 2001;**21**:4074–80.

[11] Woolf CJ, Thompson SWN: **The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states**. *Pain* 1991**; 44**:293–9.

[12] Yamamoto T, Yaksh TL.: **Spinal pharmacology of thermal hyperesthesia induced by constriction injury of sciatic nerve: excitatory amino acid antagonists**. *Pain* 1992;**49**:121–8.

[13] Saito O, Aoe T, Kozikowski A, Sarva J, Neale JH, Yamamoto T**: Ketamine and N-acetyl aspartyl glutamate peptidase inhibitor exert analgesia in bone cancer pain.** Canadian Journal of Anesthesia 2006, **53** (9): 891–8..

[14] Enarson MC, Hays H, Woodroffe MA: **Clinical experience with oral ketamine**. *J Pain Symptom Manage* 1999;**17:**384–6

[15] Mao J: **Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy**. *Pain* 2002;**100**: 213–7.

[16] Kissin I: **Preemptive analgesia**. *Anesthesiology* 2000; **93**: 1138–43.

[17] Andersen KG, Kehlet H**: Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention**. *J Pain* 2011;**12**:725–46.

[18] Cheville AL, Tchou J: **Barriers to rehabilitation following surgery for primary breast cancer.** *J Surg Oncol* 2007**; 95**:409–18.

[19] Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kulick DI, Dworkin RH: **Risk factors for acute pain and its persistence following breast cancer surgery**. *PAIN_* 2005;**119**:16–25.

[20] Lauridsen MC, Overgaard M, Overgaard J, Hessov IB, Cristiansen P: **Shoulder disability and late symptoms following surgery for early breast cancer**. *Acta Oncol* 2008;**47:**569–75.

[21] Basen-Engquist K, Hughes D, Perkins H, Shinn E, Taylor CC**: Dimensions of physical activity and their relationship to physical and emotional symptoms in breast cancer survivors**. *J Cancer Surviv* 2008;**2**:253–61.

[22] Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A**: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery.** *Acta Anaesthesiol Scand*. 1997;**41**:1124–32.

[23] Kohrs R, Durieux M: **Ketamine: teaching an old drug new tricks**. *Anesth Analg* 1998;**87:**1186–93.

[24] Chapman V, Dickenson AH: **The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn.** *Brain Res* 1992**; 573**:321–3.

[25] Bilgen S1, Köner O, Türe H, Menda F, Fiçicioğlu C, Aykaç B: **Effect of three different doses of ketamine prior to general anaesthesia on post operative pain following Caesarean delivery: a prospective randomized study** .*Minerva Anestesiologica* 2012; **78**:442-9

[26] Rakhman E1, Shmain D, White I, Ekstein MP, Kollender Y, Chazan S, Dadia S, Bickels J, Amar E, Weinbroum AA: **Repeated and Escalating Preoperative Subanesthetic Doses of Ketamine for Postoperative Pain Control in Patients Undergoing Tumor Resection: A Randomized, Placebo-Controlled, Double-Blind Tria**l. *Clin Ther*. 2011;**33**:863–73

[27] Elia N, Tramèr MR: **Ketamine and postoperative pain--a quantitative systematic review of randomised trials.** *Pain*, 2005: **113 (1–2)**:61–70.

[28] Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M: **The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair**. *Anesthesia and Analgesia* 2000;**90**:129–35.

[29] Jaksch W, Lang S, Reichhalter R, Raab G, Dann K, Fitzal S: **Perioperative small-dose S (+)-ketamine has no incremental beneficial effects on postoperative pain when standardpractice opioid infusions are used.***Anesthesia and Analgesia*2002;**94**:981–6

[30] Edwards JE, McQuay HJ, Moore RA, Collins SL**: Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain**. *J Pain Sympt Manag* 1999;**18**(6):427–37.

[31] Weinbroum AA: **A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain**. *Anest Analg* 2003;**96:**789–95.

[32] Bell R, Eccleston C, Kalso E**: Ketamine as an adjuvant to opioids for cancer pain (Cochrane review**). *Cochrane Database Syst Rev* 2003; **1:**CD003351

[33] Fisher K, Coderre TJ, Hagen NA: **Targeting the NMethyl- D-Aspartate receptor for chronic pain management: preclinical animal studies, recent clinical experience and future research directions.** *Journal of Pain and Symptom Management* 2000;20(**5**):358–73.

[34] Schmid RL, Sandler AN, Katz J: **Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes**. *Pain* 1999;**82:**111–25.

[35] Price DD, Mayer DJ, Mao J, Caruso F: **NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance**. *Journal of Pain and Symptom Management* 2000;**19(1 Suppl**):S7–S15.

[36] Michelet P, Guervilly C, Helaine A, AvaroJP,Blayac D, Gaillat F, Dantin T, Thomas P, Kerbaul F: **Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation.** *Br J Anaesth* 2007;**99:**396-403.

[37] Menigaux C1, Guignard B, Fletcher D, Sessler DI, Dupont X, Chauvin M: **Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy**. *Anesth Analg.* 2001 Sep;93(3):606-12.

[38] Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL, Kissin I: **Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia.** *Anesth and Analgesia* 1994**;78**:205–9.

[39] Cho HT, Kende H: **Expression of expansion genes is correlated with growth in deep water rice**. *Plant Cell* 1997:**9**, 1661–71.

[40] Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J: **Preoperative Small-Dose Ketamine Has No Preemptive Analgesic Effect in Patients Undergoing Total Mastectomy.** *Anesth Analg* 1999;**89**:444-7

[41] Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A: **Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia.** *Regional Anesthesia and Pain Management* 1993; **77:**1161–5.

[42] Barbieri M, Colnaghi E, Tommasino C**: Efficacy of the NMDA antagonist ketamine in preemptive analgesia**. In: Jensen TS, Turner JA, Wiesenfeld-Hallin Z, eds. Proceedings of the 8th world congress on pain. Seattle: *IASP Press*, 1997:343

[43] Fu ES, Miguel R, Scharf JE: **Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery.** *Anesth Analg* 1997;84:1086–90.

[44] Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A: **Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy**. *Anesthesiology* 2006;**105**:111–9

[45] De Kock M, Lavand'homme P, Waterloos H: **Balanced analgesia' in the perioperative period: is there a place for ketamine?** *Pain***,** (2001), **92** pp. 373–380

[46] Aveline C, Gautier JF, Vautier P, Cognet F, Hetet HL, Attali JY, Leconte V, Leborgne P, Bonnet F: **Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam**. *Eur J Pain* 2009;**13**:613–9

[47] Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D: **Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty.** *Anesth Analg* 2005;**100**:475–80

[48] Perkins FM, Kehlet H**: Chronic pain as an outcome of surgery. A review of predictive factors**. *Anesthesiology* 2000;**93**:1123–33..

[49] Perttunen K, Tasmuth T, Kalso E**: Chronic pain after thoracic surgery: a follow up study**. *Acta Anaesthesiol Scand* 1999**;43**:563–7.

[50] Wartan SW, Hamann W, Wedley JR, McColl I**: Phantom pain and sensation among British veteran amputees.** *Br J Anaesth* 1997;**78**:652–9.

[51] Dahan A, Olofsen E, Sigtermans M, Noppers I, Niesters M, Aarts L, Bauer M, Sarton E**: Population pharmacokinetic–pharmacodynamic modeling of ketamine-induced pain relief of chronic pain**. *Eur J Pain.* 2010;**15**:258–67.

[52] Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Dahan A: **Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1**. *Pain*. 2009; **145**:304–311.

DOI: 10.18056/seci2014.4

[53] Hercock T, Gillham MJ, Sleigh J, Jones SF: **The addition of ketamine to patient controlled morphine analgesia does not improve quality of analgesia after total abdominal hysterectomy**. *Acute Pain* 1999;**2**:68–72.

[54] Javery KB, Ussery TW, Steger HG, Colclough GW: **Comparison of morphine and morphine with ketamine for postoperative analgesia** .*Can J Anaesth,*1996**: 43**:212-215

[55] Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA**: Intraoperative intravenous ketamine in combination with epidural analgesia: Postoperative analgesia after renal surgery**. *Anesthesia and Analgesia* 2003**;97:**1092–6.

[56] Murdoch 2002 {published data only} Murdoch CJ, Crooks BA, Miller CD**: Effect of the addition of ketamine to morphine in patient-controlled analgesia.** *Anaesthesia* 2002**;57**:484–500.

[57] Adriaenssens G, Vermeyen KM, Hoffmann VLH, Mertens E, Adriaensen HF: **Postoperative analgesia with i.v. patient controlled morphine: effect of adding ketamine**. *British Journal of Anaesthesia* 1999;**83(**3):393–6.

[58] Bell RF, Dahl JB, Moore RA, Kalso E: **Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review).** *Acta Anaesthesiol Scand* 2005;**49**:1405–28

[59] Himmelseher S, Durieux ME: **Ketamine for perioperative pain management**. *Anesthesiology* 2005;**102**:211–20

[60] Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB**: Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery**. *Br J Anaesth* 1998; **81:**707–12.

[61] Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, Simonnet G, Chauvin M: **Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requir45.ements**. *Anesth Analg* 2002**;95**:103–8.

[62] Mathisen L, Aasbø V, Raeder J: **Lack of pre-emptive analgesic effect of (R)-ketamine in laparoscopic cholecystectomy**.*Acta Anaesthesiologica Scandinavica* 1999**;43**:220–4..

[63] Subramaniam B, Subramaniam K, Pawar DK, Sennaraj B: **Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra- and postoperative opioid-sparing effect**. *Anesth Analg* 2001**;93**:1321–6.

[64] Perel JM, Mendlewicz J, Shostak M, Kantor SJ, Glassman A: **Plasma level of imipramine in depression: environmental and genetic factors**. *Neuropsychobiology* 1976; **2**:193-202.