Dexmedetomidine Infusion for Post-Mastectomy Pain improves Patients' Quality of Life and Surgeons' Satisfaction

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Abstract

Background: Cancer breast is the commonest cancer affecting females and mastectomy is still the standard therapy. However, uncontrolled intraoperative (IO) and postoperative (PO) pain will progress for long-term and affects patients' quality of life (QOL).

Objectives: The effect of perioperative dexmedetomidine (DEX) and Ketamine/Midazolam (KET/MID) infusions on the incidence and severity of postmastectomy pain (PMP) and patients' QOL.

Patients and methods: 120 women were randomly divided into Placebo, K/M and DEX groups. Bolus dose (0.5 ml/kg) was given over 10-min before induction, followed by IO and PO infusions at rate of 0.25 and 0.1 ml/ kg/h, respectively. PMP was evaluated at time of discharge and two monthly for 6-m PO for pain sensation with assessment of the neuropathic character of pain using Douleur Neuropathique-4 questionnaire. Patients' QOL at the 6th month PO was evaluated using the Short-form questionnaire and surgeon's satisfaction was evaluated using 5-point scale.

Results: incidence of PMP was 55%, 35% and 22.5% in placebo, K/M and DEX groups, respectively. Median PMP score was significantly lower with DEX than other infusions and with K/M than Placebo infusion. Neuropathic pain scoring was significantly higher with placebo than other infusion. Patients' QOL and surgeon's satisfaction scorings were significantly higher with DEX and K/M infusions than Placebo infusion and with K/M infusion than Placebo infusion.

Conclusion: Perioperative DEX or KET infusion significantly reduced the incidence and severity of PMP with improvement of patients' QOL and surgeon's satisfaction. DEX perioperative infusion provided superior outcome than K/M infusion.

Keywords: Postmastectomy pain syndrome; Dexmedetomidine; Ketamine; Douleur Neuropathique-4 questionnaire.

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Introduction

Breast cancer is the commonest malignant tumors among women **(Jiang et al., 2021)** and mastectomy is mostly performed as definitive management for resectable breast cancer **(de Boniface et al., 2021)**. Unfortunately, about 60% of mastectomy patients experience severe postoperative (PO) acute pain, which is associated with increased morbidity and impaired quality of life **(García-Solbas et al., 2021)**.

Severe acute PO pain may predispose to the development of chronic postsurgical breast pain **(Meretoja et al., 2017)** and prolonged opioid use **(Sun et al., 2016)**. Thus, improved anesthetic factors and effective pain management are crucial for enhanced recovery and have positive significance for promoting the rehabilitation of patients after mastectomy **(Berger et al., 2020)**.

Post-mastectomy pain syndrome (PMPS) is a chronic pain of neuropathic character and affects about 20-50% of mastectomy patients **(Abbas and Reyad, 2018)**. Treatment options for neuropathic pain were variable **(Chappell et al., 2021)**. However, identification of patients who had a high risk to develop PMPS, anesthetic, and analgesic manipulation during and after surgery to control acute PO pain, the proper choice of surgical technique may be an effective way to reduce PMPS **(Chappell et al., 2020)**. Thus, this study compared the effects of perioperative infusion of dexmedetomidine (DEX) versus ketamine/midazolam (K/M) in a placebo-controlled study on PMP incidence and severity, and the effect of PMP on patients' quality of life (QOL).

Patients and methods

This prospective study was conducted at Departments of General Surgery and Anesthesia, Benha University hospital. All patients assigned for modified radical mastectomy were clinically evaluated for demographic and general clinical data, and neuropsychiatric status. Women with advanced cancer breast, distant metastasis, ASA grade III-IV, neuropsychiatric disorders, preoperative lymphedema, cardiac, hepatic or renal diseases were excluded. Women assigned for modified radical mastectomy for breast cancer and were free of exclusion criteria were enrolled in the study.

Ethical considerations

The study was started at Jan 2019 after obtaining a preliminary approval for the study protocol and ended Jan 2021 to allow at least 6-m follow-up for the last case and the final approval was obtained after completion of the data collection by number **RC: 15.10.2021.**

Sample size calculation

Review of literature for the prevalence of PMPS defined an incidence range of 25-60% among patients who received only PO analgesia without preparation **(Andersen and Kehlet, 2011)** and a prospective study for the same target found the incidence was 52% **(Fabro et al., 2012)**. Thus, the predicted incidence in the placebo group will range between 25% and 60% and both study solutions were predicted to decrease such prevalence to the minimum incidence reported in the placebo group, i.e., 25%. The sample size that allows reaching these figures with a power of 85% and α value of 0.05 and β value of 0.15 was calculated to be >34 patients per group. The study intended to include 40 patients per group to guard against missed cases during the 6-month follow-up period

Randomization

Randomization sequence was created with a 1:1 allocation using random block sizes of 2 and 4 by an independent assistant and the generated sequence were transformed as cards carrying group labels (Placebo, K/M, or DEX) put in sealed envelopes and was gave to patient to provide it to the anesthetist in charge.

Analgesic protocol

A) **Preparations:** Infusions were freshly prepared on the morning of the day of surgery by an assistant who will not participate in patients' evaluations and the anesthetist in charge will be blinded about the significance of the label. Study infusions included the following: Placebo infusion (Plain 500 ml normal saline 0.9%), K/M infusion is provided as 500 ml normal saline (0.9%) mixed with ketamine hydrochloride (250 mg) and midazolam (10 mg) to provide 0.5 mg and 20 µg per ml, respectively. DEX infusion is supplied as 500 ml normal saline (0.9%) mixed with 1000 µg of DEX to provide 2 µg/ml.

B) **Administration protocol:** On arrival to the theater, a bolus dose (0.5 ml/kg) of the study infusion was given over ten minutes. During surgery, infusions were given at a rate of 0.25 ml/kg/h that was reduced to 0.1 ml/ kg/h for 24-h PO

Anesthetic procedure

All patients underwent Modified radical mastectomy "Pattey's Procedure" under general anesthesia using the same anesthetic technique and by the same surgical team. Before induction, patients were pre-oxygenated and after administration of the bolus dose of the study drug, anesthesia was induced with intravenous (IV) fentanyl in a dose of 2 µg/kg, propofol in dose range of 1–2 mg/kg and cis-atracurium in a dose of 0.15 mg/kg to facilitate orotracheal intubation. General anesthesia was maintained with sevoflurane in oxygen and air and minute ventilation was adjusted to maintain end-tidal CO2 at 35±5mmHg. Intraoperative neuromuscular block was produced with cis-atracurium. At the end of the surgery, atropine sulfate 0.02 mg/kg and neostigmine 0.04 mg/kg were administered I.V. for reversal of muscle relaxation, and the trachea was extubated. Following extubation, the patients were maintained on supplemental O_2 until awake in the recovery room.

Intraoperative monitoring

Heart rate (HR) and mean arterial pressure (MAP) were non-invasively recorded before induction of anesthesia (T0), after intubation (T1), and after extubation (T2). Duration of surgery, duration of anesthesia, and occurrence of intraoperative complications, time till transfer to, and discharge from PACU were recorded.

Immediate PO care

Acute PO pain was evaluated using a 10-point numeric rating scale (NRS) preoperatively and 4-hourly for 24-hr PO; higher scores indicated more severe pain **(Williamson and Hoggart, 2005)**. During the immediate 24-hr after surgery, regular analgesia was provided in the form of parecoxib (Dynastat, 40 mg IV every 6-hr) and intramuscular morphine 5 mg if NRS pain score was ≥7 and can be repeated if required. The average 24-hr dose of morphine was calculated according to the patient's age as 100 minus the age and was titrated according to the effect **(Macintyre and Jarvis, 1996)**.

Outcome evaluation tools

1. **Postmastectomy pain (PMP)**
   - Pain severity was evaluated in 6 locations; breast scar, drain site, anterior chest wall, axilla,

arm, and shoulder, using a visual analog scale of 0-10 for a minimum score of 0 and a maximum score of 60 points. Pain severity was evaluated every two months for 6-m after surgery and a median score of > 3 suggested PMPS.

- The neuropathic quality of PMP was evaluated using the Douleur Neuropathique-4 (DN-4) questionnaire, which consists of 5 questions of 10 items. Each item was answered by yes (score=1) or no (score = 0) for a total score of 0-10 and at the cutoff point of ≥4 at the 6th month PO was diagnostic for neuropathic quality **(Unal-Cevik et al., 2010)**.
- Management of PMP depended on receiving Gabapentin (Gaptin 100 & 300 mg cap; Delta Pharmaceutical industries; Al-Amyria, Egypt) therapy that was initiated with 100 mg or 300 mg three times daily for patients older or younger than 60 years old, respectively and increased gradually through three days up to 3600 mg/day according to clinical response and development of side effects. Non-steroidal anti-inflammatory drugs; meloxicam (Anti-Cox II 15 mg tab; Adwia Co. Al-Amyria, Egypt) was also administered as one tab three times daily.

2. **The Short-form-36 (SF-36)** is a multi-function scale which is consisted of 36 items scored from 0-100 with maximum score indicated better quality of life **(Ware, 1996)**.
3. **Surgeon' satisfaction** by the outcome was evaluated using 5-point scale with 1 indicated totally unsatisfied, 2 indicated partially satisfied, 3 indicated satisfied, 4 indicated more than satisfied and 5 indicates very satisfactory outcome **(Wang et al., 2001)**.

Study outcomes

1. Primary outcome is the ability of the provided infusions to reduce the incidence of PMP within 6-m PO
2. Secondary outcome is the effect of the used infusions on patients' QOL and surgeon' satisfaction

Statistical analysis

One-way ANOVA test was used for analysis of inter-group differences, paired t-test for analysis of intra-group difference, Chi-square test (X^2 test) for analysis of non-numeric data and Mann-Whitney test for median values. IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) was used for analyzing the obtained data. Significance of difference was defined at P value of <0.05.

Results

During the study duration, 120 women showing non-significant difference as regards the enrolment data (**Table 1**) were randomly grouped into the three groups (**Fig. 1**).

Table 1. Enrolment and operative data of patients of the three groups

Infusion Variable	Placebo (n=40)	K/M (n=40)	DEX (n=40)
Age (years)	56.9±7.9	58±5.7	59.3±7.5
Body mass index (kg/m^2)	29.2±2.3	29.2±2.1	29.5±2.2
ASA grade; I:II	17:23	21:19	13:27

Associated morbidities	7 (17.5%)	6 (15%)	8 (20%)
Operative time (min)	116.5±14.6	121.5±11.9	123±13.7
Anesthesia time (min)	128±15.4	131.4±12.4	133.3±14.7

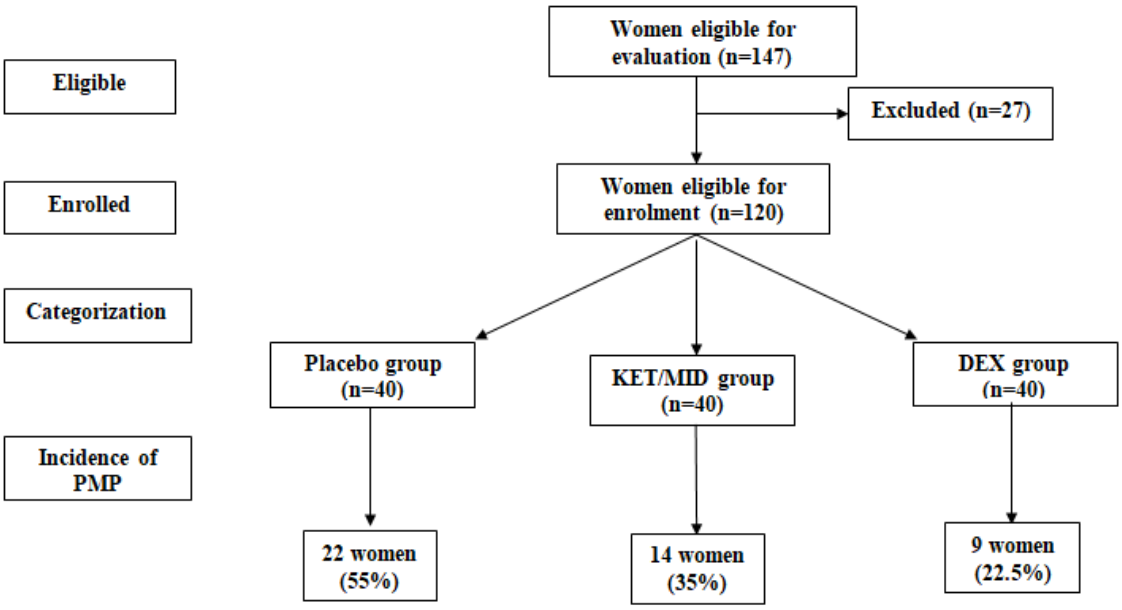

Fig. (1): Flow chart of the study

The recorded HR measures at times of intubation and extubation were significantly higher in all patients in comparison to preoperative rate. However, HR measures that were recorded at time of intubation in patients of DEX group were significantly lower compared to that of patients of placebo (P=0.0048) and K/M (P=0.007) groups. Similarly, mean values of MAP records at times of intubation and extubation were significantly higher in patients of placebo and K/M groups in comparison to their preoperative measures. On contrary, mean values of MAP measures of patients of DEX group were significantly higher at time of intubation, but non-significantly higher at time of extubation in comparison to preoperative measures. Moreover, patients of DEX group showed significantly lower MAP measures at time of intubation and extubation in comparison to patients of placebo (p=0.014 & <0.001, respectively) and K/M group (P=0.013 & <0.001, respectively), with significantly (P=0.015) lower MAP records in patients of K/M in comparison to patients of placebo group at time of extubation (**Table 2**).

Table 2. HR and MAP measures recorded after time of intubation and extubation of patients of the three groups in comparison to preoperative measures

Infusion Variable		**Placebo (n=40)**	**K/M (n=40)**	**DEX (n=40)**
HR (beats/min)	Preoperative	79.8±2.1	80.4±4.9	81±3.2
	Intubation	86.5±4*	86±2.4*	84.4±3.1*†‡
	Extubation	84.6±2*	84.1±4.1*	83.4±2.9*

MAP (mmHg)	Preoperative	87±4	89.2±3.7	87±3.9
	Intubation	93.4±3.9*	93.3±3.5*	91.2±3.5*†‡
	Extubation	94.5±3.8*	92.4±4.1*†	87.3±3.7†‡

*: indicates significance versus preoperative measures; †: indicates the significance of difference versus measures of placebo group; ‡: indicates the significance of difference versus K/M group; significance means P value was <0.05

The determined pain NRS scores throughout 24-h PO were significantly lower in groups K/M and DEX than placebo group. At 16-24-h after surgery pain scores were significantly (P=0.047, 0.016 & 0.037, respectively) lower in patients of DEX group compared to patients of K/M group. All patients of placebo group required morphine as rescue analgesia, while only 29 patients of the study groups required morphine with significant (P<0.001) differences between placebo and study groups. The duration till 1st request of morphine was significantly (P<0.001) longer in the study groups compared to placebo group (**Table 3**).

Table 3. PO pain scores and management of patients of the three groups

Infusion Variable		**Placebo (n=40)**	**KET/MID (n=40)**	**DEX (n=40)**
Median value of NRS pain score (Interquartile range)	**T0**	1 [0-1]	1 [0-1]	1 [0-1]
	4-hr	2 [1-3]	0 [0-0]*	0 [0-0]*
	8-hr	3 [2-4]	0 [0-1]*	0 [0-1]*
	12-hr	4 [1-4]	1 [0.25-1]*	1 [0-1]*
	16-hr	1.5 [0.25-2]	1 [1-2]	1 [0-2]†
	20-hr	2.5 [2-4]	1.5 [1-3]*	1 [0-1.75]*†
	24-hr	2 [0-4]	1 [0-2]	0.5 [0-1]*†
Duration till 1st request of morphine		9.9±2.9	20.7±3.1*	19.6±2.8*
No. of patients requested morphine		40 (100%)	18 (45%)*	11 (27.5%)*

*: indicates the significance versus placebo group; †: indicates the significance of difference versus K/M group;

After 6-m follow-up, 45 patients developed PMPS; 22 women (55%) in placebo, 14 women (35%) in K/M and 9 women (22.5%) in DEX groups. The incidence of PMPS was significantly lower with DEX than placebo group (P=0.0029), while was non-significantly (P=0.216) lower than the incidence of PMSP in K/M group with non-significantly (P=0.072) lower incidence in K/M group in comparison to placebo group

Median values of chronic pain score during 6-m PO were significantly (P<0.001) lower with DEX and K/M infusions than placebo and with DEX than K/M infusion. The frequency of patients had high DN-4 score and the median value of the score were significantly (P=0.007 & 0.042, respectively) lower among patients of DEX group compared to patients of placebo group. Patients' QOL scoring showed significant (P<0.001) difference with study infusions than placebo, with significant (P<0.001) difference between DEX and K/M groups. The median value of surgeon's satisfaction score was significantly higher with DEX (P<0.001) and K/M (P=0.001) infusions than with placebo and with DEX (P=0.007) than with K/M infusion (**Table 4**).

Table 4. 6-m PO data of the studied patients

Variable / Infusion		**Placebo (n=40)**	**KET/MID (n=40)**	**DEX (n=40)**
Median of the 6-m chronic pain score		3.5 [2.75-4.25]	2 [1.5-3.25]*	1.125 [0.5-1.75] *†
Douleur Neuropathique-4 questionnaire score	0-2	0	3 (7.5%)	2 (5%)
	3-4	18 (45%)	23 (57.5%)	29 (72.5%)
	>4	22 (55%)	14 (35%)	9 (22.5%)
	Median value	5 [4-7]	4 [3-5]	4 [3-4.75] *
SF-36 QOL score		37±9.5	55±11.8*	71±12.9*†
Surgeon' satisfaction score		3 [3-4]	4 [3-4]*	4 [4-5]*†

*: indicates the significance versus placebo group; †: indicates the significance of difference versus K/M group

Discussion

The applied analgesic infusions provided excellent relief of immediate PO pain with significantly lower pain scores, long duration till 1st request of rescue analgesia and lower consumption of PO rescue analgesia than placebo infusion and non-significant differences between both types of infusion. These findings indicated the efficacy of the applied analgesic procedure, irrespective of the type of analgesic used and go in hand with a previous similar comparative study, which documented that both KET and DEX infusions provided good analgesia with significant differences compared to placebo infusion and showed minimal side effects **(Garg et al., 2016).**

Both analgesic infusions lessened the pressor reflex to intubation and extubation in comparison to placebo, but the effect was more pronounced with DEX infusion than with K/M infusion, a finding suggesting a more hemodynamic stabilizing effect of DEX than KET. In line with these results, multiple recent studies documented the efficacy of DEX in terms of sedation depth, hemodynamic stability, and minimal adverse effects **(Mukherjee et al., 2020; Hu et al., 2021; Ye et al., 2021; Tekeli et al., 2022).**

During 6-m PO follow-up, the incidence of PMP was significantly lower with DEX, but was non-significantly lower with K/M infusion in comparison to placebo infusion. These data spotlight on the superiority of DEX infusion over KET or placebo infusion as a prophylactic policy against the development of PMPS.

The obtained results concerning K/M infusion supported the previous studies that found perioperative or intraoperative continuous ketamine infusion at low dose allowed reduction of the incidence of PMPS effectively **(Lou et al., 2017; Kang et al., 2020; Bi et al., 2021)**, but one study documented the shortage of KET infusion as regards PMPS severity and patients' quality of life **(Kang et al., 2020)**. On contrary, perioperative DEX infusion was documented by multiple recent studies to effectively attenuate the incidence and severity of chronic pain, improve the quality of life, decrease opioid consumption, and prevent the transition from PO acute pain to chronic pain **(Jain et al., 2012; Li et al., 2018; Rao et al., 2021)**.

Multiple suggestions were recently provided to explain the mechanism of action of DEX for alleviation of neuropathic pain, using chronic constriction injury model in rats preemptive DEX reduced the resulting neuropathic pain by

suppressing NLR family pyrin domain containing 3 through activation of nuclear factor erythroid 2-related factor 2 **(Shan et al., 2021)**, by inhibiting the Kelch-like ECH-associated protein *1-transcription factor Nrf2*-heme oxygenase-1 related antioxidant response, inflammation, and apoptosis **(Liu et al., 2021)**, or by regulating the expression of nuclear factor κb, thus decreasing expression and release of inflammatory mediators **(Wang and Liu, 2021)**.

The reported variability in response to and duration of action of DEX infusion could be attributed to an inverse relationship between the dose of DEX to achieve optimal analgesic effect and duration of action and increased G-protein signaling protein 4 expression level as evidenced by a mouse model of persistent, chronic neuropathic pain, where spared nerve injury-induced progressive increase in plasma membrane expression of G-protein signaling protein 4 leading to progressively decreasing the efficacy of α2-adrenergic receptor' agonists, but higher doses could restore the effect **(Yoon et al., 2021)**.

Conclusion

Perioperative DEX or KET infusion significantly reduced acute PO pain severity and need for opioid analgesia with decreased incidence and severity of PMP in comparison to placebo infusions. Perioperative DEX infusion provided superior control of acute and chronic PMP for a longer duration and with higher patients' QOL and surgeon's satisfaction scores.

Limitation

The type of surgery "Pattey procedure" is a limitation as the study needs to be applied for patients requiring more extensive surgery "Radical mastectomy" which most probably increases the incidence and severity of PMP.

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