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

Mohamed A. Khashaba\textsuperscript{a}, Emad El-Dein M. Abdel Hafez\textsuperscript{b}, Shereen M. Abdul Wahab\textsuperscript{c}, Mohamed H. Abdel Rahman\textsuperscript{a*}

\textsuperscript{a}Department of Anesthesia, Pain & ICU, Faculty of Medicine, Benha University, Benha, Egypt.
\textsuperscript{b}Department of General Surgery, Faculty of Medicine, Benha University, Benha, Egypt.
\textsuperscript{c}Department of Public Health, Faculty of Medicine, Benha University, Benha, Egypt.

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 6\textsuperscript{th} 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.

DOI: 10.21608/svuijm.2022.175488.1449

*Correspondence: hamed.mohamed.pf.2021@gmail.com
Received: 8 November,2022.
Revised: 18 November,2022.
Accepted: 28 November,2022.

Cite this article as: Mohamed A. Khashaba , Emad El-Dein M. Abdel Hafez , Shereen M. Abdul Wahab, Mohamed H. Abdel Rahman. (2022). Dexmedetomidine Infusion for Post-Mastectomy Pain improves Patients' Quality of Life and Surgeons' Satisfaction. SVU-International Journal of Medical Sciences. Vol.5, Issue 2, pp: 563-573.

Copyright: © Khashaba et al (2022) Immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge. Users have the right to Read, download, copy, distribute, print or share link to the full texts under a Creative Commons BY-NC-SA 4.0 International License
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 O2 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/m²) | 29.2±2.3    | 29.2±2.1  | 29.5±2.2  |
| ASA grade; I:II   | 17:23         | 21:19     | 13:27     |
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 | Intubation | Extubation |
|---|---|---|---|
| | 87±4 | 93.4±3.9* | 94.5±3.8* |
| | 89.2±3.7 | 93.3±3.5* | 92.4±4.1*† |
| | 87±3.9 | 91.2±3.5*† | 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

| Variable | Infusion | 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                       | 3 (7.5%)          | 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 I-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.

Acknowledgment
The authors deeply thank the staff members of General surgery and Anesthesia Departments for provision of help to finalize the study.

References

- Abbas D, Reyad R. (2018). Thermal Versus Super Voltage Pulsed Radiofrequency of Stellate Ganglion in Post-Mastectomy Neuropathic Pain Syndrome: A Prospective Randomized Trial. Pain Physician, 21(4):351-362.
- Andersen K, Kehlet H (2011). Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain, 12(7):725-46. Doi: 10.1016/j.jpain.2010.12.005
- Berger J, Longhitano Y, Zanza C, Sener S (2020). Factors affecting the incidence of chronic pain following breast cancer surgery: Preoperative history, anesthetic management, and surgical technique. J Surg Oncol, 122(7):1307-1314. Doi: 10.1002/jso.26176.
- Bi Y, Ye Y, Zhu Y, Ma J, Zhang X, Liu B (2021). The Effect of Ketamine on Acute and Chronic Wound Pain in Patients Undergoing Breast Surgery: A Meta-Analysis and Systematic Review. Pain Pract, 21(3):316-332. Doi: 10.1111/papr.12961.
- Chappell A, Bai J, Yuksel S, Ellis M (2020). Post-Mastectomy Pain Syndrome:
Defining Perioperative Etiologies to Guide New Methods of Prevention for Plastic Surgeons. World J Plast Surg, 9(3):247-253. Doi: 10.29252/wjps.9.3.247.

- **Chappell A, Yuksel S, Sasson D, Wescott A, Connor L, Ellis M (2021).** Post-Mastectomy Pain Syndrome: An Up-to-Date Review of Treatment Outcomes. JPRAS Open, 30:97-109. Doi: 10.1016/j.jpra.2021.07.006.

- **de Boniface J, Szulkin R, Johansson A (2021).** Survival After Breast Conservation vs Mastectomy Adjusted for Comorbidity and Socioeconomic Status: A Swedish National 6-Year Follow-up of 48 986 Women. JAMA Surg, 156(7):628-637. Doi: 10.1001/jamasurg.2021.1438.

- **Fabro EAN, Bergmann A, Silva B, Ribeiro A, de Souza Abrahão K, da Costa Leite Ferreira M, et al (2012).** Post-mastectomy pain syndrome: incidence and risks. Breast, 21(3):321-5. Doi: 10.1016/j.breast.2012.01.019.

- **García-Solbas S, Lorenzo-Liñán M, Castro-Luna G (2021).** Long-Term Quality of Life (BREAST-Q) in Patients with Mastectomy and Breast Reconstruction. Int J Environ Res Public Health, 18(18):9707. Doi: 10.3390/ijerph18189707.

- **Garg N, Panda N, Gandhi K, Bhagat H, Batra Y, Grover V, Chhabra R (2016).** Comparison of Small Dose Ketamine and Dexmedetomidine Infusion for Postoperative Analgesia in Spine Surgery--A Prospective Randomized Double-blind Placebo Controlled Study. J Neurosurg Anesthesiol, 28(1):27-31. Doi: 10.1097/ANA.000000000000000 193.

- **Hu J, Zhu M, Gao Z, Zhao S, Feng X, Chen J, et al (2021).** Dexmedetomidine for prevention of postoperative delirium in older adults undergoing oesophagectomy with total intravenous anaesthesia: A double-blind, randomised clinical trial. Eur J Anaesthesiol, 38(Suppl 1):S9-S17. Doi: 10.1097/EJA.0000000000001382.

- **Jain G, Bansal P, Ahmad B, Singh D, Yadav G (2012).** Effect of the perioperative infusion of dexmedetomidine on chronic pain after breast surgery. Indian J Palliat Care, 18(1):45-51. Doi: 10.4103/0973-1075.97354.

- **Jiang C, Liu F, Zhou Q, Deng W (2021).** Comparison of rhomboid intercostal nerve block, erector spinae plane block and serratus plane block on analgesia for modified radical mastectomy: A prospective randomised controlled trial. Int J Clin Pract, 75(10):e14539. Doi: 10.1111/ijcp.14539.

- **Kang C, Cho A, Kim K, Lee E, Lee H, Kwon J, et al (2020).** Effects of Intraoperative Low-Dose Ketamine on Persistent Postsurgical Pain after Breast Cancer Surgery: A Prospective, Randomized, Controlled,
Double-Blind Study. Pain Physician, 23(1):37-47.

- **Li C, Liu S, Zhou Y, Lu X (2018).** Effect of dexmedetomidine on perioperative stress and postoperative pain in patients with radical resection of esophageal cancer under combined thoracoscope and laparoscope. Zhonghua Yi Xue Za Zhi, 98(46):3778-3783. Doi: 10.3760/cma.j.issn.0376-2491.2018.46.011.

- **Liu Y, Liu W, Wang X, Wan Z, Liu Y, Zhang M (2021).** Dexmedetomidine Relieves Neuropathic Pain in Rats With Chronic Constriction Injury via the Keap1-Nrf2 Pathway. Front Cell Dev Biol, 9:714996. Doi: 10.3389/fcell.2021.714996

- **Lou Q, Nan K, Xiang F, Chen X, Zhu W, Zhang X, Li J (2017).** Effect of perioperative multi-day low dose ketamine infusion on prevention of postmastectomy pain syndrome. Zhonghua Yi Xue Za Zhi, 97(46):3636-3641.

- **Macintyre PE, Jarvis DA (1996).** Age is the best predictor of postoperative morphine requirements. Pain, 64(2):357-64.

- **Meretoja TJ, Andersen KG, Bruce J, Haasio L, Sipilä R, Scott NW, et al (2017).** Linical Prediction Model and Tool for Assessing Risk of Persistent Pain After Breast Cancer Surgery. J Clin Oncol. 2017 May 20; 35(15):1660-1667.

- **Mukherjee B, Backiavathy V, Sujatha R (2020).** A prospective randomized double-blinded study of dexmedetomidine versus propofol infusion for orbital surgeries. Saudi J Ophthalmol, 34(2):77-81. Doi: 10.4103/1319-4534.305021.

- **Rao J, Gao Z, Qiu G, Gao P, Wang Q, Zhong W, et al (2021).** Nalbuphine and dexmedetomidine as adjuvants to ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: A randomized, double-blind, placebo-controlled trial. Medicine (Baltimore). 2021, 100(32):e26962. Doi: 10.1097/MD.00000000000026962.

- **Shan W, Liao X, Tang Y, Liu J (2021).** Dexmedetomidine alleviates inflammation in neuropathic pain by suppressing NLRP3 via Nrf2 activation. Exp Ther Med, 22(4):1046. Doi: 10.3892/etm.2021.10479.

- **Sun EC, Darnall BD, Baker LC, Mackey S (2016).** Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med,176(9):1286-93.

- **Tekeli A, Oğuz A, Tunçdemir Y, Almali N(2020).** Comparison of dexmedetomidine-propofol and ketamine-propofol administration during sedation-guided upper gastrointestinal system endoscopy. Medicine (Baltimore), 99(49):e23317. Doi: 10.1097/MD.00000000000023317.

- **Unal-Cevik I, Sarioglu-Ay S, Evcik D (2010).** A comparison
of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DN4. J Pain., 11(11):1129-35.

- **Wang X, Liu Q (2021).** Dexmedetomidine relieved neuropathic pain and inflammation response induced by CCI through HMGB1/TLR4/NF-κB signal pathway. Biol Pharm Bull, Doi: 10.1248/bpb.b21-00329.

- **Wang Y, Tang T, Tang JE (2001).** An instrument for measuring customer satisfaction toward web sites that market digital products and services. J Elec. Commerce Research, 2(3): 89-103.

- **Ware JE Jr (1996).** The SF-36 health survey. In Quality of Life and Pharmacoeconomics in Clinical Trials Second edition. Edited by: Spilker B. Philadelphia PA: Lippincott-Raven Press.337-45.

- **Williamson A, Hoggart B (2005).** Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005; 14(7):798-804.

- **Ye Q, Wang F, Xu H, Wu L, Gao X (2021).** Effects of dexmedetomidine on intraoperative hemodynamics, recovery profile and postoperative pain in patients undergoing laparoscopic cholecystectomy: a randomized controlled trial. BMC Anesthesiol, 21(1):63. Doi: 10.1186/s12871-021-01283-z.

- **Yoon S, Roh D, Yeo J, Woo J, Han S, Kim K (2021).** Analgesic Efficacy of α2 Adrenergic Receptor Agonists Depends on the Chronic State of Neuropathic Pain: Role of Regulator of G Protein Signaling 4. Neuroscience, 455:177-194. Doi: 10.1016/j.neuroscience.2020.12.021.