Randomized Trial

Effect of Dexmedetomidine Added to Modified Pectoral Block on Postoperative Pain and Stress Response in Patient Undergoing Modified Radical Mastectomy

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Background: The most common surgical procedure for breast cancer is the modified radical mastectomy (MRM), but it is associated with significant postoperative pain. Regional anesthesia can reduce the stress response associated with surgical trauma.

Objectives: Our aim is to explore the efficacy of 1 µg/kg dexmedetomedine added to an ultrasound (US)-modified pectoral (Pecs) block on postoperative pain and stress response in patients undergoing MRM.

Study Design: A randomized, double-blind, prospective study.

Setting: An academic medical center.

Methods: Sixty patients with American Society of Anesthesiologists (ASA) physical status I–II (18–60 years old and weighing 50–90 kg) scheduled for MRM were enrolled and randomly assigned into 2 groups (30 in each) to receive a preoperative US Pecs block with 30 mL of 0.25% bupivacaine only (group 1, bupivacaine group [GB]) or 30 mL of 0.25% bupivacaine plus 1 µg/kg dexmedetomidine (group II, dexmedetomidine group [GD]). The patients were followed-up 48 hours postoperatively for vital signs (heart rate [HR], noninvasive blood pressure [NIBP], respiratory rate [RR], and oxygen saturation [Sao2]), visual analog scale (VAS) scores, time to first request of rescue analgesia, total morphine consumption, and side effects. Serum levels of cortisol and prolactin were assessed at baseline and at 1 and 24 hours postoperatively.

Results: A significant reduction in the intraoperative HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) starting at 30 minutes until 120 minutes in the GD group compared to the GB group ($P < 0.05$) was observed. The VAS scores showed a statistically significant reduction in the GD group compared to the GB group, which started immediately up until 12 hours postoperatively ($P < 0.05$). There was a delayed time to first request of analgesia in the GD group (25.4 ± 16.4 hrs) compared to the GB group (17 ± 12 hrs) ($P = 0.029$), and there was a significant decrease of the total amount of morphine consumption in the GD group (9 + 3.6 mg) compared to the GB group (12 + 3.6 mg) ($P = 0.001$). There was a significant reduction in the mean serum cortisol and prolactin levels at 1 and 24 hours postoperative in the GD patients compared to the GB patients ($P < 0.05$).

Limitations: This study was limited by its sample size.

Conclusion: The addition of 1 µg/kg dexmedetomidine to an US-modified Pecs block has superior analgesia and more attenuation to stress hormone levels without serious side effects, compared to a regular Pecs block in patients who underwent MRM.

Key words: Postoperative pain, dexmedetomidine, Pecs block, stress response, breast surgery

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Breast surgeries are one of the most common forms of surgery conducted in hospitals, and even relatively minor breast surgery can be associated with significant postoperative pain (1). The most common surgical procedure for breast cancer is modified radical mastectomy (MRM), which removes a generous amount of skin and entire breast with axillary evacuation (2). Nearly 60% of breast surgery patients experience severe acute postoperative pain. Most of the pain originates from the axillary component of the surgery (3).

The ultrasound (US) pectoral (Pecs) block I is an easy and reliable superficial block that targets to place local anesthetics at the interfascial plane between the pectoralis major and minor muscles under direct vision (4). The modified Pecs block (Pecs II block) is a simple alternative to the conventional paravertebral and neuroaxial blocks for breast surgery and is a second version of the Pecs block that aims at blocking the pectoral nerves, intercostobrachial, intercostals (III, IV, V, and VI), and long thoracic nerve. These nerves need to be blocked to provide complete analgesia during breast surgery. The Pecs II block aims to block the serratus muscle area together with the lateral branches of the intercostal nerves that exit at the level of the midaxillary line to innervate the mammary gland and the skin from T2 to T6 (4,5). Poorly controlled postoperative pain has negative physiological and psychological consequences. Furthermore, effective acute pain control preserves immune function both by suppressing the surgical stress response and decreasing the need for general anesthetics and opioids (6). It has been suggested that regional anesthesia can reduce the stress response associated with surgical trauma (7).

Dexmedetomidine is a selective α_2 agonist with 8 times more affinity for α_2 adrenergic receptors compared to clonidine and possesses all the properties of α_2 agonist without respiratory depression. Dexmedetomidine has been a focus of interest for its broad spectrum (sedative, analgesic, and anesthetic sparing) properties, making it a useful and safe adjunct in many clinical applications. The intravenous, intramuscular, intrathecal, epidural, and perineural use of this agent enhances analgesic effects (8,9).

Our aim was to explore the efficacy of 1 µg/kg dexmedetomedine added to US-guided modified Pecs block on postoperative pain and stress response in patients undergoing MRM.

Methods

This randomized, double-blinded study was approved by the local ethics committee of the South Egypt Cancer Institute, Assuit University, Assuit, Egypt. It was registered at https://clinicaltrials.gov with Identifier No: NCT03046238. After written informed consent, 60 patients with American Society of Anesthesiologists (ASA) physical status I–II (aged 18–60 years and weighing 50–90 kg) scheduled for MRM surgery were enrolled in this study. Patients with history of bleeding diathesis, relevant drug allergy, opioid dependence, and sepsis, as well as those with psychiatric illnesses that would interfere with perception and assessment of pain, were excluded from the study. Preoperatively, the patients were taught how to evaluate their own pain intensity using the visual analog scale (VAS) (0–10, where 0 = no pain and 10 = the worst pain imaginable) and how to use a patient-controlled analgesia (PCA) device. On arrival to the operating room, monitoring included electrocardiogram, noninvasive arterial blood pressure (NIBP), pulse oximeter, and capnography, and a 2 mL blood sample was withdrawn in a plasma tube for determination of the baseline level of stress hormones (cortisol and prolactin). Anesthesia was induced for all patients with 2 µg/kg fentanyl, 2–3 mg/kg propofol, and 1.5 mg/kg lidocaine. Endotracheal intubation was facilitated by 0.15 mg/kg cisatracurium. The patients were randomly assigned using an online research randomizer (https://randomizer.org) into 2 groups (30 patients in each):

Group I (bupivacaine group) (GB): the patients were given US-guided modified Pecs block with 30 mL of 0.25% bupivacaine (Markyrene, Sigma Tec, Egypt) divided into 10 mL injected between the 2 pectoralis muscles on the interfasial plane and 20 mL injected between the pectoralis minor and serratus anterior muscles

Group II (dexmedetomidine group) (GD): the patients were given US-guided modified Pecs block with 30 mL of 0.25% bupivacaine plus 1 µg/kg dexmedetomidine (Precedex, Hospira Inc., Lake Forest, IL) divided into 10 mL injected between the 2 pectoralis muscles on the interfasial plane and 20 mL injected between the pectoralis minor and serratus anterior muscles.

The investigated drugs were prepared in a sterile syringe by the hospital pharmacy and given to the investigator who was blinded to the identity of the drugs. The observer was also masked to the treatment group assignment.

Two anesthetists experienced in the technique, under US guidance, performed the block under the direct supervision of the study investigator. US-guided

Pecs block was performed immediately after induction of anesthesia and about 15 minutes before skin incision. Modified Pecs block was performed with 100 mm 21 G needle (SonoPlex Stim cannula, Pajunk®, Geisingen, Germany), using linear array US probe of high frequency (5–12 MHz) (Sonosite, Inc., Bothwell, WA) with an imaging depth of 4–6 cm. The US probe was placed under the lateral third of the clavicle. After locating the axillary artery and vein, we moved the probe distally towards the axilla until the 2 pectoralis muscles were identified (Image 1). Next, the needle was inserted in plane with the US probe to the fascial plane between the 2 pectoralis muscles and 10 mL of bupivacaine 0.25% was injected between the 2 pectoralis muscles. Then the probe was moved towards the axilla until the serratus anterior muscle was identified above the second, third, and fourth ribs, and the needle was inserted into the fascial plane between the pectoralis minor and serratus anterior muscles (Image 2), and 20 mL of bupivacaine 0.25% was injected after negative aspiration. This broke through the axilla and reached the long thoracic nerve and reliably at least 2 intercostal nerves. Anesthesia was maintained by 1–1.5 MAC isoflurane in a 50% oxygen/air mixture and 0.03 mg/kg cisatracurium, respectively, in ventilation parameters to maintain end-tidal CO2 of approximately 35–45 mmHg. Intraoperative vital signs included heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP), which were observed and recorded at 30 minutes and at 1- and 2-hour time-points. Tracheal extubation was performed at the end of surgery, and all patients were transmitted to the post-anesthesia care unit, where they were followed-up and assessed immediately and at 2, 4, 6, 12, 24, 36, and 48 hours postoperatively for vital signs (HR, noninvasive arterial blood pressure [NIBP], respiratory rate [RR], and oxygen saturation [Sao2]) and pain intensity by VAS score. When the patient expressed pain or VAS score $\geq$ 3, postoperative PCA was begun with an initial morphine dose of 0.1 mg/kg followed by a 1 mg bolus with a lockout interval of 15 minutes with no background infusion allowed; time to first request of rescue analgesia, total morphine consumption in the 48 hours, and sedation by sedation score (0–4, 0 = fully awake, 1 = somnolent and responsive to verbal commands, 2 = somnolent and responsive to tactile stimulation, 3 = sleep and responsive to painful stimulation, and 4 = not arousable) were recorded. Side effects including nausea, vomiting, hypotension, bradycardia, arrhythmia, vascular injury, and pneumothorax were treated and recorded. Another 2 blood samples were withdrawn in a serum tube for further assessment of stress hormone levels (cortisol and prolactin) at 1 and 24 hours postoperatively. All blood samples were collected in serum tubes, centrifuged, and stored at -20 C° until assayed. Serum levels of prolactin and cortisol were measured by chemiluminescence immunoassay on an Immulite® 1000 automated analyzer (Siemens Healthineers, Erlangen, Germany).

Statistical Analysis

Our primary end-point was the total dose of intravenous PCA morphine consumption in the first 48 hours postoperative. The secondary end-points were the postoperative VAS score, first request of analgesia, level of stress hormones, and safety profile of the studied drugs. A calculated sample size of 28 would have 80% power and a type I error of 0.05 using a confidence interval of 95% to detect a difference at a level 0.05 of significance. Considering potential drop-outs, we decided to enroll 30 patients in each group for the study.

All data were collected by an Excel program (Microsoft Corporation, Redmond, WA) and were then analyzed with SPSS Version 20.0 (IBM Corporation, Armonk, NY). Qualitative data were described by numbers and percentages, while quantitative data were described using mean and standard deviation. A chi-square test was used to test the relationship between qualitative variables and independent samples, and a t-test was used to compare between 2 groups of quantitative data. $P < 0.05$ was considered significant.

Results

Sixty patients were consented, enrolled, and successfully completed the study (Fig. 1). There was no significant difference among the 2 groups regarding demographic data (age, weight, and height) and the duration of both surgery and anesthesia ($P > 0.05$) (Table 1).

Regarding hemodynamic variables measured during the intraoperative period, there was a significant reduction in HR, SBP, and DBP starting at 30 minutes until 120 minutes in the GD group compared to the GB group ($P < 0.05$). The hemodynamic variables (SBP, DBP, and HR) measured during the postoperative period showed that there was no significant difference between the 2 groups ($P > 0.05$).

The mean VAS scores showed a statistically significant reduction in the GD group compared to the GB group, which started immediately postoperative until 12 hours ($P < 0.05$) (Fig. 2).

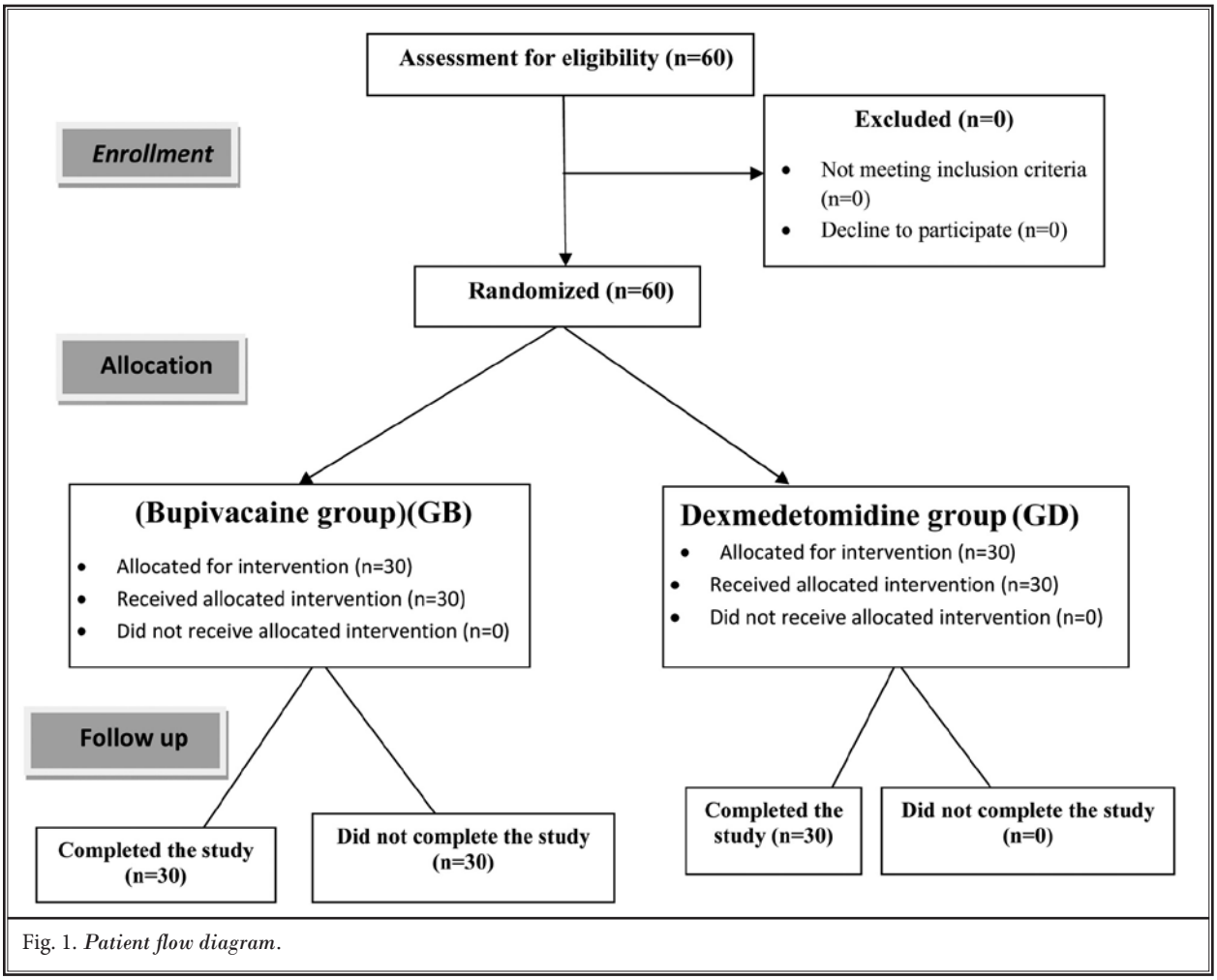

Fig. 1. *Patient flow diagram.*

Table 1. *Demographic and clinical data of the study groups.*

Demographic and Clinical Data	GB	GD	*P*-Value
	Mean + SD	Mean + SD	
Age (yrs)	48.5 ± 13.7	47.3 ± 9.7	0.878
Weight (kg)	69.1 ± 9.7	72.8 ± 6.1	0.067
Site of Surgery			0.796
Right MRM	17 (56.7%)	15 (50.0%)	
Left MRM	13 (43.3%)	15 (50.0%)	
Duration of Surgery (hrs)	2.1 ± 0.7	2.3 ± 0.7	0.273
Duration of Anesthesia (hrs)	2.8 ± 0.8	2.9 ± 0.9	0.651

GB = bupivacaine group; GD = dexmedetomidine group; MRM = modified radical mastectomy

The number of patients who requested morphine based on the protocol of the study in the GD group was only 15 (50%) patients compared to 30 (100%) patients in the GB group. The mean time to first request of analgesia was significantly prolonged in the GD group (25.4 ± 16.4 hrs) compared to the GB group (17 ± 12 hrs) (*P* =

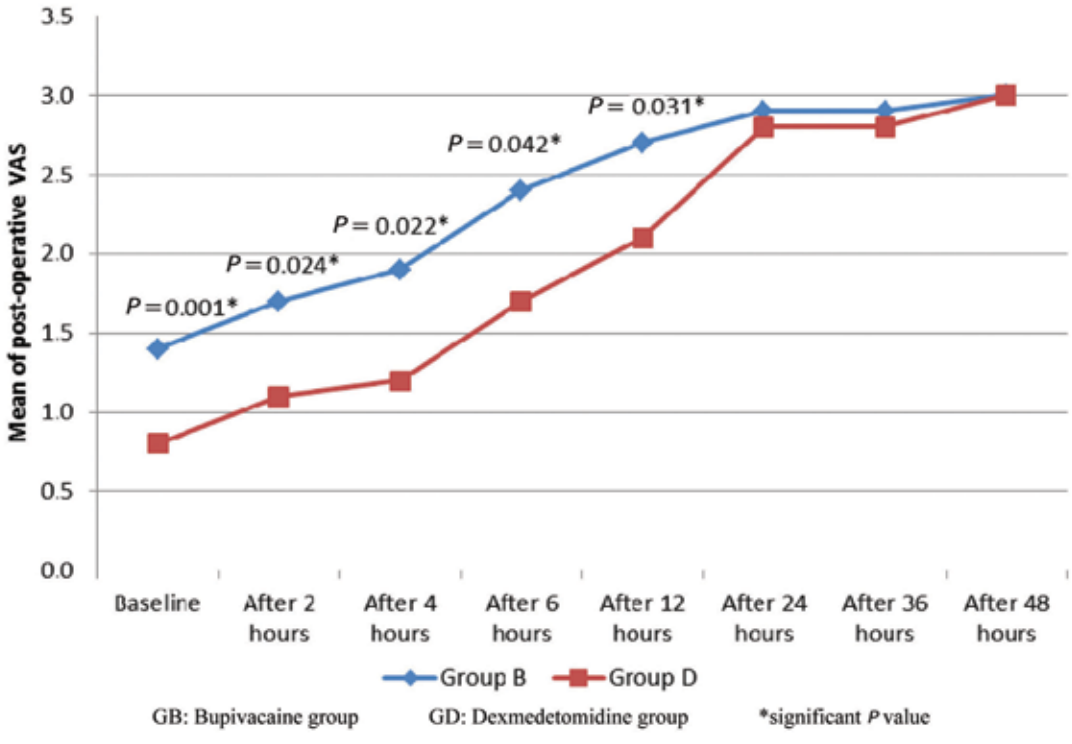

Fig. 2. *VAS scores of the study groups during 48 hours postoperatively.*

Table 2. *Time to first request of analgesia and total amount of PCA morphine of the study groups during 48 hours postoperatively.*

	GB	GD	*P*-Value
Time to First Request of Analgesia (hrs)			0.029*
Mean + SD	17 ± 12	25.4 ± 16.4	
Total PCA Morphine (mg)			0.002**
Range	7–16	0–14	
Mean + SD	12 ± 3.6	9 ± 3.6	
No. of Patients Requested (%)	30 (100%)	15 (50%)	

GB = bupivacaine group; GD = dexmedetomidine group; PCA = patient-controlled analgesia
*Significant P-value
** Highly significant P-value

0.029), and there was a statistically significant decrease in the total amount of intravenous PCA morphine consumption in the GD group (9 + 3.6 mg) in comparison to the GB group (12 + 3.6 mg) ($P = 0.001$) (Table 2).

There was a significant increase in the sedation score in the GD patients compared to the GB patients, which started immediately postoperative until 2 hours postoperative ($P < 0.05$) (Fig. 3). Four patients in the GB group developed itching, while this occurred in no patients in the GD group ($P = 0.010$). There was no significant difference in the incidence of the other postoperative side effects between the 2 groups (Fig. 4).

There was no significant difference between the 2 groups in the mean serum cortisol and prolactin levels at the baseline values ($P > 0.05$), but there was a significant reduction in the mean serum cortisol and prolactin levels at 1 and 24 hours postoperative in the GD patients compared to the GB patients ($P < 0.05$) (Tables 3,4).

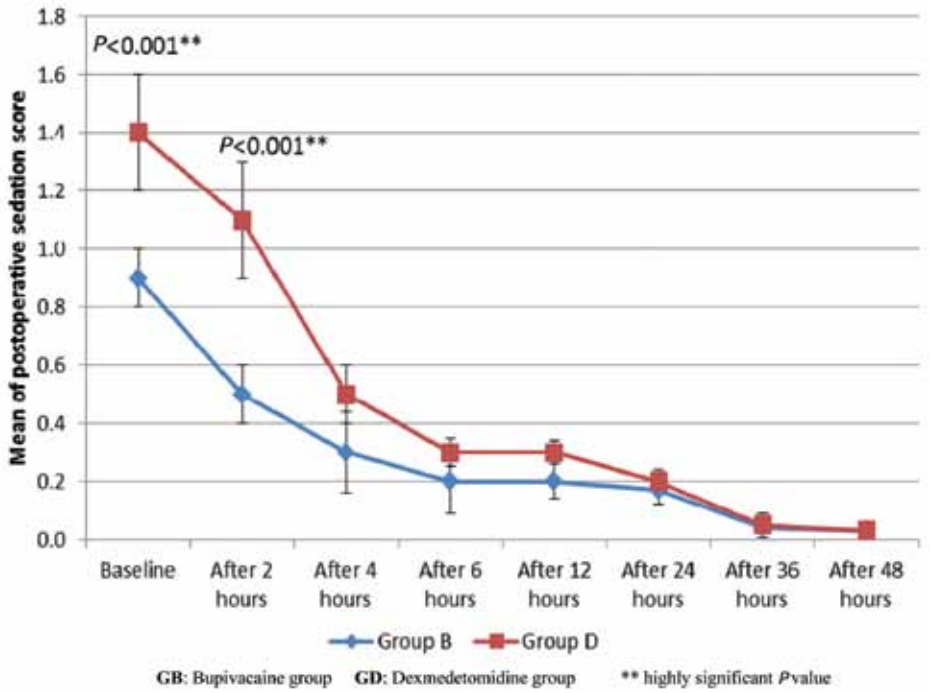

Fig. 3. *Sedation score of the study groups during 48 hours postoperatively.*

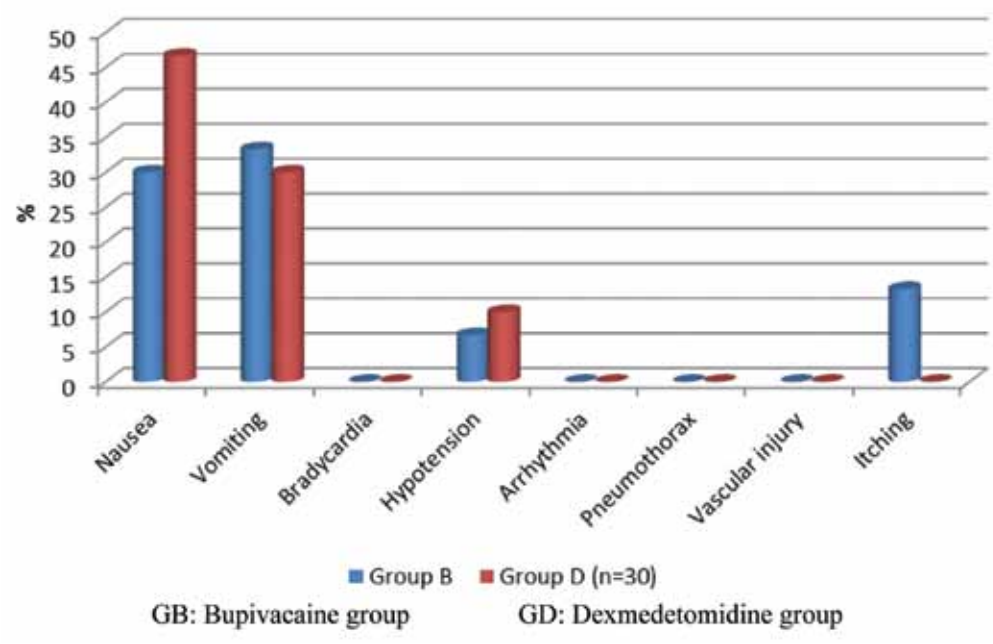

Fig. 4. *Postoperative side effects observed during the study period.*

Table 3. *Serum cortisol level changes of the study groups (μg/dL).*

Cortisol Level	GB	GD	*P*-Value
	Mean ± SD	Mean ± SD	
Baseline	277 ± 203.4	291.7 ± 143.4	0.762
After 1 hr Postoperatively	298.5 ± 65.0	262.2 ± 70.0	0.042*
After 24 hrs Postoperatively	257.3 ± 163.2	205.9 ± 142.6	0.044*

GB = bupivacaine group; GD = dexmedetomidine group
*Significant *P*-value

Table 4. *Serum prolactin level changes of the study groups (ng/mL).*

Prolactin Level	GB	GD	*P*-Value
	Mean ± SD	Mean ± SD	
Baseline	37.2 ± 19.3	42.4 ± 41.4	0.535
After 1 hr Postoperatively	44.8 ± 24.2	31.6 ± 25.7	0.045*
After 24 hrs Postoperatively	41.7 ± 21.2	28.3 ± 22.1	0.020*

GB = bupivacaine group; GD = dexmedetomidine group
*Significant *P*-value

Discussion

Breast surgeries are one of the most common forms of surgery conducted in hospitals. MRM is the common surgical procedure for breast cancer, but is associated with significant postoperative pain (1,2). Several forms of regional techniques like local anesthetic infiltration (10), intercostal nerve block (11), epidural block (12), and paravertebral nerve block (PVB) have been used for the management of breast surgery pain.

Modified Pecs block is a novel approach that aims to block the axilla and the intercostal nerves, which is necessary for wide excisions and several types of mastectomies (1). Pecs blocks are peripheral approaches based on good anatomical knowledge and on the use of US. It blocks both motor and sensory nerves, compared only with sensory nerves blocks in wound infiltration techniques and also no sympathetic block as in PVBs and epidural blockades (13).

In our study, we found that patients in the GD group experienced superior postoperative analgesia, prolongation of time to first rescue of analgesia, decreased mean total morphine consumption, with more attenuation of the stress hormone levels (prolactin and cortisol), compared with the GB group in the first 48 hours postoperative, without serious side effects. Similar findings were shown in a study by Wahba and Kamal (14), who concluded that Pecs block reduced postoperative morphine consumption in the first 24 hours in comparison to PVB. Also, Bashandy and Abbas (15) concluded that patients receiving Pecs block showed a reduction in postoperative pain scores up to 24 hours and decreased opioid consumption compared to the control group. Those results are in accordance with our findings, as the VAS score was < 3 in the first 12 hours, with reduction in morphine consumption with the addition of dexmeteomidine to bupivacaine in the GD group, which could be explained by the additive effect of dexmeteomidine.

Local anesthetic acts by its well known mechanism (reversible block of the conduction of impulse in the peripheral nervous system, inhibiting the excitation -conduction process). Moreover, α_2 adrenoceptor agonist acts by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons; they might produce analgesia by depressing the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons (16-20). The principal mechanism for the analgesic action of dexmedetomidine is the spinal mechanism, even though there is clear evidence for a peripheral site of action (21). The local analgesic effect of dexmedetomidine is caused by the enhancement of the hyperpolarization activated cation current, which prevents the nerve from returning from a hyperpolarized state to a resting membrane potential for subsequent firing (22).

Many previous studies have investigated the additive effect of dexmedetomidine to local anesthetics in regional techniques, as Mohamed et al (23) reported

that the addition of 1 μg/kg dexmedetomidine to bupivacaine in PVB improved the quality and duration of analgesia and provided an analgesic sparing effect. Moreover, Gupta et al (24) found that the addition of 5 μg of dexmedetomidine to ropivacaine intrathecally produced good acute pain relief. Dexmedetomidine shortened the onset time and prolonged the duration of the block and postoperative analgesia, when added to levobupivacaine for axillary brachial plexus block (25). Peripheral analgesic effects of dexmedetomidine that potentiate local anesthetics are mediated by α2A-AR binding (26,27) and have been utilized to enhance postoperative analgesia after intraarticular administration and direct infiltration of dexmedetomidine in a dose of 1 μg/kg as an adjunct to local anesthetics (27-29).

A significant reduction in the intraoperative hemodynamic variables was found in the GD group compared to the GB group, which was similar to what happened with Mohamed et al (23) as the use of dexmedetomidine in PVB was associated with decreased HR and NIBP. The same happened with Al-Ghanem et al's study (30) when dexmetedomidine was used intrathecally, on the contrary to Shukla et al (31) and Gupta et al (24), who found that the addition of dexmedetomidine to bupivacaine is associated with hemodynamic stability. The hypotensive effect of dexmedetomidine might be from the stimulation of α_2 inhibitory neurons in the medullary vasomotor center of the brain stem, which leads to a reduction in norepinephrine release and sympathetic nerve outflow from the central nervous system to the peripheral tissue. Bradycardia is caused by an increase in the vagal tone resulting from central stimulation of parasympathetic outflow, as well as a reduced sympathetic drive (32).

Stress responses to surgical trauma and postoperative pain elicit diffuse changes in hormonal secretion such as adrenocorticotrophic hormone, cortisol, and prolactin. Postoperative analgesia reduces the stress response, which may have deleterious metabolic and cardiovascular effects (33).

The levels of cortisol and prolactin in our study were significantly lower in the GD group compared to the GB group. The stress response to surgery is expected to be attenuated by sympatholytic effects of central α_2-adrenergic receptor activation, leading to reductions in blood pressure, HR, and anti-inflammatory effects; this reflects attenuation of sympathoadrenal response by dexmedetomidine.

The patients receiving dexmedetomidine had significantly lower cortisol levels, as compared with those who did not receive it in accordance with a study by Aho et al (34). Also, similar findings were shown by Uyar et al (35), who found that plasma concentration of cortisol and glucose had increased significantly in the placebo group than in the dexmedetomidine group. In addition, Mukhtar et al (36) found that dexmedetomidine did inhibit the hyperglycemic response to surgery more than the placebo. Abd El-Moneim et al (37) proved that dexmedetomidine alleviated the stress response in patients undergoing cancer surgeries, but it was associated with higher sedation.

The stress attenuation effect of dexmedetomidine in regional technique was similar to Nasr and Abdelhamid (38), who reported that caudal dexmedetomidine attenuated the stress response to surgical trauma and provided better postoperative analgesia. Dexmedetomidine lowering the level of cortisol could be explained by it being an imidazole that may lead to inhibition of cortisol synthesis (39) when administered by all routes.

In the contrary to our finding, Aantaa et al (40) found that there was no significant difference between dexmedetomidine and placebo in the serum cortisol level.

Limitations

This study was limited by its small sample size and the relatively short follow-up period. Also, the lack of assessment of the serum level of dexmedetomidine to explore its analgesic effect was locally only or due to its systemic absorption. Studies with follow-up periods of more than 48 hours to explore its effect on chronic post-mastectomy pain are needed.

Conclusion

In conclusion, the addition of 1 μg/kg dexmedetomidine to US-guided modified Pecs block had superior analgesia and more attenuation to stress hormone levels without serious side effects, compared to regular block in patients who underwent MRM.

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References

1. Klein SM, Bergh A, Steele SM, Georgiade GS, Greengrass RA. Thoracic paravertebral block for breast surgery. *Anesth Analg* 2000; 90:1402-1405.
2. Bland KI, Vezedis MP, Copeland EM III. Breast. In: Schwartz SI (ed). *Principles of Surgery. 7th ed.* McGraw-Hill, New York 1999, pp 576-579.
3. Fecho K, Miller NR, Merritt SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. *Pain Med* 2009; 10:708-715.
4. Blanco R. The 'pecs block': A novel technique for providing analgesia after breast surgery. *Anaesthesia* 2011; 66:847-888.
5. Blanco R, Garrido García M, Diéguez P, Nebril BA, López Álvarez S, Pensado Castiñeiras A. [Eficacia analgésica del bloqueo de los nervios pectorales en cirugía de mama]. *Cir Mayor Ambulat* 2011; 16:89-93.
6. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA* 2009; 302:1985-1992.
7. Bozkurt P, Kaya G, Yeker Y, Altintaş F, Bakan M, Hacibekiroglu M, Bahar M.. Effectiveness of morphine via thoracic epidural vs. intravenous infusion on post thoracotomy pain and stress response in children. *Paediatr Anaesth* 2004; 14:748-754.
8. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small dose dexmedetomidine infusions. *Anesth Analg* 2000; 90:699-705.
9. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: A review of clinical applications. *Curr Opin Anaesthesiol* 2008; 21:457-461.
10. Talbot H, Hutchinson SP, Edbrooke DL, Wrench I, Kohlhardt SR. Evaluation of a local anesthesia regimen after mastectomy. *Anesthesia* 2004; 59:664-667.
11. Huang TT, Parks DH, Lewis SR. Outpatient breast surgery under intercostals blocks anesthesia. *Plast Reconstr Surg* 1979; 63:299-303.
12. Lynch EP, Welch KJ, Carabuena JM, Eberlein TJ. Thoracic epidural anesthesia improves outcome after breast surgery. *Ann Surg* 1995; 222:663-669.
13. Porzionato A, Macchi V, Stecco C, Loukas M, Tubbs RS, De Caro R. Surgical anatomy of the pectoral nerves and the pectoral musculature. *Clin Anat* 2012; 25:559-575.
14. Wahba SS, Kamal SM. Thoracic paravertebral block versus pectoral nerve block for analgesia after breast surgery. *Egyptian J Anaesth* 2014; 30:129-135.
15. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery. *Reg Anesth Pain Med* 2015; 40:68-74.
16. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. *Anesthesiology* 1996; 85:655-674.
17. Lawhead R, Blaxall H, Bylund B. Alpha-2A is the predominant Ş-2 adrenergic receptor subtype in human spinal cord. *Anesthesiology* 1992; 77:983-991.
18. Smith MS, Schumbra UB, Wilson KH, Page SO, Hulette C, Light AR, Schwinn DA. Alpha 2 adrenergic receptor in human cord: Specific localized expression of mRNA encoding alpha 2-adrenergic receptor subtypes at four distinct levels. *Brain Res* 1995; 34:109-117.
19. Yaksh TL, Jage J, Takano Y. Pharmacokinetics and pharmacodynamics of medullar agents: The spinal actions of α2-adrenergic agonists as analgesics. *Baillière's Clinical Anaesthesiology* 1993; 7:597-614.
20. Fairbanke CA, Wilcox GL. Spinal antinociceptive synergism between morphine and clonidine persists in mice made acutely or chronically tolerant to morphine. *J Pharmacol Exp Ther* 1999; 288:1107-1116.
21. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine a novel Ş2-adrenoceptor agonist in healthy volunteers. *Pain* 1991; 46:281-285.
22. Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. *Anesthesiology* 2011; 115:836-843.
23. Mohamed SA, Fares KM, Mohamed AA, Alieldin NH. Dexmedetomidine as an adjunctive analgesic with bupivacaine in paravertebral analgesia for breast cancer surgery. *Pain Physician* 2014; 17:E589-E598.
24. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. *Indian J Anaesth* 2011; 55:347-351.
25. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. *Anesth Analg* 2010; 111:1548-1551.
26. Grosu I, Lavand'homme P. Use of dexmedetomidine for pain control. *F1000 Med Rep* 2010; 2:90.
27. Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. *Anesth Analg* 2008; 107:96-101.

28. Al-Metwalli R, Mowafi HA, Ismail SA, Siddiqui AK, Al-Ghamdi AM, Shafi MA, El-Saleh AR. Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br J Anaesth* 2008; 101:395-399.
29. Cheung CW, Ng KF, Choi WS, Chiu WK, Ying CL, Irwin MG. Evaluation of the analgesic efficacy of local dexmedetomidine application. *Clin J Pain* 2011; 27:377-382.
30. Al-Ghanem SM, Massad I, Al-Mustafa MM, Al Zaben K, Qudaisat I, Qatawneh AM, Abu-Ali HM. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. *Am J Appl Sci* 2009; 6:882-887.
31. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. *J Anesthesiol Clin Pharmacol* 2011; 27:495-499.
32. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, Heard S, Cheung A, Son SL, Kallio A. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg* 2000; 90:834-839.
33. Solak M, Ulusoy H, Sarihan H. Effects of caudal block on cortisol and prolactin responses to postoperative pain in children. *Eur J Pediatr Surg* 2000; 10:219-223.
34. Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. *Anesth Analg* 1992; 75:932-939.
35. Uyar AS, Yagmurdur H, Fidan Y, Topkaya C, Basar H. Dexmedetomidine attenuates hemodynamic and neuroendocrinal responses to skull-pin the headholder application during craniotomy. *J Neurosurg Anesthesiol* 2008; 20:174-179.
36. Mukhtar A, Obayah EM, Hassona AM. The use of dexmedetomidine in pediatric cardiac surgery. *Anesth Analg* 2006; 103:52-56.
37. Abd El-Moneim NM, Samy M, Ebrahim WA, Boules NS. Effect of morphine versus low and high dose dexmedetomidine on postoperative stress response in patients undergoing cancer surgeries. *Med J Cairo Univ* 2015; 83:41-46.
38. Nasr DA, Abdelhamid HM. The efficacy of caudal dexmedetomidine on stress response and postoperative pain in pediatric cardiac surgery. *Ann Card Anaesth* 2013; 16:109-114.
39. Maze M, Virtanen R, Daunt D, Banks SJ, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole sedative anesthetic agent, on adrenal steroidogenesis: In vivo and in vitro studies. *Anesth Analg* 1991; 73:204-208.
40. Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an a2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; 73:230-235.