Randomized Trial

Dexmedetomidine as an Adjunctive Analgesic with Bupivacaine in Paravertebral Analgesia for Breast Cancer Surgery

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Background: There is little systematic research on the efficacy and tolerability of the addition of adjunctive analgesic agents in paravertebral analgesia. The addition of adjunctive analgesics, such as fentanyl and clonidine, to local anesthetics has been shown to enhance the quality and duration of sensory neural blockades, and decrease the dose of local anesthetic and supplemental analgesia.

Objectives: Investigation of the safety and the analgesic efficacy of adding 1 µg/kg dexmedetomidine to bupivacaine 0.25% in thoracic paravertebral blocks (PVB) in patients undergoing modified radical mastectomy.

Study Design: A randomized, double-blind trial.

Setting: Academic medical center.

Methods: Sixty American Society of Anesthesiologists physical status –I – III patients were randomly assigned to receive thoracicPVB with either 20 mL of bupivacaine 0.25% (Group B, n = 30), or 20 mL of bupivacaine 0.25% + 1 µg/kg dexmedetomidine (Group BD, n= 30). Assessment parameters included hemodynamics, sedation score, pain severity, time of first analgesics request, total analgesic consumption, and side effects in the first 48 hours.

Results: There was a significant reduction in pulse rate and diastolic blood pressure starting at 30 minutes in both groups, but more evidenced in group BD ($P < 0.001$). Intraoperative Systolic blood pressure showed a significant reduction at 30 minutes in both groups ($P < 0.001$) then returned to baseline level at 120 minutes in both groups. There was a significant increase in pulse rate starting 2 hours postoperative until 48 hours postoperatively in group B but only after 12 hours until 48 hours in group BD ($P < 0.001$). The time of the first rescue analgesic requirement was significantly prolonged in the group BD (8.16 ± 42 hours) in comparison to group B (6.48 ± 5.24 hours) ($P = 0.04$). The mean total consumption of intravenous tramadol rescue analgesia in the postanesthesia care unit in the firtst 48 hours postoperatively was significantly decreased in group BD (150.19 ± 76.98 mg) compared to group B (194.44 ± 63.91 mg) ($P = 0.03$). No significant serious adverse effects were recorded during the study.

Limitations: This study is limited by its sample size.

Conclusion: The addition of dexmedetomidine 1 µg/kg to bupivacaine 0.25% in thoracic PVB in patients undergoing modified radical mastectomy improves the quality and the duration of analgesia and also provides an analgesic sparing effect with no serious side effects.

Key words: Dexmedetomidine, paravertebral block, postoperative analgesia, breast cancer surgery

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Breast cancer is perhaps the most common cancer in women that requires frequent surgery (1). Nearly 40% of postoperative breast surgery patients experience significant acute postoperative pain, with a pain score above 5 reflecting the inadequacy of conventional pain management (2). Most of the responses of the human body to postsurgical pain have been proven to be detrimental to the patient's homeostasis and recovery. Moreover, the incidence of chronic postoperative pain in breast surgery patients is as high as 50% and inadequate analgesia is considered as an independent risk factor (3). Hence, a number of therapeutic measures have been accepted as a part of the "multi-modal" approach to postoperative pain control. Thoracic paravertebral block (PVB) is used for pain relief after thoracotomy (4,5) and mastectomy (6-9). PVB can provide profound, long-lasting sensory deafferentation. The resulting greater attenuation of surgical stress response may translate into reduced inotropic stimulation of the heart. Additionally, unlike general anesthesia, PVB can provide superior postoperative analgesia, less nausea and vomiting, shorter recovery time, require fewer analgesic, earlier mobilization, and earlier home readiness for discharge. The use of PVB in patients undergoing ambulatory breast surgery has a cost-saving potential (10). There is little systematic research on the efficacy and tolerability of the addition of an adjunctive analgesic agent in paravertebral analgesia. The addition of adjunctive analgesics, such as fentanyl and clonidine, to local anesthetics has been shown to enhance the quality and duration of sensory neural blockade, and decrease the dose of local anesthetic and supplemental analgesia (11).

Dexmedetomidine is a highly selective α2-adrenorceptor agonist recently introduced to anesthesia; it produces a dose-dependent sedation, anxiolysis, and analgesia (involving spinal and supraspinal sites) without respiratory depression (12,13). α2-agonists are known to reduce anesthetic requirements, and because of their sympatholytic properties, they afford hemodynamic stability during the intraoperative period (14). Administration of an α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal central nervous system (CNS) sites from excessive drug exposure, resulting in robust analgesia without heavy sedation (15). The adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, and hypoxia (16,17).

The aim of this study was to investigate the safety and the analgesic efficacy of adding 1 μg/kg dexmedetomidine to bupivacaine 0.25% in thoracic PVB in patients undergoing modified radical mastectomy.

Methods

This randomized, double-blind study was approved by the local ethics committee of South Egypt Cancer Institute, Assuit University, Assuit, Egypt. After written informed consent, 60 ASA I – III patients (aged 25-70 years, weight 50 – 85 kg) who were scheduled for elective modified radical mastectomy with axillary dissection were enrolled in the study. Patients with a known allergy to the study drugs, conduction abnormalities, bleeding diathesis, infection at the injection site, central neuropathy, liver or renal impairment, drug or alcohol abusers, and those with psychiatric illnesses that would interfere with perception and assessment of pain were excluded from the study. Preoperatively, patients were taught how to evaluate their own pain intensity using the Visual Analogue Scale (VAS). Scored from 0 to 10 (where 0 = no pain and 10 = the worst pain imaginable). Oral diazepam (5 mg) was taken the night before surgery. Upon arrival at the operating room a 16-gauge catheter was inserted intravenously in the dorsum of the hand; lactated ringer's solution 10 mL/kg was infused intravenously over 10 minutes before the initiation of anesthesia. Basic monitoring probes (electrocardiography, noninvasive blood pressure, O2 saturation, and temperature) were applied. The patients were seated for placement of the block and were sedated with incremental intravenous doses of midazolam (1 – 3 mg) and fentanyl (50 – 100 μg). Thoracic PVB were then performed as described by Moore (18) and Katz (19). Intradermal lidocaine was used at the site of the needle insertion. The superior aspect of the spinous processes of T1 – T6 were marked. The skin entry points were 3 cm lateral to the marks. A 22-gauge quincke spinal needle attached through extension tubing to a syringe containing the study drugs was used. The needle was inserted perpendicular to the skin for a distance of 2 to 4 cm until the transverse process was contacted. The needle was withdrawn and walked cephald off the transverse process and advanced for a further 1.5 to 2 cm. Patients were allocated into 2 groups of 30 patients each using a computer-generated random number assignment in sealed opaque envelopes. A staff anesthesiologist not involved in the management of the patient or the study prepared the injectate according to randomization. The patients and all staff involved in patient management

and data collection were unaware of the group assignment. In group B, the bupivacaine group, patients received 20 mL of bupivacaine 0.25% paravertebrally, divided into 3 – 4 mL in each level. In group BD, the bupivacaine + dexmedetomidine group, patients received 20 mL of bupivacaine 0.25% + 1 µg/kg dexmedetomidine paravertebrally divided into 3 – 4 mL in each level. The time for performance of the block ranged from 10 to 15 minutes. The success of the block was tested by decrease pin prick sensation at the expected dermatomal level (from T1- T6). Immediately after the block, the patients were placed in the supine position. General anesthesia was induced by fentanyl 1.5 µg/kg, propofol 2 – 3 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cisatracurium 0.15 mg/kg. Anesthesia was maintained by isoflurane 1 – 1.5 MAC. Fentanyl 0.5 µg/kg and cisatracurium 0.03 mg/kg were given when indicated. Patients were mechanically ventilated to maintain ETCO2 between 33 and 36 mmHg. Heart rate and systolic and diastolic blood pressures were recorded preoperatively and after 30 minutes, 60 minutes, and 120 minutes. Hypotension was defined as a 15% decrease in systolic blood pressure from the baseline. Bradycardia was defined as a heart rate slower than 50 beats per minute or as an inappropriately slow heart rate despite hypotension. Hypoxia was defined as an oxygen saturation value < 90%. Hypotension was treated with intravenous boluses of ephedrine 0.1 mg/kg and normal saline 5mL/kg, the same doses were repeated as required, bradycardia was treated with intravenous atropine 0.01 mg/kg. At the end of the operation patients were transferred to the postanesthesia care unit and were monitored for vital signs (heart rate, noninvasive blood pressure, respiratory rate, and saturation of peripheral oxygen. The level of sedation was recorded using a modified observer's Assessment of Alertness/ Sedation Scale where 1 = awake/alert to 5 = sleep/unarousable. VAS at rest (VAS.R) and during movement or ipsilateral arm abduction (VAS.M) were assessed immediately postoperatively and at hours 2, 4, 6, 12, 24, 36. and 48 of the postoperative period. Intravenous tramadol 100 mg was given when the VAS was ≥ 3 or upon patient request. The time of the first request for analgesia and the total analgesic consumption in the first 48 hours were recorded. Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, and cardiac arrhythmia were recorded and treated, also postoperative complications of the block such as accidental pnemothorax and vascular puncture were recorded and treated.

Statistical Analysis

The power of the study was based on a calculated sample size of 30 patients which would have 80% power of detecting a difference at a 0.05 level of significance, using a confidence interval of 95%. Analysis was performed using SPSS version 17 (Chicago-USA). Data was presented as mean ± SD, numbers, and percentages. Repeated measures ANOVA was used to test the change of different parameters having normal distribution overtime in both study groups (time effect) and also to test the difference between group B and BD over time (group interaction). Bonferroni test was used for multiple pairwise comparisons. For VAS score, Friedman test was used to show effect of time in each study group. Pairwise comparisons were done using Wileoxan rank test. $P < 0.05$ was considered significant.

Results

There were no significant differences among the 2 groups in demographic data as regard to age, weight, height, BMI, and duration of surgery ($P > 0.05$) (Table 1). Regarding hemodynamic parameters measured during the intraoperative period, there was a significant reduction in pulse rate starting at 30 minutes in both groups, but more evidenced in group BD (*P*-value for group interaction < 0.001). Pulse rate became stable in group B until 120 minutes and started to rise but not to baseline rate in group BD (Table 2, Fig. 1). Intraoperative Systolic blood pressure showed a significant reduction at 30 minutes in both groups then returned to baseline level at 120 minutes in both groups (P-value for interaction < 0.001) (Table 3, Fig. 2). Changes in intraoperative diastolic blood pressure were similar to pulse rate where a significant drop occurred at 30 minutes, but more evidenced in group BD, then became stable until 120 minutes in group B and increased but not to baseline in group BD (Table 4, Fig. 3) (*P*-value for group interaction < 0.001). There was a significant increase in

Table 1. *Demographic data and duration of surgery.*

Variable	Group I (B) N = 30	Group II (BD) N = 30	*P*-value
Age (years)	50.36 ± 6.005	50.50 ± 7.74	0.948
Weight (kg)	73.43 ± 9.35	73.23 ± 9.32	0.934
Height (cm)	164.63 ± 11.90	166.23 ± 6.20	0.516
BMI	27.96 ± 8.93	26.75 ± 4.89	0.517
Surgical time (hours)	2.17 ± 0.35	2.11 ± 0.38	0.604

Data are expressed as mean ± SD, BMI (body mass index)

Table 2. *Intraoperative changes in heart rate in studied groups.*

Groups	HR 0 time mean ± SD	HR 30 min mean ± SD	HR 60 min mean ± SD	HR 120 min mean ± SD	* *P*-value for Time Effect
G (B)	83.00 ± 6.86 (a)	79.33 ± 6.62 (b)	80.40 ± 8.45 (b)	80.40 ± 8.45 (b)	< 0.001
G (BD)	84.20 ± 6.95 (a)	69.8 ± 8.29 (c)	74.43 ± 11.03 (bc)	77.63 ± 9.70 (b)	< 0.001

P-value group effect (interaction) < 0.001. SD = standard deviation, HR = heart rate, within the same group (in each row) same letters. indicate no significant difference between measurements across time. *P*-value for time effect indicates the difference within groups, and for group interaction indicates the difference between groups.
* *P*-value is significant ≤ 0.05.

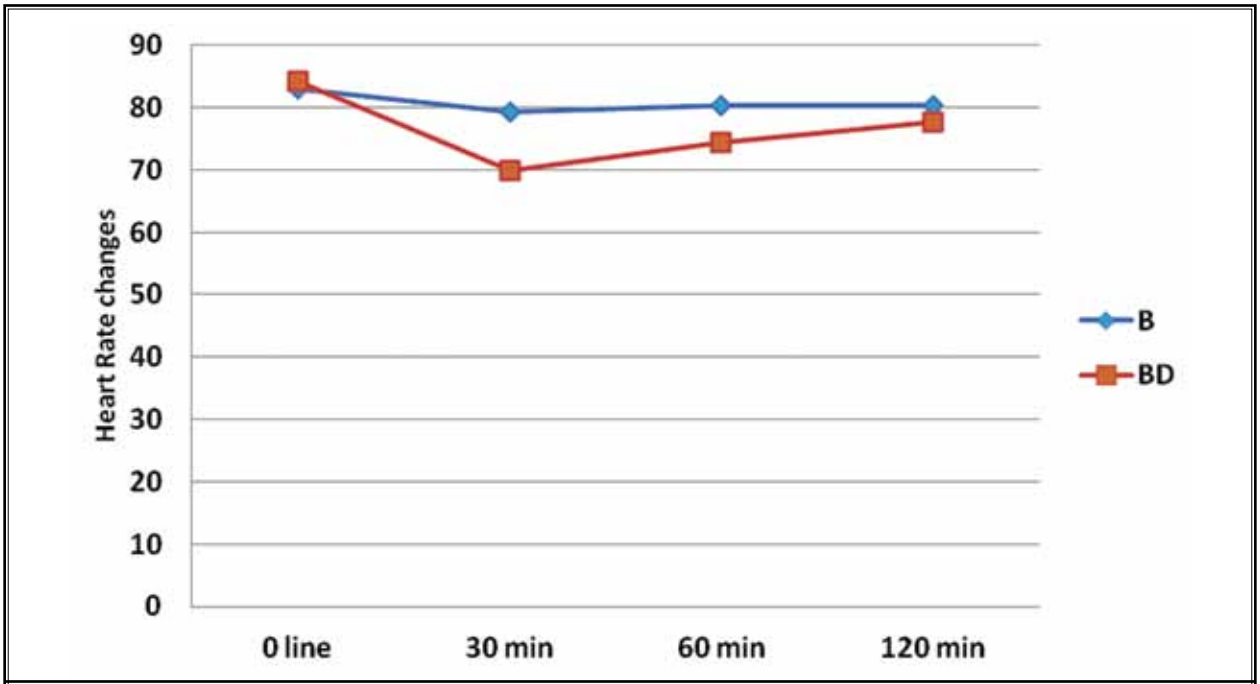

Fig. 1 . *Intraoperative heart rate.*

Table 3. Intraoperative changes in systolic blood pressure in studied groups.

Groups	SBP 0 time mean ± SD	SBP 30 min mean ± SD	SBP 60 min mean ± SD	SBP 120 min mean ± SD	* *P*-value for Time Effect
G (B)	126.57 ± 13.39 (ab)	118.60 ± 13.16 (b)	132.90 ± 12.86 (a)	134.0 ± 8.46 (a)	< 0.001
G (BD)	130.00 ± 11.49 (a)	101.33 ± 11.67 (b)	124.20 ± 12.79 (a)	127.20 ± 12.79 (a)	< 0.001

P-value group effect (interaction) < 0.001. SD = standard deviation, within the same group (in each row) same letters indicates no significant difference between measurements across time. *P*-value for time effect indicates the difference within groups, and for group interaction indicates the difference between groups. * *P*-value is significant ≤ 0.05.

pulse rate starting 2 hours postoperative until 48 hours postoperatively in group B but only after 12 hours until 48 hours in group BD (*P*-value for group interaction = 0.001), (Table 5, Fig. 4). No significant changes were recorded in the 2 study groups in systolic and diastolic blood pressure measured during the postoperative period ($P > 0.05$). VAS.R score measured at resting did not show significant reduction in group BD but showed a significant reduction after 2 hours postoperative in group B then started to increase with no significant difference from baseline after 12 hours (Fig. 5). There was no significant changes in VAS.M in either study

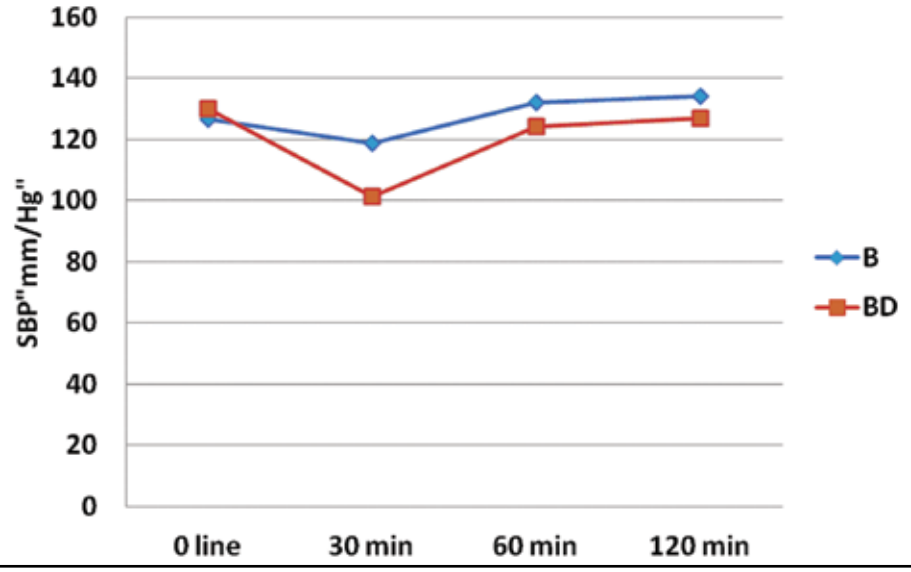

Fig. 2. *Intraoperative systolic blood pressure.*

Table 4. *Intraoperative changes in diastolic blood pressure in studied groups.*

Groups	DBP 0 time mean ± SD	DBP 30 min mean ± SD	DBP 60 min mean ± SD	DBP 120 min mean ± SD	* *P*-value for Time Effect
G (B)	81.33 ± 7.76 (a)	76.33 ± 7.18 (b)	77.67 ± 7.73 (ab)	77.33 ± 6.91 (ab)	< 0.001
G (BD)	81.50 ± 7.32 (a)	65.70 ± 7.73 (c)	75.00 ± 5.72 (b)	77.33 ± 5.20 (b)	< 0.001

P-value group effect (interaction) < 0.001. SD = standard deviation, HR = heart rate, within the same group (in each row) same letters. indicate no significant difference between measurements across time. *P*-value for time effect indicates the difference within groups, and for group interaction indicates the difference between groups.

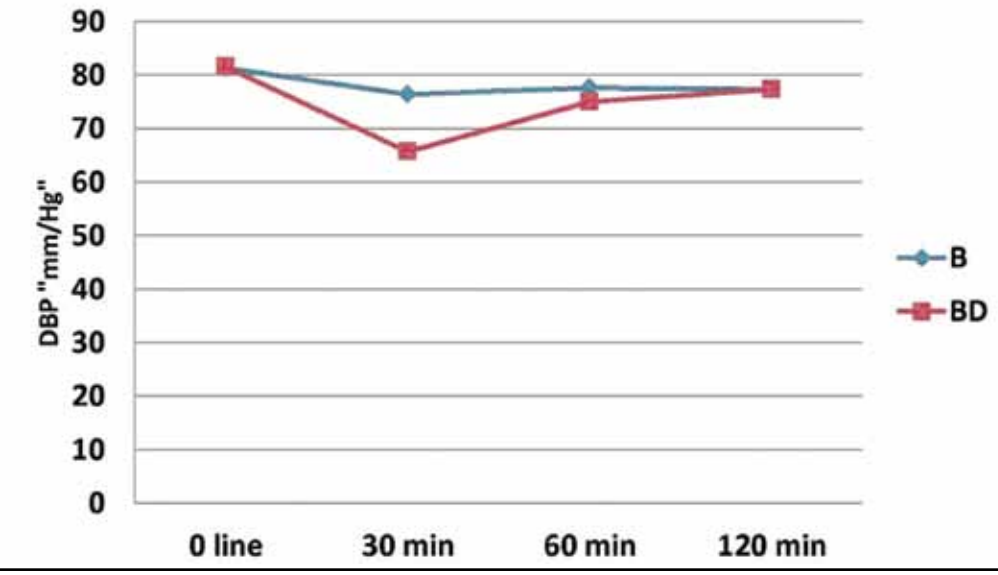

Fig. 3. *Intraoperative diastolic blood pressure.*

group postopertive (Fig. 6). The time of the first rescue analgesic requirement was significantly prolonged in group BD (8.16 ± 42 hours) in comparison to group B (6.48 ± 5.24 hours) (P = 0.04) (Table 6). The mean total consumption of intravenous tramadol rescue analgesia in the postanesthesia care unit in the first 48 hours postoperatively was significantly lower in group BD (150.19 ± 76.98 mg) in comparison to group B (194.44 ± 63.91mg) (P = 0.03) (Table 6). Regarding adverse effects noted in the first 48 hours postoperatively 3 patients in group B and 2 patients in group BD had postoperative nausea and vomiting (PONV). Pneumothorax occurred in one patient in group B, with a nonsignificant difference in the incidence of postoperative adverse effects noted between the 2 groups (P > 0.05) (Table 7). No hypotension, bradycardia, cardiac arrhythmia, or vascular puncture was recorded.

Table 5. *Postoperative heart rate.*

Time	G (BD)	G (B)
P0	76.97 ± 10.82 (d)	78.57 ± 9.50 (c)
P2	80.13 ± 10.67 (abcd)	81.30 ± 8.64 (ab)
P4	78.20 ± 9.00 (d)	82.80 ± 7.91 (ab)
P6	81.23 ± 8.32 (cd)	83.13 ± 7.76 (ab)
P12	84.40 ± 9.06 (a)	84.07 ± 6.95 (ab)
P24	82.53 ± 8.04 (ab)	84.43 ± 6.62 (a)
P36	84.00 ± 8.27 (ab)	84.70 ± 6.29 (a)
P48	84.37 ± 8.48 (ab)	84.90 ± 5.82 (a)

P-value group effect (interaction) < 0.001. SD = standard deviation, HR = heart rate, within the same group (in each row) same letters. indicate no significant difference between measurements across time. *P*-value for time effect indicates the difference within groups, and for group interaction indicates the difference between groups.
* P value is significant ≤0.05,

Discussion

In this study, we have demonstrated that patients who received PVB with 0.25% bupivacaine and 1 µg/kg dexmedetomidine in addition to general anesthesia experienced superior postoperative analgesia, prolongation of the time to the first rescue analgesic requirement, and decreased mean total intravenous tramadol consumption as compared with PVB with 0.25% bupivacaine alone and general anesthesia in the first 48 hours after breast cancer surgery.

Burlacu et al (20) noted that paravertebral fentanyl and clonidine in combination with diluted levobupivacaine (0.05%) are effective analgesics as demonstrated by a significant decrease in supplemental postoperative morphine consumption. At the doses used, the addition of fentanyl is associated with nau-

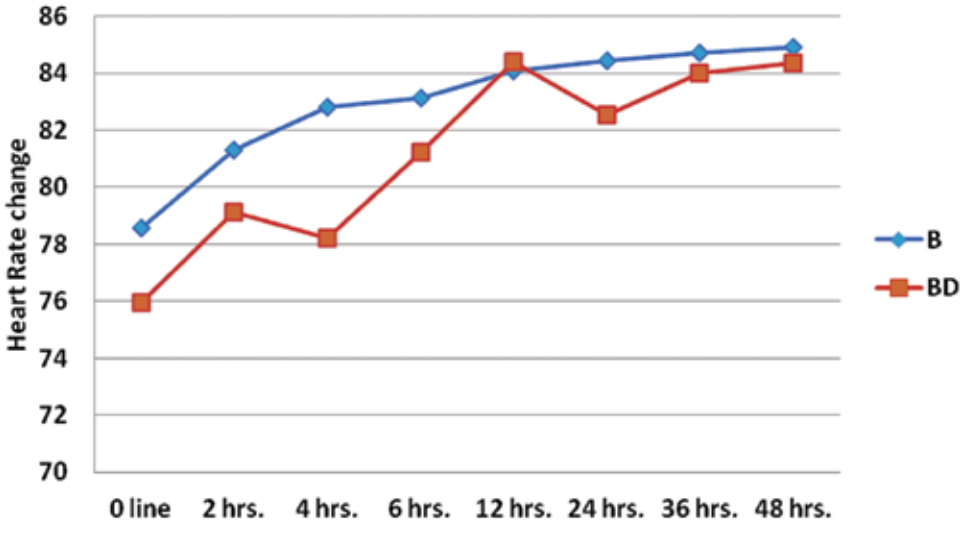

Fig. 4. *Postoperative heart rate.*

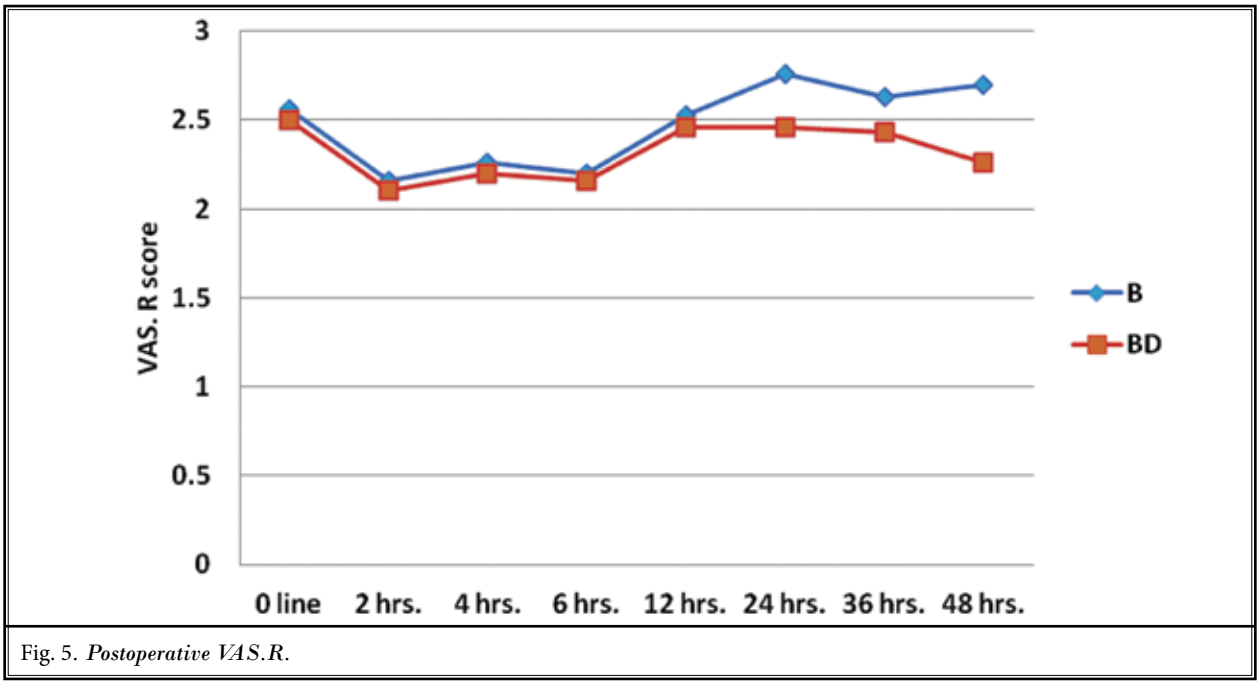

Fig. 5. *Postoperative VAS.R.*

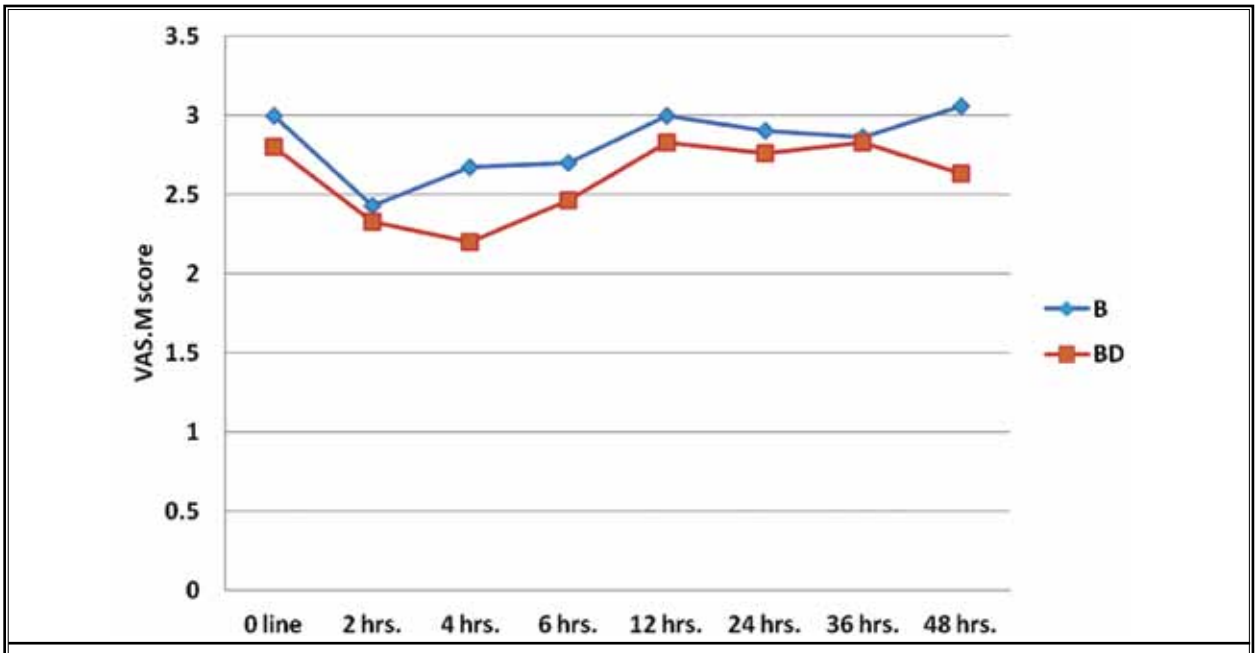

Fig. 6. *Postoperative VAS.M.*

Table 6. *Postoperative pain profile.*

Variable	Group (B) N = 30	Group (BD) N = 30	*P*-value
Time to first request (hours)	6.48 ± 5.24	8.16 ± 6.42	0.041
Tramadol consumption (mg)	194.44 ± 63.91	150.19 ±7 6.98	0.032

Data are expressed as mean±SD

Table 7. *Adverse effects*.

Variable	Group (B) N = 30	Group (BD) N =3 0	*P*-value
1-nausea	3 (10%)	2 (6.6%)	0.40
2-vomiting	3 (10%)	2 (6.6%)	0.40
3-Cardiac arrhythmia	-	-	-
4- pnemothorax	1 (3.3%)	0 (0.0%)	0.306
5-braycardia	-	-	-
6-hypotension	-	-	-
7-Vascular puncture	-	-	-

Data are expressed as number (%)

sea and vomiting, and clonidine with arterial hypotension. A study by Buhuvaneswari et al (21) demonstrated that the rescue analgesic consumption as well as cumulative pain scores at rest and on movement were significantly lower in 0.25% bupivacaine + epinephrine with fentanyl and 0.5% bupivacaine groups. They concluded that lower concentrations of bupivacaine can be combined with fentanyl to achieve analgesic efficacy similar to bupivacaine at higher concentrations, decreasing the risk of toxicity in PVB. Previous studies (22-24) report that multiple injections do improve the duration and quality of analgesia, with a higher probability of procedural complications. On the other hand, a single injection provides more patient comfort and lowers the need for sedation during performance of PVB, thereby improving patient satisfaction (25,26). Small doses of multiple injections are supposed to provide better consistency in the optimal spread of the injectate (27). A few clinical studies have examined the epidural usual dose of 1 – 2 µg/kg dexmedetomidine in thoracic and upper abdominal surgery. Unsurprisingly, epidural dexmedetomidine potentiates neuroaxial local anesthetics, decreases intraoperative anesthetic requirements, and improves postoperative analgesia hence reducing pulmonay complications associated with thoracotomy (28). Local anesthetic acts by blocking sodium channels, whereas an α2-adrenoceptor agonist acts by binding to presynaptic C- fibers and postsynaptic dorsal horn neurons; they produce analgesia by depressing the release of C-fiber transmitters and hyerpolarization of postsynaptic dorsal horn neurons (29-33). On the other hand, Gupta et al (34) compared the role of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine, and concluded that intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 hours as compared to fentanyl. In another study, Gupta et al (35) found that the addition of 5 µg of dexmedetomidine to 3 mL 0.75% isobaric ropivacaine intrathecally produced a prolongation in the duration of the motor and sensory block in lower limb surgeries. Good acute pain relief is associated with a lower risk of development of chronic pain in the operative area (36). Kairaluoma et al (37) reported that preincisional PVB provided good acute postoperative pain relief and prevented pain conditions for up to one year after breast cancer surgery. In our study, there were no significant differences in sedation scores between the 2 groups. Also our study showed that the addition of 1 µg/kg dexmedetomidine to 0.25% bupivacaine in PVB before induction of general anesthesia induced significant reduction in pulse rate and systolic blood pressure at 30 minutes intraoperatively, also diastolic blood pressure showed a significant reduction at 30 minutes intraoperatively. In the postoperative period systolic and diastolic blood pressure showed no significant difference between the 2 groups, but heart rate significantly increased 12 hours postoperatively until 48 hours in the dexmedetomidine + bupivacaine group. Burlacu et al (20) found that when they administered 150 µg clonidine followed by an infusion of levobupivacaine 0.05% with clonidine 3 µgmL-1 in PVB systolic blood pressure at any measured time interval was significantly lower in the levobupivacaine + clonidine group when compared with other groups. Also the number of patients experiencing bradycardia (heart rate < 50 beats/min.) over the 24 hours was 2 (16.6%) in this group. In our study only 3 patients in group B and 2 patients in group BD developed PONV and were treated by antiemetic. Pneumothorax occurred only in one patient in group B and was managed. No patients suffered hypotension, bradycardia, cardiac arrhythmia, or vascular puncture.

Conclusion

In conclusion, the addition of dexmedetomidine 1 µg/kg to bupivacaine 0.25% in thoracic PVB in patients undergoing modified radical mastectomy improves the quality and the duration of analgesia and also provides an analgesic sparing effect with no serious side effects.

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