Randomized Trial

Paravertebral Dexmedetomidine in Video-Assisted Thoracic Surgeries for Acute and Chronic Pain Prevention

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Disclaimer: TThis research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Support was provided solely from departmental resources.Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 08-19-2018
Revised manuscript received: 10-14-2018
Accepted for publication: 11-12-2018

Free full manuscript: www.painphysicianjournal.com

Background: Video-assisted thoracoscopic surgery (VATS) is considered as one of the minimally invasive surgeries. Early postoperative pain alleviation is very important to avoid complications, at the same time, proper early pain control is an established fact to decrease the incidence of chronic pain.

Objectives: To evaluate the efficacy of thoracic paravertebral block (PVB) by a bupivacaine/dexmedetomidine mixture on acute and chronic post-thoracoscopic surgery pain in patients undergoing VATS.

Study Design: A randomized prospective double-blinded trial.

Setting: Assiut University Hospitals, Orman Cardiology Hospital.

Methods: Sixty adult patients underwent elective VATS surgery under general anesthesia randomly allocated into 2 groups; Group I received thoracic PVB with isobaric bupivacaine 0.5% (0.3 mL/kg) and Group II received PVB with isobaric bupivacaine 0.5% (0.3 mL/kg) and dexmedetomidine (1 mcg/kg). Postoperative pain (at rest, with cough, and with movement) was assessed through a visual analog scale (VAS) every 30 minutes in the first 2 hours, then at the second, fourth, eighth, and 24th hours. Time to first analgesia request and consumption of intravenous rescue analgesia (ketorolac tromethamine 30 mg/dose) was recorded. Follow-up of the patients regarding the incidence of chronic post-thoracoscopic pain by the end of the third and sixth months after the procedure was reviewed through the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale.

Results: VAS score was significantly lower in Group II during the early postoperative 90 minute records. Pain with cough and with movement persisted to be significantly lower in Group II up to the second postoperative hour. Time to first analgesia requirement was significantly longer in Group II in comparison to Group ($P < 0.001$). There was less ketorolac consumption in Group II than in Group I ($P = 0.002$). At the third month, Group II showed significantly lower incidence of LANSS pain scale than Group I ($P = 0.04$).

Limitations: There was the heterogeneity of surgical procedures in the patients.

Conclusions: Dexmedetomidine as an adjuvant to bupivacaine PVB offers better pain relief during the early postoperative hours, and it carries a favorable effect on chronic postoperative pain.

Clinical trial registry number: NCT03632161.

Key words: Dexmedetomidine, paravertebral block, video-assisted thoracoscopic surgery, postoperative pain, chronic pain

Pain Physician 2019: 22:271-280

Most video-assisted thoracoscopic surgery (VATS) procedures are considered low-risk interventions requiring short hospital stays or even outpatient settings, so that VATS has not raised much interest regarding its postoperative pain management. However, it is a fact that pain following VATS could be severe and long-lasting (1). According to Richardson et al (2), 38% of VATS procedures present persistent pain 2 months after surgery as a result of acute nerve damage during the surgical procedure.

Postoperative pain alleviation modalities described in the literature are numerous including nonsteroidal anti-inflammatory drugs (NSAIDs), systemic opioids, epidural analgesia, thoracic paravertebral block (PVB) with local anesthetics, patient-controlled analgesia, cryoanalgesia, surgical wound infiltration, transcutaneous electrical nerve stimulations, and others (3). The use of PVB for thoracic procedures is well accepted, and could be comparable to epidural block concerning pain relief and demonstrated to be even superior (4-7). PVB is characterized by effective unilateral blockade of pain stimuli over several dermatomes that is attributed to ipsilateral blockade of the spinal nerves and sympathetic chain (8).

A safe side-effect profile and low complication rate make PVBs popular in clinical settings. Indeed, PVB reduces opioid consumption and related side effects, as well as the incidence of chronic pain after surgery (9-11). A recent meta-analysis reported that although PVBs and thoracic epidural analgesia provide equivalent pain relief, only PVB reduces the incidence of pulmonary complications following thoracotomies (12-14).

Several adjuvants can be added to the local anesthetics during infiltration to augment efficacy and or duration of analgesia. One of the very safe adjuvants is the highly selective $\alpha 2$ receptor agonist dexmedetomidine. It is evident that perineural dexmedetomidine can prolong the duration of analgesia through blocking of the hyperpolarization-activated cation current (15).

Our hypothesis' questions to what extent could the use of dexmedetomidine as an adjuvant to bupivacaine in PVB be helpful to decrease both acute and chronic post-thoracoscopic surgical pain, and its implications on the postoperative pulmonary function tests.

The primary aim has involved the acute pain assessment during the early 24 postoperative hours. The secondary goals included the incidence of post-thoracoscopic chronic pain, and any suspected difference in postoperative pulmonary function tests.

Methods

This prospective randomized double-blind study was approved by the local ethics committee of the Faculty of Medicine, Assiut University, and registered at Clinical Trials under the number of (NCT03632161). It adhered to the Declaration of Helsinki and involved 60 adult patients of American Society of Anesthesiologists score I-II who underwent elective VATS surgeries at Assiut University Heart Hospital. Exclusion criteria included patients with hepatic or renal impairment, any known contraindication for regional techniques, and or an allergy to drugs used.

An informed consent was obtained from all patients who were randomly and equally allocated into 2 groups through a web-based randomizer (https://www.randomizer.org/). All patients received ultrasound-guided PVB after the induction of general anesthesia. PVB was performed with isobaric bupivacaine 0.5% (0.3 mL/kg) in Group I, whereas in Group II, PVB was performed with isobaric bupivacaine 0.5% (0.3 mL/kg) and dexmedetomidine (1 mcg/kg). The patients and the outcome assessing physician were kept blinded to the grouping process (double-blind study). Patients were trained to record their postoperative pain on the visual analog scale (VAS) during the preanesthetic visit, in which VAS = 0 indicates no pain and VAS = 10 indicates the worst pain.

In both groups, general anesthesia was induced with propofol (2 mg/kg) and fentanyl (1 mcg/kg). Tracheal intubation with lung isolation (by a double lumen tube) was facilitated with cisatracurium (0.1 mg/kg). Anesthesia was maintained with isoflurane (1%-2%) and cisatracurium (0.05 mg/kg per dose). Fentanyl administration (0.5 mcg/kg) was repeated if heart rate and or mean arterial pressure rose 20% above baseline values. The ultrasound-guided PVB was performed after the anesthesia induction. Intraoperative monitoring included electrocardiogram, noninvasive blood pressure, temperature, oxygen saturation, exhaled CO_2 (end-tidal capnography), and train of four.

Technique of Ultrasound-Guided PVB

After an initial anatomic scan to confirm the thoracic levels, appearance, and depth of the structures, the procedural site was marked, the patient's back was then sterilized and draped in a sterile fashion, and a 5-12 MHz linear array ultrasound transducer was placed in a sterile sheath. An in-plane paramedian sagittal block was performed with the probe in a vertical position (approximately 2.5-3 cm lateral to the midline). A

touchy needle was introduced in a cephalic direction, and its tip was advanced under direct visualization until it pierced the superior costotransverse ligament. If the superior costs transverse ligament was not easily seen, the needle was advanced until it was directly seen above the pleura. Because of the steep angle at which the block needle enters the tissue (making its visualization somewhat difficult), we injected a small amount of normal saline solution intermittently during its advancement to confirm the position of the tip. When the needle tip was located immediately above the pleura, aspiration was performed to confirm the absence of blood or air before injection of the local anesthetic. At the end of the surgery, anesthesia was discontinued, the wound dressing was applied, and extubation of the patient was completed after reversal of muscle relaxant by neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). The patients were transferred to the high postoperative dependency intensive care unit. Postoperative rescue analgesia was attained with intravenous ketorolac tromethamine (30 mg per dose), which was administered when VAS score was ≥ 3.

Data Collection

The data collection included the pain VAS score (the primary outcome) to assess the quality of effective analgesia at rest, on coughing, and during movement every 30 minutes in the first 2 hours, then at the second, fourth, eighth, and 24th hours. Time to first analgesia request and consumption of intravenous rescue analgesia were recorded. Follow-up of the patients regarding the incidence of chronic post-thoracoscopic pain by the end of the third and sixth months after the procedure was reviewed through the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale (16). The LANSS pain scale > 12 denotes that neuropathic mechanism is likely to be a contributing cause of the patient's chronic pain when present.

Respiratory monitoring included respiratory rate and peripheral arterial oxygen saturation (SpO_2) through the pulse oximetry along with 24 hours of pain monitoring. Pre- and postoperative (24 hours postoperatively) pulmonary function tests were evaluated. Sedation score was assessed through the Ramsay Sedation Scale (17).

Statistical Analysis

We have determined a significant difference in the occurrence of postoperative pain score by using the power of 80% and a significance level of 5%, and accordingly sample size was determined to be 30 patients in each group. Collected data were first assessed by the Kolmogorov-Smirnov test for the normality, and were presented as a number, percentage, mean ± standard deviation, or median (range). The Chi-square test and the Fisher exact test were used to compare qualitative variables. Continuous variables were compared with the t test (parametric data) or the Mann-Whitney U test (nonparametric data). A 2-tailed $P < 0.05$ was considered statistically significant. Data entry and data analyses were performed using Statistical Package for Social Science version 19 (IBM Corporation, Armonk, NY).

Results

Table 1 shows the demographic and operative data of the patients. The 60 patients were equally randomized between the 2 groups as shown in the Consolidated Standards of Reporting Trials (CONSORT) flow-chart (Fig. 1), and they were comparable regarding their demographic, operative, and postoperative details, with insignificant differences in between.

Postoperative pain (at rest, with cough, and with movement) as assessed by the VAS was significantly lower in Group II during the early postoperative 90 minute records. Pain with cough and with movement persisted to be significantly lower in Group II up to the second postoperative hour (Table 2). Time to first analgesia requirement was significantly longer in Group II in comparison to Group I (7.65 ± 2.54 hours vs. 4.13 ± 1.76 hours) with $P < 0.001$. Analgesia consumption (ketorolac) in Group II was 10 ± 14.6 mg versus 32 ± 21.1 mg in Group I with $P = 0.002$.

Follow-up of the chronic pain incidence is shown in Table 3, and it was found that at the third month, Group II showed a significantly lower incidence of LANSS pain scale >12 in comparison to Group I; however, no significant difference was found between groups by the sixth month in this aspect.

Respiratory monitoring during the early 24 postoperative hours revealed an insignificant difference between both groups in regard to respiratory rate and SpO_2 (Fig. 2). Spirometry showed insignificant differences between the 2 groups apart from the postoperative measured forced expiratory volume in the first second (FEV1) in which it was significantly lower in Group II only (Figs. 3-5).

With regard to the Ramsay Sedation Scale, the recorded scales were nearly the same, but there were significant differences between the 2 groups at 30 and

Table 1. *Demographic and clinical data in the 2 studied groups.*

Variables	Group I n = 30	Group II n = 30	*P* Value
Age (years)	33.67 ± 13.33	35.00 ± 11.98	0.66
Gender Male Female	 16 (53.3%) 14 (46.7%)	 18 (60%) 12 (40%)	0.71
Weight (Kg)	68.20 ± 9.10	64.67 ± 10.08	0.35
Height (cm)	166.27 ± 6.95	162.53 ± 7.44	0.15
Body mass index	24.66 ± 2.83	24.38 ± 2.67	0.71
ASA score: ASA II ASA III	 5 (33.3%) 10 (66.7%)	 6 (40%) 9 (60%)	0.7
Total anesthesia time (min)	90.00 ± 19.64	85.00 ± 19.36	0.36
Total surgical time (min)	63.67 ± 17.27	69.00 ± 19.48	0.45
Type of operation Hyperhidrosis for sympathectomy Mediastinal mass for biopsy or excision Lobectomy Lymph node biopsy Empyema	 10 (33.3%) 4 (13.3%) 6 (20%) 4 (13.3%) 6 (20%)	 8 (26.7%) 4 (13.3%) 8 (26.7%) 4 (13.3%) 6 (20%)	0.97
Time to chest tube removal (days)	4.13 ± 2.36	3.60 ± 1.12	0.14
Length of hospital stay (days)	4.13 ± 2.85	3.13 ± 1.55	0.59

Data were presented as mean ± standard deviation and number (%).
$P < 0.05$ is considered statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists.

60 minutes only as shown in Figure 6. No postoperative complication related to the technique or dexmedetomidine has been noticed.

Discussion

This study has demonstrated better postoperative pain alleviation in the group that received dexmedetomidine in a dose of 1 mcg/kg in conjunction with bupivacaine through PVB, especially in the early 2 postoperative hours. In consequence, time to first analgesia was longer, and there was less rescue analgesia consumption in the dexmedetomidine group.

PVB itself carries better postoperative pain alleviation than the conventional in such minimally invasive surgery. Fibla et al (18) demonstrated that PVB with a catheter insertion in the paravertebral space using ropivacaine has provided an excellent postoperative pain alleviation modality in VATS surgeries

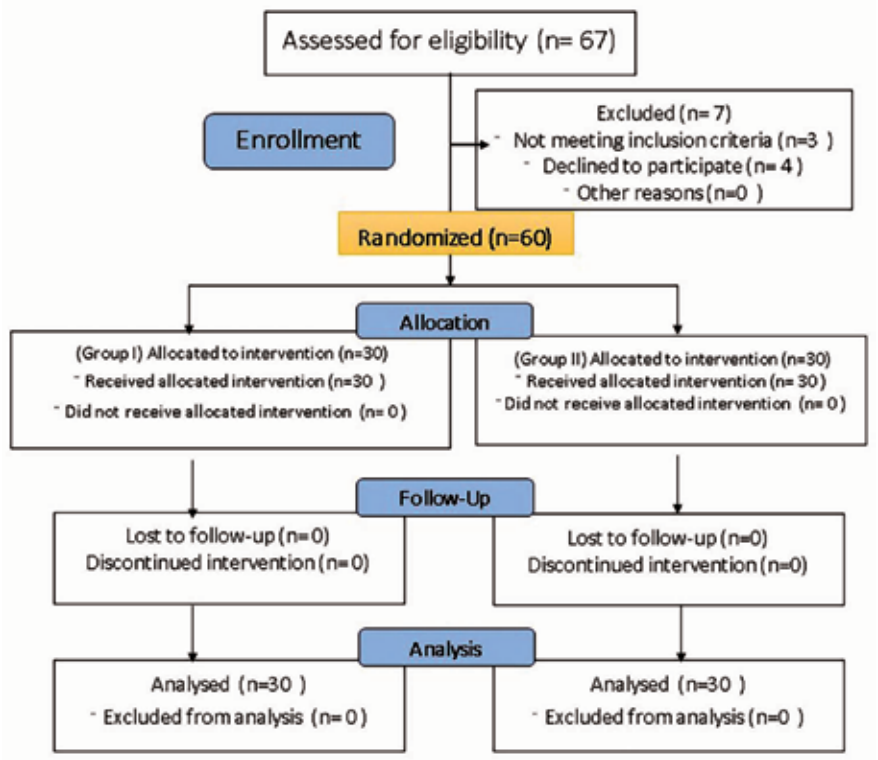

Fig. 1. *CONSORT flow-chart of the patients.*

Table 2. *Postoperative acute pain (VAS) in the 2 studied groups.*

Variables	Group I n = 30			Group II n = 30			*P* Value		
	VAS1	VAS2	VAS3	VAS1	VAS2	VAS3	P1	P2	P3
30 min	2 (1-3)	4 (2-6)	4 (2-6)	1(1-4)	2 (1-5)	2 (1-3)	0.001*	<0.001*	0.001*
60 min	2 (1-3)	4 (2-6)	3 (2-6)	1 (1-3)	2 (1-5)	2 (1-3)	<0.001*	<0.001*	0.001*
90 min	2 (1-4)	4 (2-7)	3 (2-6)	1 (1-3)	2 (1-5)	2 (1-3)	0.003*	<0.001*	<0.001*
Second hr	1 (1-3)	3 (1-6)	3 (2-6)	1 (1-4)	2 (1-4)	2 (1-4)	0.168	0.008*	0.020*
Fourth hr	1 (1-3)	3 (1-6)	3 (1-8)	1 (1-4)	2 (1-4)	3 (1-4)	0.140	0.122	0.241
Eighth hr	1 (1-2)	3 (1-6)	2 (1-8)	1 (1-3)	3 (1-4)	3 (1-4)	0.260	0.702	0.741
24th hr	1 (1-3)	3 (1-6)	2 (1-8)	1 (1-3)	3 (1-4)	2 (1-4)	0.654	0.757	0.745

Data are presented as median (range). VAS score (1 at rest, 2 on cough, 3 with movement).
*Statistically significant difference ($P < 0.05$).

Table 3. *LANSS pain scale in the 2 studied groups.*

Variable	Group I n = 30	Group II n = 30	*P* Value
3-month LANSS <12 >12	 24 6	 29 1	0.04*
6-month LANSS <12 >12	 28 2	 29 1	0.5

Data are presented as number of patients.
*Statistically significant difference ($P < 0.05$).

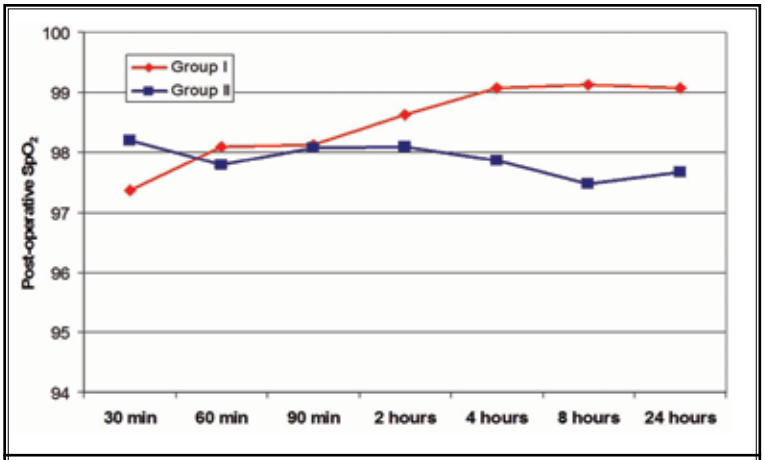

Fig. 2. *Postoperative peripheral arterial oxygen saturation (SpO_2). Data are expressed as mean. $P < 0.05$ is considered statistically significant.*

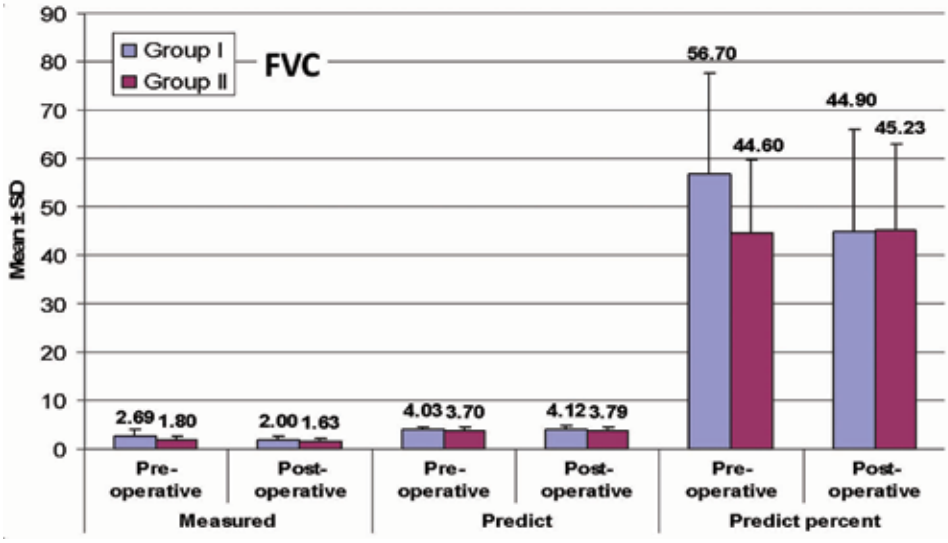

Fig. 3. *Preoperative and postoperative FVC in the 2 studied groups. Data are expressed as mean ± standard deviation. *Significant difference between the 2 groups. $P < 0.05$ is considered statistically significant.*

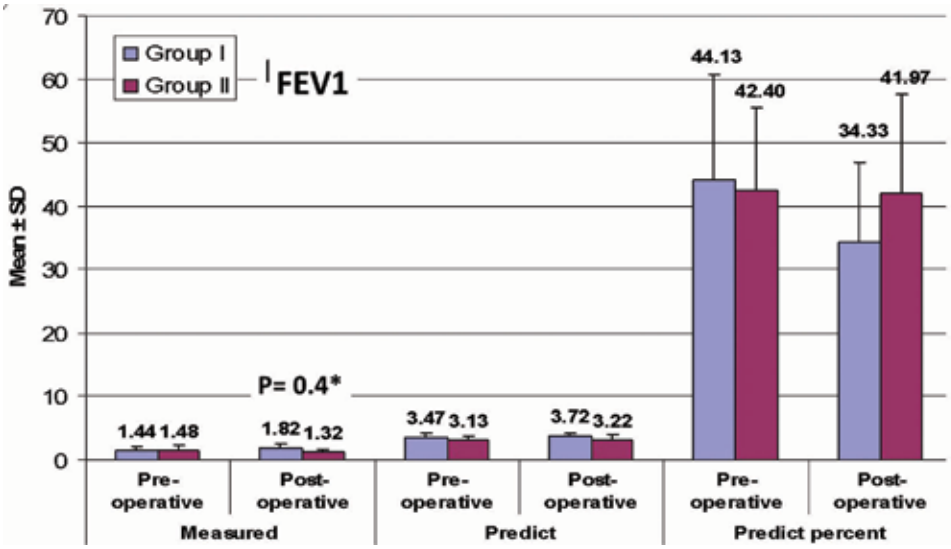

Fig. 4. *Preoperative and postoperative FEV1 in the 2 studied groups. Data are expressed as mean ± standard deviation. *Significant difference between the 2 groups. P < 0.05 is considered statistically significant.*

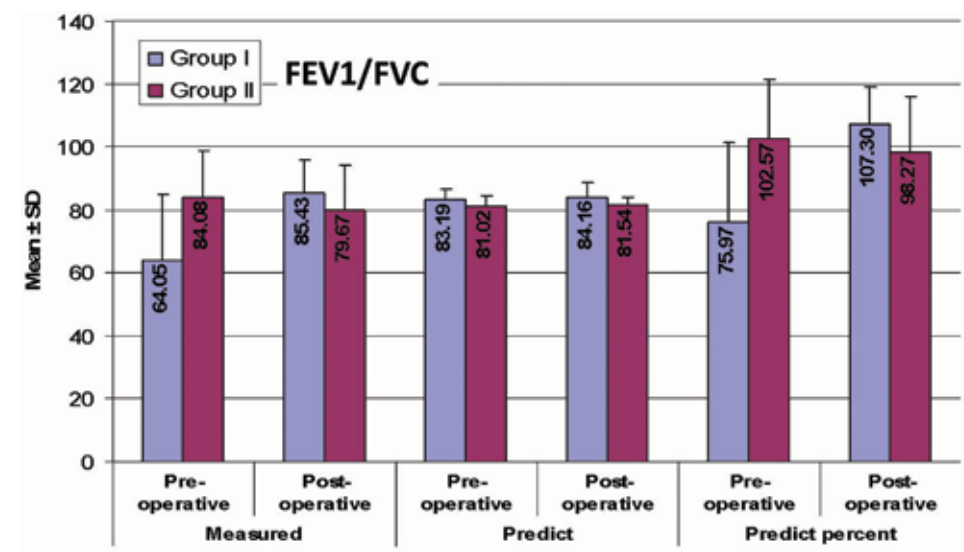

Fig. 5. *Preoperative and postoperative FEV1/FVC in the 2 studied groups. Data are expressed as mean ± standard deviation. *Significant difference between the 2 groups. P < 0.05 is considered statistically significant.*

when compared to conventional postoperative NSAID administration.

We have used dexmedetomidine as an adjuvant to bupivacaine in PVB because of its already evident ability to prolong the duration of analgesia as shown by the study of Xu et al (19) in their prospective randomized controlled study using multilevel thoracic PVB with ropivacaine with or without dexmedetomidine in VATS. They found that adding dexmedetomidine 1 mcg/kg had prolonged the duration of analgesia and improved the patient's satisfaction compared to the ropivacaine only group. In addition, dexmedetomidine use in such a dose has not caused side effects nor complications as we have found also (19).

We have used perineural dexmedetomidine in PVB because it carries an optimal prolonged blocking effect when it is used locally rather than systemic administration. Jung et al (20) have compared variable doses of perineural dexmedetomidine when injected through interscalene brachial plexus block (with ropi-

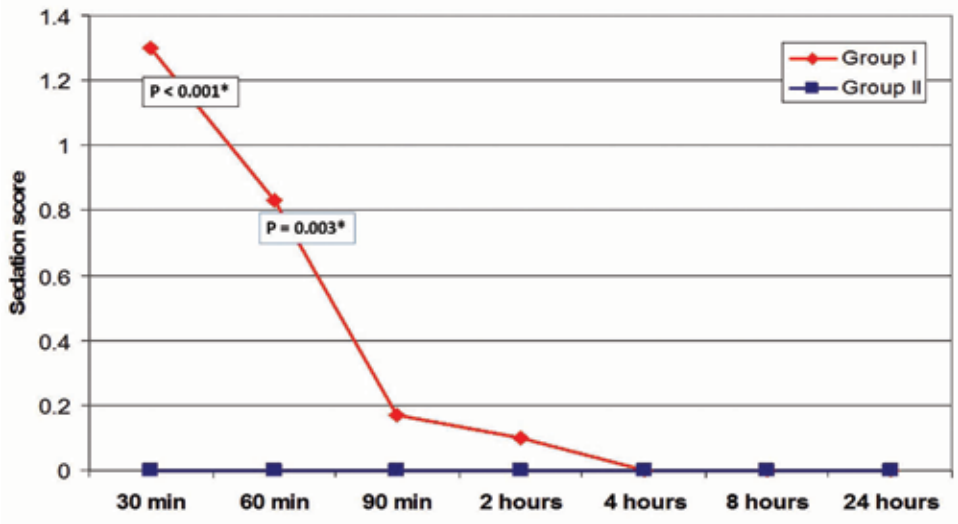

Fig. 6. *Postoperative Ramsay Sedation Scale. Data are expressed as median. *Significant difference between the 2 groups. P < 0.05 is considered statistically significant.*

vacaine as a local anesthetic) for arthroscopic shoulder surgeries. They have found that the dose of 1 mcg/kg was effective in prolongation of analgesia duration as well as duration of sensory and motor block, and devoid of neurotoxicity and or systemic side effects. This was in line with our findings in regard to the analgesia; however, we have not noticed any reaction of motor effect on the intercostal muscles that could affect the respiratory functions as demonstrated in our results. Marhofer et al (21) mentioned that dexmedetomidine is a new ideal preferable adjuvant to local anesthetic, in which they designed a randomized double-blind study on 36 volunteers who underwent ulnar nerve block with either 3 mL ropivacaine 0.75% only versus ropivacaine with dexmedetomidine 20 µg, or ropivacaine with systemic dexmedetomidine 20 µg. They noticed the longest duration of ulnar nerve bock with the group who received perineural dexmedetomidine, and this is what we have noticed in regard to the pain sensation. Systemic dexmedetomidine has offered some prolongation of ulnar nerve block in the Marhofer study (21).

The mechanism by which dexmedetomidine offers better analgesia is assumed to be the inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of α2 receptor in the locus coeruleus. Suppression of activity in the descending noradrenergic pathway that modulates nociceptive neurotransmission terminates propagation of pain signals leading to analgesia (22).

It is well-known that the contents of the thoracic paravertebral space include the intercostal nerves, the dorsal rami, the rami communicants, the intercostal vessels, the sympathetic chain, loose connective tissue, and fatty tissue. The nerves remain for the most part unsheathed in the thoracic paravertebral space (23). We believe that the analgesic effects of dexmedetomidine, when added to bupivacaine, could also be attributed to its perineural (on the nerve tissues in the paravertebral space) as well as central α2 receptor-mediated effects (15,20-22).

We have found that time to first analgesia request was shorter, and higher ketorolac consumption in the bupivacaine only group. This is in agreement with studies that denoted that single dose PVB (with local anesthetic only) could be insufficient to cover a satisfactory postoperative period in regard to pain relief (12,14).

Another study used the same dose of dexmedetomidine (1 mcg/kg) that we have used with 0.25% bupivacaine in ultrasound-modified pectoral block for postoperative pain relief after mastectomy. They have found less morphine consumption (as a rescue analgesia) in comparison to the other group that received bupivacaine only. Time to first analgesia request was also longer in the dexmedetomidine group (24).

Following up pain during the next 6 months was one of our concerns, so we have used the LANSS pain scale especially because it is well known that the most common cause for chronic pain after such procedures is the intercostal nerve affected during surgery (2).

Chronic pain following thoracic surgery is defined as "persistent pain for at least 3 months after thoracic surgery, the pain differs in character from the preoperative pain, and other causes for chronic pain such as continuing malignancy or chronic infection have been excluded" (25).

The significant difference in LANSS pain scale was seen by the third month rather than the sixth month with LANSS > 12 (neuropathic pain is likely to be contributing to patient's pain) in 6 patients in the bupivacaine only group versus one patient only in the dexmedetomidine group.

The value of PVB in VATS regarding the incidence of chronic pain was demonstrated by Yornuk et al (26). They conducted a study on 140 patients who underwent VATS under general anesthesia and randomly assigned them into 2 groups; one group received thoracic PVB using 0.5% bupivacaine after anesthesia induction. The incidence of chronic pain at the third and sixth months was significantly lower in the PVB group (26). Indeed, our results showed some difference from this study in regard to the pain after the sixth month, and this could be because of the different method for pain assessment (we have used the LANSS pain scale) and different modality of analgesia in which they had used intravenous morphine and tramadol in one group versus PVB in the other group.

A randomized study involved 180 women who underwent modified radical mastectomy under general anesthesia and were randomly assigned into 3 groups; one group received conventional general anesthesia only, the other group received additional single shot thoracic PVB, and the third group received a continuous infusion of local anesthetic through a thoracic paravertebral-inserted catheter. Chronic pain incidence and severity of symptoms were less in the groups that received thoracic PVB at the third and sixth month follow-ups (23).

To our knowledge, there is no study that has focused on the incidence of post-VATS chronic pain when dexmedetomidine is used. The impact of intraoperative dexmedetomidine administration was studied by Lee et al (27). They have studied intraoperative dexmedetomidine infusion 0.7 mcg/kg/h in 64 patients who underwent open heart surgery through sternotomy and compared the incidence of 3-month chronic pain with another 69 patients who underwent the same surgery but without dexmedetomidine (standard group). They found that the incidence of chronic pain was significantly higher in the standard care group ($P = 0.04$) (27).

The authors in this study have made a preoperative pulmonary function test record for patients undergoing VATS with respect to forced vital capacity (FVC), FEV1, and FEV1/FCV ratio. Pulmonary function was an extra parameter to be studied in our trial and to gather relevant data regarding it. It was observed that the postoperative mean measured FEV1 was significantly higher in Group I than in Group II. Considering the blinded distribution of thoracic pathologies among the 2 group patients as well as the staged disappearance of etiology could have contributed to the means of measured FEV1/FVC variation through pre- and postoperative intervals, but at least we can demonstrate that Group I showed better postoperative values of FEV1/FVC, and the addition of dexmedetomidine did not show any deterioration of early postoperative pulmonary function test. Moreover, no patient in our 2 groups showed hypoxemia during the early 24 postoperative period, and this is in agreement with the Xu et al (19) study that reached the same findings in their trial.

Previous studies demonstrated that α2-adrenergic agonists carry no or even minimal effect on the respiratory functions, and this is what we have found in our trial (28,29).

The Wu et al (30) meta-analysis revealed that neuraxial dexmedetomidine was associated with a significant increase of postoperative sedation within 24 hours compared with a placebo group, this was somehow consistent with our results in which the dexmedetomidine group showed more sedation (lower values according to Ramsay Sedation Scale) during the first postoperative hour. The sedation we have noticed was characterized by being of short term, and the patients were easily arousable.

Dexmedetomidine has both supraspinal analgesic and hypnotic actions attributed to the inhibited release of inhibitory control trigger neurotransmitters that can decrease histamine release, and the net result is hypnosis resembling normal sleep without ventilatory suppression (31). Delirium, which is a common drawback from the other known sedatives, is not an issue here in our study when we used dexmedetomidine as it has no effect on the gamma-aminobutyric acid system (32).

What we have found in this group of patients was very beneficial regarding acute and chronic pain. No systemic effects of respiratory function drawbacks were noticed with the use of perineural dexmedetomidine in the postoperative period.

Limitations

The heterogeneity of surgical procedures in the patients is the first limitation. Some patients experienced pain during the postoperative spirometry that could have some effects on the pulmonary functions. Another group could be compared in which bupivacaine PVB can be used in conjunction with intravenous dexmedetomidine.

Conclusions

Dexmedetomidine as an adjuvant to bupivacaine PVB offers better pain relief during the early postoperative hours, and it carries a favorable effect on chronic postoperative pain.

Acknowledgments

Author contributions: Emad Zarief Kamel and Sayed Kaoud Abd-Elshafy had full access to all the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. Fatma Abdallal, Heba Edwar, and Essam Abd Allah designed the study protocol. Hatem Hassan Mohamed Maghraby, Jehan Ahmed Sayed, and Mohamed Shaaban Ali managed the literature searches and summaries of the previous related work and wrote the first draft of manuscript. Ghada Shalaby Khalaf Mahran and Hussein Elkhayat were responsible for the operative and postoperative respiratory functions.

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