Comparison of Intercostal Nerve Block with Ropivacaine and Ropivacaine-Dexmedetomidine for Postoperative Pain Control in Patients Undergoing Thoracotomy: A Randomized Clinical Trial

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Abstract

Background: Thoracotomy is one of the most painful surgeries, and failure to alleviate patients' pain can have dangerous consequences.

Objectives: This study aimed to evaluate the addition of dexmedetomidine to ropivacaine in the intercostal block for postoperative pain control in patients undergoing thoracotomy.

Methods: In this randomized clinical trial, 74 patients aged 18 to 60 years with ASA class I or II, BMI less than 40, and no severe systemic problems referred to a teaching hospital in Ahvaz to undergo thoracotomy were included in the study and randomly divided into two groups. After surgery, an ultrasound-guided intercostal block was done with ropivacaine (5 cc of 0.25% solution; group R) or ropivacaine (5 cc of 0.25% solution) plus dexmedetomidine (0.5 μg/kg; group RD) per dermatome. Two dermatomes above and two dermatomes below the level of surgical incision were used. Pain, total opioid consumption, length of ICU stays, time to first rescue analgesic, and time to get out of bed were compared between the two groups.

Results: The intercostal block significantly reduced pain in both groups (P < 0.0001). The pain was lower in the RD group than in the R group from six hours after the intervention up to 24 hours after (P < 0.001). The number of patients who needed rescue analgesia at 12 hours was significantly lower in the RD group (P < 0.05). The RD group also had lower total opioid consumption and a longer time to receive the first rescue analgesia (P < 0.01). There was no significant difference between the two groups in the length of hospitalization and the time to get out of bed.

Conclusions: Dexmedetomidine is an effective and safe choice to be used as an adjunct to ropivacaine in ICB, and it extends the duration of analgesia in combination with ropivacaine after thoracotomy.

Keywords: Intercostal Nerve Block, Ropivacaine, Dexmedetomidine, Intensive Care Unit, Thoracotomy, Postoperative Pain

1. Background

Pain after thoracotomy is often very severe and can be associated with severe complications such as atelectasis ([1]). Due to the retention of pulmonary secretions caused by pain during chest movements, this pain can also lead to severe pneumonia ([2-4]). The pain prevents effective coughing, deep breathing, and mobility of the patient. In general, severe postoperative pain increases postoperative complications and may also lead to chronic pain ([5-7]). There are many different ways to control acute pain after thoracic surgery. These treatments include systemic opioid-based treatment regimens, intercostal nerve block (ICB), newer methods of fascial plate blocking including serratus anterior plane block (SAPB) and pectoral nerves II block (Pecs II), thoracic paravertebral block ([8]), erector spinae plane block ([9]), and thoracic epidural block. There is considerable evidence that ICBs and fascial plate blocks are superior to systemic opioid-based regimens ([10]).

The intercostal nerve block is an effective method of

post-thoracotomy pain relief that can be done with the help of anatomic landmarks, ultrasound, or fluoroscopy (8, 11-13). Unlike the use of systemic opioids that suppress the central nervous system and respiration and cause nausea and suppression of the cough reflex, ICB does not suppress the central nervous system. It is also relatively easy to perform and provides segmental analgesia when used at the desired dermatomal level (10). The use of ultrasound in guiding the block can significantly reduce the time and amount of medication use, as well as the risk of complications for the patient (14-17). Dexmedetomidine, an alpha-2 receptor agonist, is a drug with strong analgesic effects that appears to have synergistic effects with opioids due to opioid-sparing effects (18, 19). It has been shown to prolong analgesic effects of peripheral nerve and neuraxial blocks, with hypotension and bradycardia as its side effects (20-26). Ropivacaine is a long-acting topical analgesic with low-fat solubility, cardiac and central nervous system toxicity, and potency similar to bupivacaine (27).

2. Objectives

This study aimed to evaluate the effect of the intercostal nerve block with ropivacaine alone or in combination with dexmedetomidine for reducing postoperative pain after thoracotomy.

3. Methods

This study was a randomized clinical trial performed on 74 patients aged 18 to 60 years referred to a medical-educational center in Ahvaz, Khuzestan, Iran, between July 28, 2019, and February 3, 2021. The protocol of this study was reviewed and approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1398.041) and was registered on the Iranian Registry of Clinical Trials (IRCT20190107042264N2). This study followed the CONSORT 2010 statement (Figure 1). Inclusion criteria included ASA class I or II, BMI less than 40, no history of substance or alcohol abuse, no pregnancy or breastfeeding, no history of coagulation problems or use of anticoagulants, ejection fraction greater than 30%, no history of cardiac blocks, no kidney or liver disease requiring treatment, and absence of diseases involving peripheral nerves. Exclusion criteria included the withdrawal of consent, uncontrolled seizure disorder, injection site infection, and allergies to the study drugs. After explaining the study protocol to the patients, informed consent was taken. All patients who were eligible to enter the study were randomized into two groups by block randomization (freely available

at: www.randomizer.org). Patient allocation was then concealed with the use of a sealed opaque envelope. Envelopes were opened by a pain fellowship in charge of injection before the intervention to clarify the type of injection. Patients then underwent the intervention. After the intervention, the outcomes were assessed by another physician. Patients and outcome assessors were blinded to the type of intervention.

3.1. Anesthesia Protocol

All patients fasted for at least eight hours prior to the surgery. After entering the operating room, patients were monitored for Non-invasive Blood Pressure (NIBP), electrocardiogram (ECG), heart rate (HR), and blood oxygen saturation (SPO$_2$). Patients received midazolam (0.03 - 0.05 mg/kg), fentanyl (3 μg/kg), propofol (1 mg/kg), and then atracurium (0.5 mg/kg). After intubation, they received isoflurane (1 MAC) intraoperatively. Then, patients underwent End-Tidal CO$_2$ (ET CO$_2$) monitoring, which was maintained at 35 - 45 mmHg during surgery. The tidal volume was kept at 7 - 10 mL/kg. Remifentanil (0.1 μg/kg/min) was infused during surgery. At the end of the operation and after extubation, the patients were transferred to the recovery room.

3.2. Ultrasound-guided Intercostal Nerve Block

In recovery after hemodynamic stability, an ultrasound-guided intercostal block (M7, MindRay, China) was performed by a pain fellowship. Group R received ropivacaine (Molteni, Italy) 5 cc of 0.25% solution, and group RD received ropivacaine (Molteni, Italy) 5 cc of 0.25% solution plus 0.5 μg/kg dexmedetomidine (Medonex 200 μg/2 mL, Exir Pharmaceutical, Iran). Next, the prep and drape intercostal block was performed in a sterile manner in the supine position along the posterior axillary line. The linear (high frequency) transducer was placed in the longitudinal plane. After identifying the external intercostal muscle on the outside, internal intercostal muscle, innermost intercostal muscle, upper and lower rib, and pleura, a Quinke spinal needle gauge 22 (Dr. Japan, Japan) was inserted in the in-plane view until reaching the lower edge of the rib between internal and innermost intercostal muscles and it was aspirated. If no blood or air entered the syringe, the local anesthetic solution was injected. Figure 2 shows the ultrasonographic view of injection. This process was repeated in two intercostal spaces above and two intercostal spaces below the level of surgical incision. The pain fellowship responsible for performing the intercostal block was aware of the injected drug but did not participate in the data collection and analysis process. The patient was monitored after transfer
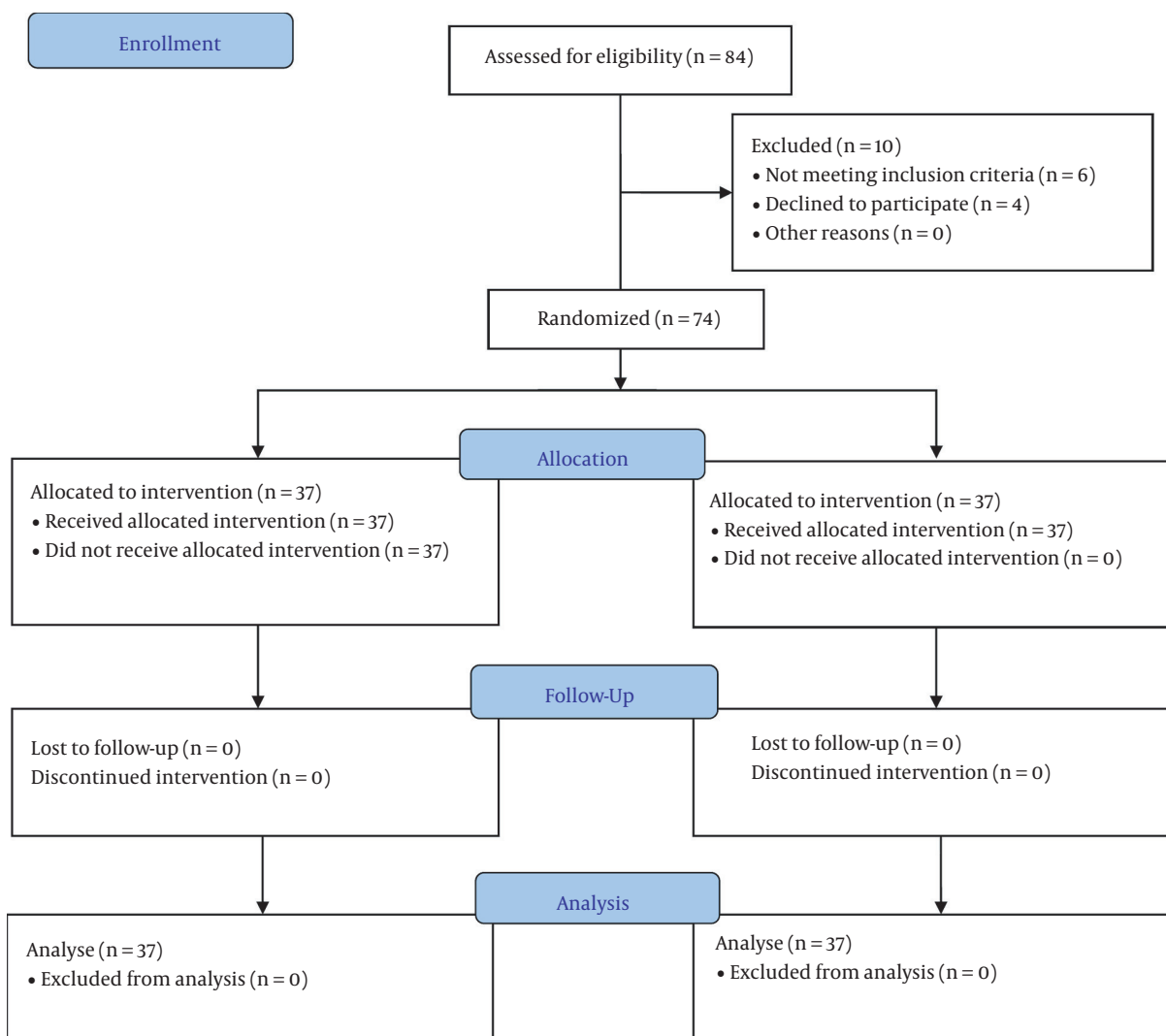
Figure 1. CONSORT flow diagram

to the ICU using non-invasive methods, and the study measures were recorded.

3.3. Measures

The data, including pain score, total opioid intake, length of ICU stay, and time to get out of bed, were recorded on a checklist for each patient. Prior to surgery, the patient's height and weight were measured and added to the patient checklist. The duration of surgery was recorded at the end of surgery and noted in the patient checklist. Study variables were measured six times (time 0 before, first hour, sixth hour, 12th hour, 24th hour, and 48th hour after the intervention). Patient pain was assessed using the Verbal Numerical Rating Scale (VNS). This scale is rated from 0 to 10, where 0 indicates no pain and 10 indicates the worst pain imaginable. When the VNS score was above 3, the patient was given pethidine (1 mg/kg) or opioid equivalent intravenously. The total opioid consumed by each patient was recorded.

3.4. Statistical Analysis

The sample size was calculated based on the study by Agamohammdi et al. (28), where the mean difference in pain scores between the bupivacaine group and the bupivacaine plus dexmedetomidine group was reported to be 2.0, and the highest standard deviations observed in the groups were 3.5 and 2.4, respectively. Hence, 37 patients per group were required to ensure an 80% power at α =
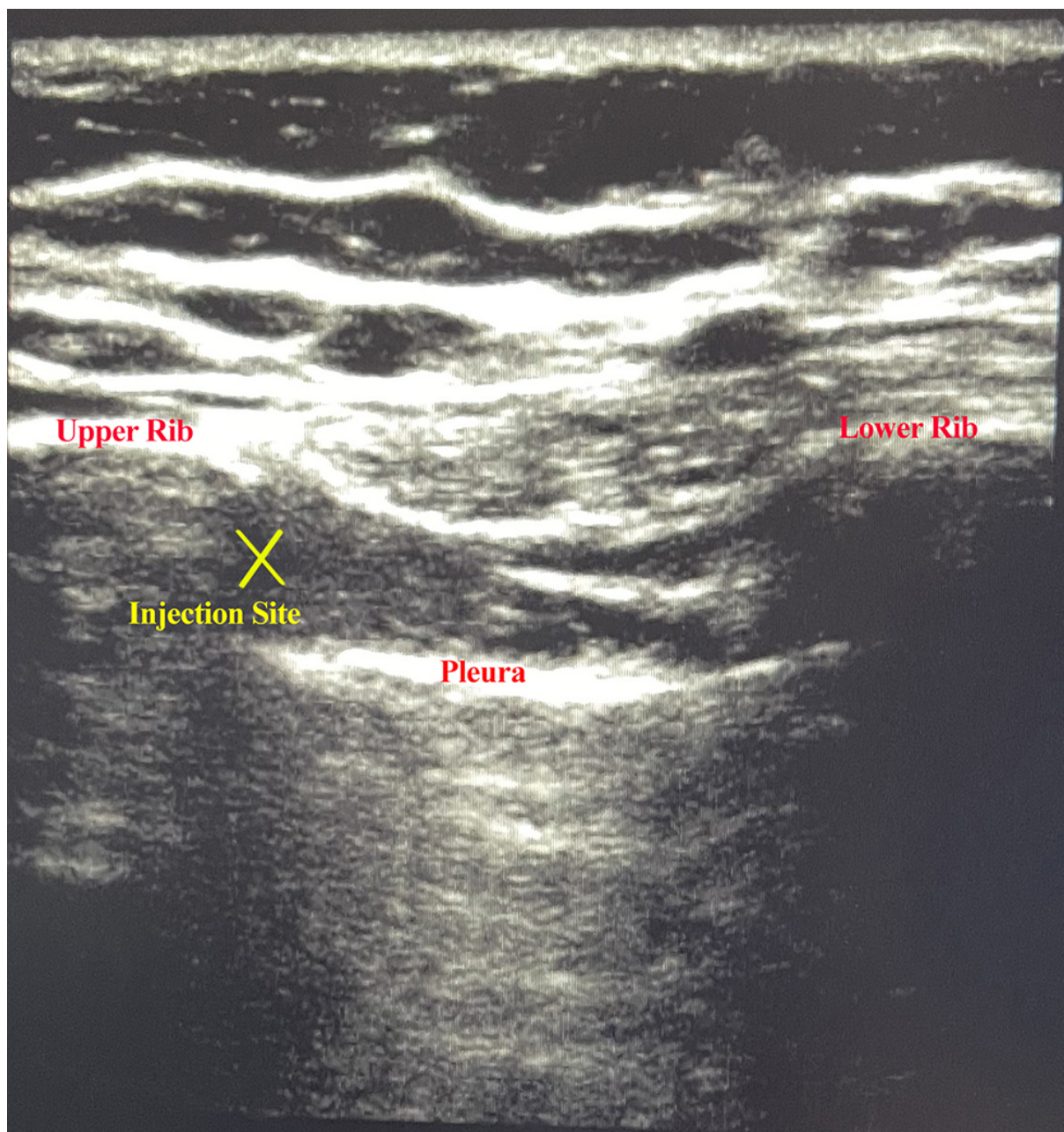
Figure 2. Ultrasonographic picture of injection site

0.05. Statistical analysis was performed using SPSS (version 18.0, IBM) and Prism (version 8, Graphpad). The outputs of the analyses were expressed as mean ± standard deviation. The comparisons between and within groups (at various times) were performed using the one-way Analysis of Variance (ANOVA) and repeated measures ANOVA. The comparison between the number of patients was made using the chi-square test. The significance level in all tests was set at a p value of less than 0.05.

4. Results

Of 74 patients enrolled in this study, 44 (59.46%) were males, and 30 (40.54%) were females. The mean age of the

participants was 40.57 ± 12.20 (range 19 to 60) years. The patients' demographic characteristics and operation time are presented in Table 1. There were no significant differences between the groups in age, height, weight, BMI, sex, and operation time (P value > 0.05). Table 2 and Figure 3 compare the mean VNS score between the two groups. At the beginning of the study and before the block, the RD group reported more pain than the R group, although this difference was not significant (P = 0.201). One hour after the intervention, there was a significant reduction in pain in both groups (a decrease of 7.459 units in the R group and 7.649 units in the RD group; P < 0.0001). At the sixth hour, the VNS score showed an increase of 1.757 units in the R group and 0.486 units in the RD group. At this time, the difference between the two groups was significant (P < 0.0001). At the 12th hour, the pain continued to increase (1.865 units in the R group and 1.189 units in the RD group). At this time, the difference between the two groups was significant (P < 0.0001). At the 24th hour, the R group continued to experience increased pain with the same intensity as before (1.676 units), but in the RD group, the amount of pain at this hour showed a sudden surge (2.568 units increase). At the 24th hour, the difference between the two groups was still significant (P < 0.001). Finally, there was no significant difference between the two groups in the final measurement at the 48th hour (P = 0.5393). Except for VNS at the 48th hour in the RD group (P = 1.000), the difference between all measurements was significant in both groups (P < 0.001).

Table 1. Patients' Demographic Characteristics and Baseline Values of the Block [a]

| Measure | Assigned Group | | P-Value |
	R	RD	
Age	39.7 ± 12.0	41.3 ± 12.4	0.584
Height (cm)	172.6 ± 8.4	173.1 ± 9.3	0.815
Weight (Kg)	82.1 ± 13.8	85.2 ± 13.5	0.329
BMI (Kg/m^2)	27.4 ± 3.2	28.3 ± 3.6	0.221
Sex (M/F)	24/13	20/17	0.344
Operation time (hour)	2.5 ± 0.96	2.7 ± 1.1	0.272

Abbreviations: R, ropivacaine; RD, ropivacaine plus dexmedetomidine.
[a] Values are expressed as mean ± SD.

Figure 4 and Table 3 compare pain-free patients between the two study groups. The log-rank test showed that the two groups were significantly different (P = 0.0037, and $\chi^2 = 8.433$), and patients in the RD group were pain-free for a longer period. The median time to rescue analgesia was 13 hours in the R group and 16 hours in the RD group. Maximum pethidine consumption was significantly lower in

Table 2. The Mean Verbal Numeral Rating Scale Score in Groups R and RD

| Time | VNS (Assigned Group) | | P-Value |
	R	RD	
Pre-block	7.8 ± 1.3	8.3 ± 1.3	0.2
First hour	0.4 ± 0.6	0.6 ± 0.7	0.164
Sixth hour	2.1 ± 0.7	1.1 ± 0.8	< 0.0001
12th hour	4.0 ± 0.9	2.3 ± 1.0	< 0.0001
24th hour	5.7 ± 0.9	4.8 ± 1.0	0.0008
48th hour	5.1 ± 0.7	5.0 ± 0.7	0.539

Abbreviations: VNS, Verbal Numeric Rating Scale; R, ropivacaine; RD, ropivacaine plus dexmedetomidine.

the RD group than in the R group (190 mg vs. 235 mg, P value = 0.0003). The time to injection of rescue analgesics was significantly longer in the RD group, but there was no significant difference in the ICU stay and time to get out of bed (P value > 0.05). Table 4 shows the comparison between these values.

Table 3. Pain-free Patients Between Measurement Times

| Time | Pain-free Patients (Assigned Group) | | P-Value |
	R	RD	
First hour	37	37	1.0000
Sixth hour	37	37	1.0000
12th hour	24	34	0.0050
24th hour	2	6	0.136
48th hour	1	3	0.3070

Abbreviations: R, ropivacaine; RD, ropivacaine plus dexmedetomidine.

Two patients in the RD group developed bradycardia (50 < heart rate < 60), which was resolved without any treatment. No bradycardia was observed in the R group.

5. Discussion

Dexmedetomidine is an alpha-2-agonist whose effects have been extensively studied, which include the reduction of preoperative stress and inflammation, improvement of gastrointestinal function, reduction of opioid use, and prolongation of analgesia in patients after various surgeries (20, 29-34). The patients in our study had higher age and BMI than in many previous studies (31, 35, 36). The intercostal block with ropivacaine was very effective in both groups of patients and significantly reduced pain during the first hour after the intervention; this reduction was evident even up to 48 hours later. The addition of dexmedetomidine to ropivacaine prolonged the analgesic effect and reduced pain in this group compared to
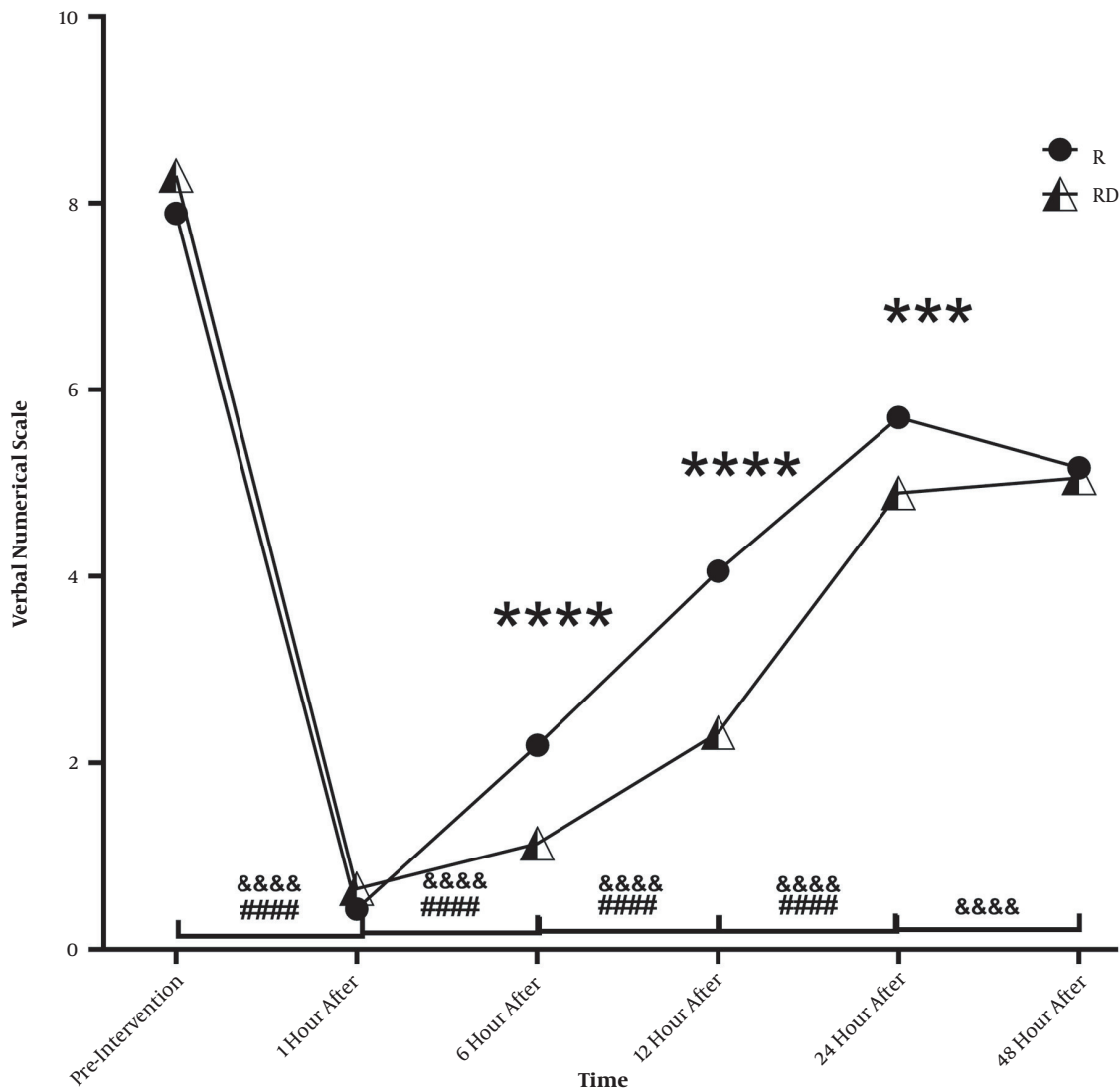
Figure 3. Pain comparison at measurement times between R and RD groups, ****, P < 0.0001; ***P < 0.001 between two groups; ####, P < 0.0001 in group RD compared to previous measurement; &&&&, P < 0.0001 in group R compared to previous measurement. Abbreviations: R, ropivacaine; RD, ropivacaine plus dexmedetomidine.

the ropivacaine group in the first 24 hours of the study. The dexmedetomidine group had less pain than the ropivacaine group at the sixth (P < 0.001), 12th (P < 0.001), and 24th hours (P < 0.01). This finding was similar to the study by Yao et al. (37), who compared two different routes of dexmedetomidine administration and showed that the perineural administration of dexmedetomidine at 0.5 μg/kg led to significantly lower pain at the 12th hour after lumpectomy. Also, Shen et al. (38) showed similar results in adenomyomectomy when comparing the low, medium, and high doses of dexmedetomidine. In this study, the VAS score was significantly lower in the mod-

erate and high-dose groups than in the control and low-dose groups (P < 0.05), while no statistical difference was observed between the medium and high-dose groups (P > 0.05). Similar results were also reported by Abdallah et al. (39) for the addition of dexmedetomidine to levobupivacaine in the serratus anterior plane block, where the amount of pain reported in the dexmedetomidine group was significantly lower at six hours after the block up to 24 hours after. In a study by Talebi et al. (40), a combination of dexmedetomidine (0.5 μg/kg) and 20 cc of Marcaine 0.125 was used in the Transverse Abdominis Plane (TAP) block under ultrasound guidance, and the addition of dexmedeto-
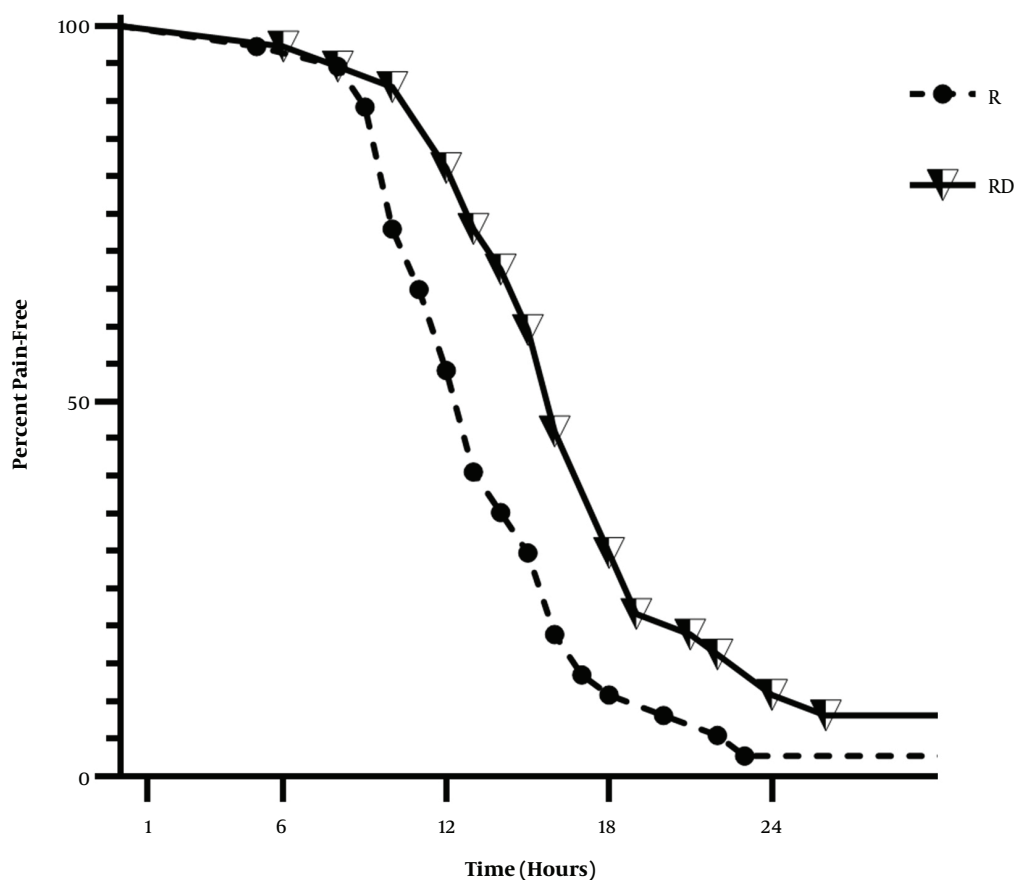
Figure 4. Kaplan-Meier curves of time to rescue analgesic. Abbreviations: R, ropivacaine; RD, ropivacaine plus dexmedetomidine.

Table 4. Mean Time to First Rescue Analgesia Injection, ICU Stay, Out of Bed, and Opioid Consumption in the Two Study Groups [a]

Measure	Assigned Group		P-Value
	R	**RD**	
Time to rescue analgesic	13.2 ± 3.8	16.0 ± 4.4	0.584
N	36	34	
ICU stay (day)	3.2 ± 2.6	3.2 ± 2.5	0.815
N	37	37	
Time to get out of bed (day)	4.2 ± 3.1	4.3 ± 3.3	0.329
N	37	37	
Total opioid consumption (mg)	180 ± 55.5	130.1 ± 57.9	0.221
N	37	37	

Abbreviations: R, ropivacaine; RD, ropivacaine plus dexmedetomidine.
[a] Values are expressed as mean ± SD unless otherwise indicated.

midine resulted in the increased duration of the block, less pain during the first 24 hours, and less opioid use. There was no use of rescue analgesia in the first four hours, which was similar to our study. Margulis et al., who compared the addition of dexmedetomidine and dexamethasone as adjuvants to ropivacaine in ultrasonic-guided arthroscopic

shoulder surgery, found that adding dexmedetomidine reduced opioid use in the first 48 hours, similar to our results (41). Omar Mostafa et al., who used 1 μg/kg dexmedetomidine as an adjuvant to bupivacaine in the paravertebral block to control postoperative pain in mastectomy, found that this addition increased the time to first rescue analgesia (42).

The addition of dexmedetomidine did not make a significant difference between the groups in terms of time to get out of bed and the length of ICU stay, but reduced the total amount of opioid consumption ($P < 0.01$) and increased the time to first rescue analgesia ($P < 0.05$). These findings confirm the report of Agamohammdi et al. (28), who compared the effect of bupivacaine and the combination of dexmedetomidine with bupivacaine in 64 patients with multiple rib fractures and reported a longer pain reduction effect in the dexmedetomidine group. On average, the dexmedetomidine group received 60 mg less opioid, and the first use of rescue analgesia happened about 2.5 hours later. Similarly, the study by Akhondzadeh et al. used 1 μg/kg dexmedetomidine as an adjuvant to lidocaine in the supraclavicular block. This addition increased the time to first rescue analgesia and decreased total opioid consumption compared to lidocaine alone (43). Many studies had already stated this effect of dexmedetomidine, as noted in a systematic review by Habibi et al. (44).

5.1. Conclusions

Dexmedetomidine is an effective and safe choice that can be used as an adjunct to ropivacaine in ICB. The combination of dexmedetomidine with ropivacaine for the intercostal nerve block can prolong the duration of analgesia after thoracotomy.

Footnotes

Authors' Contribution: Study concept and design: K.M. and M.R.; Analysis and interpretation of data: E.H. and P.R.; Drafting of the manuscript: E.H. and P.R.; Critical revision of the manuscript for important intellectual content: K.M., F.S., M.S., and M.R.; Statistical analysis: P.R.

Clinical Trial Registration Code: IRCT20190107042264N2.

Conflict of Interests: The authors declare no conflicts of interest.

Data Reproducibility: The data presented in this study are available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Informed Consent: All patients signed the informed consent form, in which the pros and cons of taking part in the study were discussed. Patients were made aware that they were under no obligation to take part nor did it affect the quality of their care in any way.

References

1. Raveglia F, Rizzi A, Leporati A, Di Mauro P, Cioffi U, Baisi A. Analgesia in patients undergoing thoracotomy: epidural versus paravertebral technique. A randomized, double-blind, prospective study. *J Thorac Cardiovasc Surg.* 2014;**147**(1):469–73. doi: 10.1016/j.jtcvs.2013.09.024. [PubMed: 24183908].

2. Ochroch EA, Gottschalk A, Augostides J, Carson KA, Kent L, Malayaman N, et al. Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. *Anesthesiology.* 2002;**97**(5):1234–44. doi: 10.1097/00000542-200211000-00029. [PubMed: 12411810].

3. Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg.* 2002;**94**(1):11–5. doi: 10.1213/00000539-200201000-00003. [PubMed: 11772793].

4. Muehling BM, Halter GL, Schelzig H, Meierhenrich R, Steffen P, Sunder-Plassmann L, et al. Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway. *Eur J Cardiothorac Surg.* 2008;**34**(1):174–80. doi: 10.1016/j.ejcts.2008.04.009. [PubMed: 18490173].

5. Dowling R, Thielmeier K, Ghaly A, Barber D, Boice T, Dine A. Improved pain control after cardiac surgery: results of a randomized, double-blind, clinical trial. *J Thorac Cardiovasc Surg.* 2003;**126**(5):1271–8. doi: 10.1016/s0022-5223(03)00585-3. [PubMed: 14665996].

6. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. *Eur J Cardiothorac Surg.* 2009;**36**(1):170–80. doi: 10.1016/j.ejcts.2009.02.005. [PubMed: 19307137].

7. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *The Lancet.* 2003;**362**(9399):1921–8. doi: 10.1016/s0140-6736(03)14966-5.

8. Hadzic A. *Hadzic's Textbook of Regional Anesthesia and Acute Pain Management.* 2nd ed. McGraw-Hill Education; 2017. 1536 p.

9. Peng P, Finlayson R, Lee SH, Bhatia A. *Ultrasound for Interventional Pain Management: An Illustrated Procedural Guide.* Springer Nature; 2019.

10. Kaushal B, Chauhan S, Saini K, Bhoi D, Bisoi AK, Sangdup T, et al. Comparison of the Efficacy of Ultrasound-Guided Serratus Anterior Plane Block, Pectoral Nerves II Block, and Intercostal Nerve Block for the Management of Postoperative Thoracotomy Pain After Pediatric Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 2019;**33**(2):418–25. doi: 10.1053/j.jvca.2018.08.209. [PubMed: 30293833].

11. Thiruvenkatarajan V, Cruz Eng H, Adhikary SD. An update on regional analgesia for rib fractures. *Curr Opin Anaesthesiol.* 2018;**31**(5):601–7. doi: 10.1097/ACO.0000000000000637. [PubMed: 30020155].

12. Raj PP, Lou L, Erdine S, Staats PS, Waldman SD, Racz G, et al. *Interventional pain management: image-guided procedures*. 2nd ed. Elsevier Health Sciences; 2008.

13. Waldman SD. *Comprehensive Atlas of Ultrasound-Guided Pain Management Injection Techniques*. Lippincott Williams & Wilkins; 2019.

14. Lewis SR, Price A, Walker KJ, McGrattan K, Smith AF. Ultrasound guidance for upper and lower limb blocks. *Cochrane Database Syst Rev*. 2015;(9). CD006459. doi: 10.1002/14651858.CD006459.pub3. [PubMed: 26361135]. [PubMed Central: PMC6465072].

15. McNaught A, Shastri U, Carmichael N, Awad IT, Columb M, Cheung J, et al. Ultrasound reduces the minimum effective local anaesthetic volume compared with peripheral nerve stimulation for interscalene block. *Br J Anaesth*. 2011;**106**(1):124–30. doi: 10.1093/bja/aeq306. [PubMed: 21059701].

16. Wilson AT. Ultrasound reduces the minimum effective local anaesthetic volume. *Br J Anaesth*. 2011;**106**(4):600. author reply 601-2. doi: 10.1093/bja/aer051. [PubMed: 21421606].

17. Barrington MJ, Uda Y. Did ultrasound fulfill the promise of safety in regional anesthesia? *Curr Opin Anaesthesiol*. 2018;**31**(5):649–55. doi: 10.1097/ACO.0000000000000638. [PubMed: 30004951].

18. Omote K, Kitahata LM, Collins JG, Nakatani K, Nakagawa I. Interaction between opiate subtype and alpha-2 adrenergic agonists in suppression of noxiously evoked activity of WDR neurons in the spinal dorsal horn. *Anesthesiology*. 1991;**74**(4):737–43. doi: 10.1097/00000542-199104000-00018. [PubMed: 1672579].

19. Gold M, Redmond JDE, Kleber H. Clonidine blocks acute opiate-withdrawal symptoms. *lancet*. 1978;**312**(8090):599–602. doi: 10.1016/S0140-6736(78)92823-4.

20. Edinoff AN, Houk GM, Patil S, Bangalore Siddaiah H, Kaye AJ, Iyengar PS, et al. Adjuvant Drugs for Peripheral Nerve Blocks: The Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Non-steroidal Anti-inflammatory Drugs. *Anesth Pain Med*. 2021;**11**(3). e117197. doi: 10.5812/aapm.117197. [PubMed: 34540647]. [PubMed Central: PMC8438706].

21. Gousheh M, Akhondzadeh R, Rashidi M, Olapour A, Moftakhar F. Comparison of Dexmedetomidine and Morphine as Adjuvants to Bupivacaine for Epidural Anesthesia in Leg Fracture Surgery: A Randomized Clinical Trial. *Anesth Pain Med*. 2019;**9**(4). e91480. doi: 10.5812/aapm.91480. [PubMed: 31803587]. [PubMed Central: PMC6829178].

22. Imani F, Farahmand Rad R, Salehi R, Alimian M, Mirbolook Jalali Z, Mansouri A, et al. Evaluation of Adding Dexmedetomidine to Ropivacaine in Pediatric Caudal Epidural Block: A Randomized, Double-blinded Clinical Trial. *Anesth Pain Med*. 2021;**11**(1). e112880. doi: 10.5812/aapm.112880. [PubMed: 34221950]. [PubMed Central: PMC8241816].

23. Janatmakan F, Nassajian N, Jarirahmadi S, Tabatabaee K, Zafari M. Comparison of the Effect of Dexmedetomidine and Remifentanil on Pain Control After Spinal Surgery: A Double-Blind, Randomized Clinical Trial. *Anesth Pain Med*. 2021;**11**(2). e111533. doi: 10.5812/aapm.111533. [PubMed: 34336614]. [PubMed Central: PMC8314072].

24. Ismail AA, Mohamed Hamza H, Ali Gado A. Efficacy of Dexmedetomidine Versus Morphine as an Adjunct to Bupivacaine in Caudal Anesthesia for Pediatric Thoracic Surgeries: A Randomized Controlled Trial. *Anesth Pain Med*. 2021;**11**(2). e112296. doi: 10.5812/aapm.112296. [PubMed: 34336616]. [PubMed Central: PMC8314090].

25. Hadipourzadeh F, Mousavi S, Heydarpur A, Sadeghi A, Ferasat-Kish R. Evaluation of the Adding Paracetamol to Dexmedetomidine in Pain Management After Adult Cardiac Surgery. *Anesth Pain Med*. 2021;**11**(3). e110274. doi: 10.5812/aapm.110274. [PubMed: 34540629]. [PubMed Central: PMC8438704].

26. Imani F, Rahimzadeh P, Faiz HR, Nowruzina S, Shakeri A, Ghahremani M. Comparison of the Post-Caesarean Analgesic Effect of Adding Dexmedetomidine to Paracetamol and Ketorolac: A Randomized Clinical Trial. *Anesth Pain Med*. 2018;**8**(5). e85311. doi: 10.5812/aapm.85311. [PubMed: 30538943]. [PubMed Central: PMC6252045].

27. McClellan KJ, Faulds D. Ropivacaine: an update of its use in regional anaesthesia. *Drugs*. 2000;**60**(5):1065–93. doi: 10.2165/00003495-200060050-00007. [PubMed: 11129123].

28. Agamohammdi D, Montazer M, Hoseini M, Haghdoost M, Farzin H. A Comparison of Continuous Thoracic Epidural Analgesia with Bupivacaine Versus Bupivacaine and Dexmedetomidine for Pain Control in Patients with Multiple Rib Fractures. *Anesth Pain Med*. 2018;**8**(2). e60805. doi: 10.5812/aapm.60805. [PubMed: 30009148]. [PubMed Central: PMC6035480].

29. Li CS, Liu SF, Zhou Y, Lu XH. [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*. 2018;**98**(46):3778–83. Chinese. doi: 10.3760/cma.j.issn.0376-2491.2018.46.011. [PubMed: 30541221].

30. Li M, Wang T, Xiao W, Zhao L, Yao D. Low-Dose Dexmedetomidine Accelerates Gastrointestinal Function Recovery in Patients Undergoing Lumbar Spinal Fusion. *Front Pharmacol*. 2019;**10**:1509. doi: 10.3389/fphar.2019.01509. [PubMed: 31920678]. [PubMed Central: PMC6930906].

31. Xu SQ, Li YH, Wang SB, Hu SH, Ju X, Xiao JB. Effects of intravenous lidocaine, dexmedetomidine and their combination on postoperative pain and bowel function recovery after abdominal hysterectomy. *Minerva Anestesiol*. 2017;**83**(7):685–94. doi: 10.23736/S0375-9393.16.11472-5. [PubMed: 28094477].

32. Rahimzadeh P, Faiz SHR, Imani F, Derakhshan P, Amniati S. Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. *BMC Anesthesiol*. 2018;**18**(1):62. doi: 10.1186/s12871-018-0531-7. [PubMed: 29875020]. [PubMed Central: PMC5991430].

33. Imani F, Zaman B, De Negri P. Postoperative Pain Management: Role of Dexmedetomidine as an Adjuvant. *Anesth Pain Med*. 2020;**10**(6). e112176. doi: 10.5812/aapm.112176. [PubMed: 34150582]. [PubMed Central: PMC8207883].

34. Akhondzadeh R, Olapour A, Rashidi M, Elyasinia F. Comparison of Sedation with Dexmedetomidine Alfentanil Versus Ketamine-Alfentanil in Patients Undergoing Closed Reduction of Nasal Fractures. *Anesth Pain Med*. 2020;**10**(4). e102946. doi: 10.5812/aapm.102946. [PubMed: 33134144]. [PubMed Central: PMC7539046].

35. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. *Anesth Analg*. 2010;**111**(6):1548–51. doi: 10.1213/ANE.0b013e3181fa3095. [PubMed: 20889939].

36. Xu S, Hu S, Ju X, Li Y, Li Q, Wang S. Effects of intravenous lidocaine, dexmedetomidine, and their combination on IL-1, IL-6 and TNF-alpha in patients undergoing laparoscopic hysterectomy: a prospective, randomized controlled trial. *BMC Anesthesiol*. 2021;**21**(1):3. doi: 10.1186/s12871-020-01219-z. [PubMed: 33407156]. [PubMed Central: PMC7786488].

37. Yao F, Xu S, Zhang W, Xiong H, Han J, Zhu A. Impacts of different administration modes of dexmedetomidine with 0.5% ropivacaine on intercostal nerve block. *Ann Palliat Med*. 2020;**9**(2):447–50. doi: 10.21037/apm.2020.03.25. [PubMed: 32268771].

38. Shen Y, Fang J, Yang YU, Jie K, Chen P. Comparison of the effects of different doses of dexmedetomidine combined with intercostal nerve block in regional adenomammectomy. *Chinese Journal of Endocrine Surgery*. 2017;**11**(3):228–32.

39. Abdallah NM, Bakeer AH, Youssef RB, Zaki HV, Abbas DN. Ultrasound-guided continuous serratus anterior plane block: dexmedetomidine as an adjunctive analgesic with levobupivacaine for post-thoracotomy pain. A prospective randomized controlled study. *J Pain Res*. 2019;**12**:1425–31. doi: 10.2147/JPR.S195431. [PubMed: 31118760]. [PubMed Central: PMC6500444].

40. Talebi G, Moayeri H, Rahmani K, Nasseri K. Comparison of Three Different Doses of Dexmedetomidine Added to Bupivacaine

in Ultrasound-Guided Transversus Abdominis Plane Block; A Randomized Clinical Trial. *Anesth Pain Med*. 2021;**11**(2). e113778. doi: 10.5812/aapm.113778. [PubMed: 34336630]. [PubMed Central: PMC8314081].

41. Margulis R, Francis J, Tischenkel B, Bromberg A, Pedulla D, Grtisenko K, et al. Comparison of Dexmedetomidine and Dexamethasone as Adjuvants to Ultra-Sound Guided Interscalene Block in Arthroscopic Shoulder Surgery: A Double-Blinded Randomized Placebo-Controlled Study. *Anesth Pain Med*. 2021;**11**(3). e117020. doi: 10.5812/aapm.117020. [PubMed: 34540645]. [PubMed Central: PMC8438728].

42. Omar Mostafa M, Makram Botros J, Sayed Khaleel AM. Effect of Dexmedetomidine Versus Nalbuphine as an Adjuvant on Paravertebral Block to Manage Postoperative Pain After Mastectomies. *Anesth Pain Med*. 2018;**8**(2). e13308. doi: 10.5812/aapm.13308. [PubMed: 30027066]. [PubMed Central: PMC6045777].

43. Akhondzadeh R, Rashidi M, Gousheh M, Olapour A, Baniahmad A. The Effect of Adding Dexmedetomidine as an Adjuvant to Lidocaine in Forearm Fracture Surgeries by Supraclavicular Block Procedure Under Ultrasound-Guided. *Anesth Pain Med*. 2018;**8**(4). e74355. doi: 10.5812/aapm.74355. [PubMed: 30250821]. [PubMed Central: PMC6139532].

44. Habibi V, Kiabi FH, Sharifi H. The Effect of Dexmedetomidine on the Acute Pain After Cardiothoracic Surgeries: A Systematic Review. *Braz J Cardiovasc Surg*. 2018;**33**(4):404–17. doi: 10.21470/1678-9741-2017-0253. [PubMed: 30184039]. [PubMed Central: PMC6122757].