Original Article

Comparison of the Effect of Adding Dexmedetomidine as an Adjuvant to Bupivacaine for Postoperative Pain Management in Patients Undergoing Shoulder Rotator Cuff Repair – A Randomized Clinical Trial

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Abstract

Background: Shoulder rotator cuff repair postoperative pain management is more critical than orthopedic surgeries in other limbs. This study aimed to investigate the effect of adding dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management.

Materials and Methods: This double-blind, randomized clinical trial was performed on 80 patients aged 20 to 60 with ASA I and II who were candidates for elective shoulder rotator cuff repair. Forty candidates in the control group received 0.1% bupivacaine intra-articular and extra-articular before surgical wound closure, and 40 patients in the intervention group received 0.1% bupivacaine and dexmedetomidine 1 μg/kg intra-articular and extra-articular. Postoperative sleep disturbance and pain intensity were measured at recovery, 4, 8, 12, 18, and 24 hours after surgery. The results were analyzed by SPSS software version 23, and a P value ≤0.05 was considered significant.

Results: There were no significant differences between the two groups regarding the hemodynamic variations ($P > 0.05$), except 4 hours after surgery when the mean arterial pressure in the intervention group was significantly lower than the control group ($P = 0.026$). There was a significant reduction in pain scores at 8 and 12 hours after surgery in the intervention group. The night after surgery, sleep quality and the overall RCSQ score in the intervention group were significantly higher than those in the control group.

Conclusion: Administering 0.1% bupivacaine and dexmedetomidine 1 μg/kg intra-articular and extra-articular before surgical wound closure effectively reduced the pain intensity and analgesic consumption. Also, it maintained patients' hemodynamic stability and enhanced sleep quality without significant adverse effects.

Keywords: Bupivacaine, dexmedetomidine, pain Management, Rotator Cuff Injuries, shoulder pain

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Introduction

Modern orthopedic surgery is a new surgical concept aiming at a faster onset of postoperative activity, early ambulation, discharge, and return to activities of daily living.[1,2] In shoulder surgeries, poor postoperative pain management can lead to complications and prolonged rehabilitation.[3] Shoulder postoperative pain management is more critical than orthopedic surgeries in other limbs. Effective postoperative pain management can reduce the length of stay, alleviate the

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pain severity, reduce bedtime and hospitalization costs, and improve shoulder function. To achieve these goals, multimodal analgesia techniques and applying adjuvant drugs with different local anesthetics should be used.

Using opioids is one of the conventional methods of pain control.[4] Narcotics cause adequate analgesia after surgery, but they are associated with side effects such as nausea, vomiting, respiratory depression, gastrointestinal complications, sedation, and a decreased level of consciousness. Today, there is not much desire to use this method. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in surgical pain control.[5-7] In addition to pain control, NSAIDs play a role in reducing inflammatory mediators at the surgical site. However, it is associated with adverse effects, especially in geriatric patients and people with digestive diseases. They also reduce platelet function and increase the risk of bleeding at the operation site and gastrointestinal ulcers. Interscalan block (ISB) has been considered for pain control after shoulder surgeries, which causes pain relief during and postoperative. Of course, this method has complications such as spinal and epidural anesthesia, cord injury, brain damage, brachial plexus injury, vagal paralysis, recurrent laryngeal nerve paralysis, and pneumothorax.[5,8]

One of the best pain control methods is injecting a local anesthetic into the wound. It has fewer side effects than the other mentioned methods, but there is controversy regarding their effectiveness, especially in shoulder surgeries; there is much less experience. In some previous studies, the injection of ropivacaine, epinephrine, and ketorolac compounds has been associated with good results in controlling patients' pain. Also, the combination of bupivacaine, morphine, and epinephrine has shown promising effectiveness in controlling pain at the surgical site.[6-8]

Bupivacaine is an amino amide local anesthetic widely used for prolonged local and regional anesthesia. Bupivacaine is administrated in various ways and with different purposes, such as local infiltration, peripheral nerve blocks, spinal anesthesia, epidural anesthesia/analgesia for labor pain, and a caudal block. One of the rare adverse effects of this drug is sudden cardiac arrest following an accidental intravascular injection.[9] Adjuvant drugs are often added to local anesthetics for nerve blocks to prolong the anesthetic effects of local anesthetics. Some trials have shown that alpha-2 agonist drugs, such as clonidine or dexmedetomidine in combination with local anesthetics, significantly increased sensory and motor block duration.[10] Dexmedetomidine is an active D-isomer of medetomidine and is similarly related to clonidine.[10]

The efficacy of multimodal pain interventions in surgeries undergoing nerve blocks and regional blocks has been assessed and demonstrated valuable results,[11-13] but it still needs to be completed in other types of administration (wound infiltration) and specific operations like shoulder surgeries. Therefore, we aimed to investigate the effect of adding dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management in patients undergoing shoulder rotator cuff repair.

Materials and Methods

A randomized, double-blind clinical trial was done on 80 patients with ASA classifications I and II, with ages from 20 to 60 years. The sample size was calculated regarding 80% power two-sided test and 5% significance level. Following patient satisfaction and approval from the University's Ethics Committee (IR.UMSU.REC.1397.388), patients who were eligible for elective shoulder rotator cuff repair were included in the study. The ID for this double-blind, randomized clinical trial is IRCT20160430027677N16, and it is registered with Iranian randomized clinical trials. In accordance with the random number table, patients were split into two intervention and control groups at random. The personnel, orthopedic surgeon, and anesthesiologist were not told which patients were in which group, Figure 1.

Subjects and settings

A day before the procedure, an anesthesiologist visited each candidate. Before surgery, patients were required to fast for a minimum of 8 hours. Every procedure was carried out by a single specialization of shoulder surgeons at a single facility. All the syringes were the same, and the orthopedic surgeon, crew, and anesthesiologist had no idea what was inside. In the operating room, the patients were hooked up to an electrocardiogram, a noninvasive blood pressure monitoring device, a standard pulse oximetry monitor, and a partial pressure of carbon dioxide [end-tidal carbon dioxide (ETCO2)]. Ringer was administered at a rate of 10 ml/kg following the insertion of an 18-cm venous catheter. The blood pressure, oxygen saturation, and baseline heart rate were measured.

Inclusion criteria

Patients between the ages of 18 and 60 years who had a body mass index of less than 30 kg/m2 were eligible for elective shoulder rotator cuff repair. The preoperative MRI results showed that the rotator cuff did not incur severe damage, as indicated by the rupture of three or more components. Patients who had completed the consent form to take part in the study and those with ASA classes I and II (American Society of Anesthesiologists) were included.

Exclusion criteria

Exclusion criteria included being under the age of 18 and over 60, being pregnant, having coagulopathy, having a body mass index of higher than 30 kg/m2, having a history of systemic disease, mental illness, having an allergy to any of the medications used in the study, having a history of peptic ulcer disease and antacid therapy, abusing drugs, or having taken part in another experimental study within the previous 30 days. Serious side effects include heavy bleeding and unanticipated surgical prolongation, and uncommon issues during the procedure may also be noticed by the surgeon or anesthetist.

Intervention design

Control group (40 patients): Prior to surgical wound closure, candidates in the control group received intra-articular and

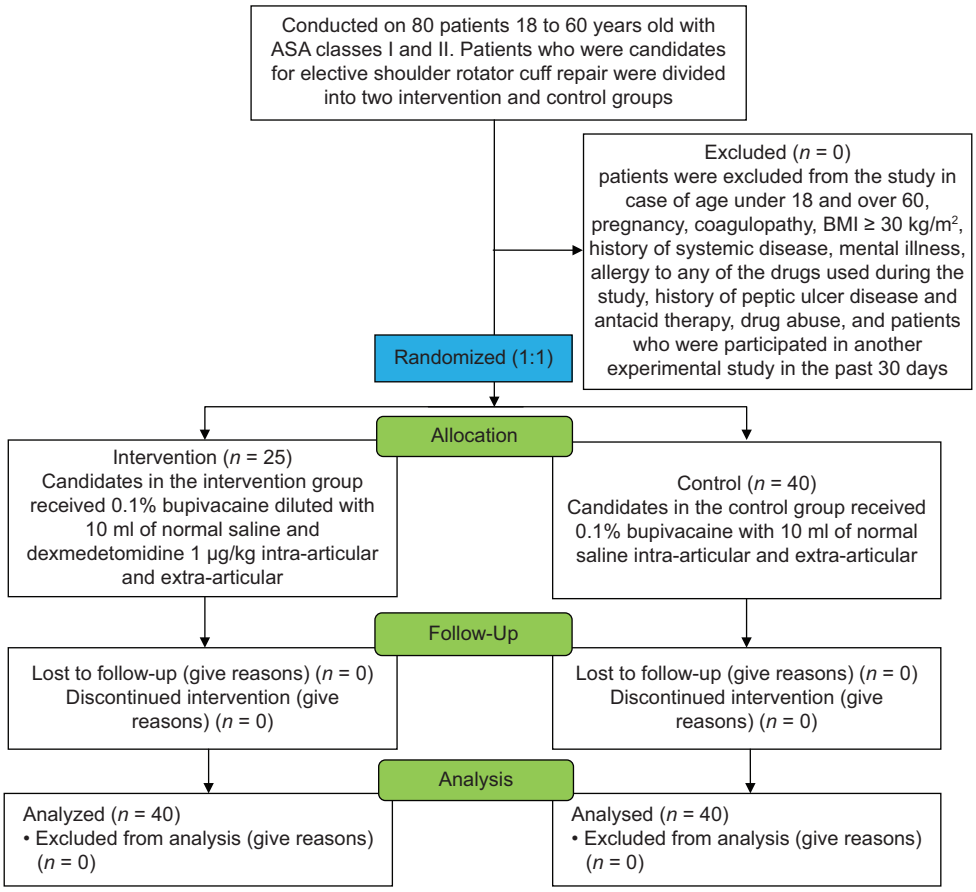

Figure 1: Study flow diagram

extra-articular injections of 0.1% bupivacaine and 10 milliliters of normal saline.

Intervention group (40 patients): Prior to surgical wound closure, candidates in the intervention group received intra-articular and extra-articular injections of 0.1% bupivacaine diluted with 10 ml of normal saline and 1 µg/kg of dexmedetomidine.

In the clinical assessment room for anesthesia, patients received sufficient explanations and adequate instruction regarding the visual analog scale (VAS), which ranges from 0 for no pain to 10 for the greatest agony they have ever encountered. Additionally, the Richards-Campbell Sleep Questionnaire (RCSQ) was used to assess the quality of sleep for both patient groups 1 day prior to and 1 day following surgery. According to Rllo *et al.* study, the total score of the RCSQ showed a good degree of concordance with the sleep efficiency index of PSG. The accuracy of the RCSQ was 70%, with a sensitivity of 71% and a specificity of 68%. The RCSQ is a good tool for screening the sleep quality, and it could be useful to select the patients who might beneficiate from an instrumental sleep evaluation. Sleep depth, sleep latency, number of awakenings, returning to sleep, and overall sleep quality are the five elements that make up the RCSQ, a self-reported assessment of nocturnal sleep perception. Items were scored between 0 and 100 points, with higher scores denoting greater sleep, and were recorded based on sleep conditions. The overall RCSQ score is determined by taking the mean of the five items.[14] Patients were given conventional general anesthesia while being regularly monitored following the insertion of an 18-cm venous catheter. All patients got intravenous injections of 0.03 midazolam and 1 mcg/kg of fentanyl as premedication. Atracurium besylate (0.4–0.5 mg/kg) and propofol (2–2.5 mg/kg) were injected to induce anesthesia. Propofol 60 mcg/kg/min, oxygen, atracurium besylate at repeated dosages of 0.1 mg/kg, and 1 mcg/kg fentanyl were then used to maintain anesthesia. Both groups received injections of the prepared solutions prior to surgical wound closure and under direct vision. Using 0.04 mg/kg neostigmine and 0.02 mg/kg atropine, the neuromuscular block was reversed following the procedure. The patient's tracheal tube was withdrawn once it was confirmed that they could defend their airway and breathe on their own with adequate tidal volume and motor function. After that, the patient was moved to the postanesthesia care unit or PACU. At recovery, 4, 8, 12, 18, and 24 hours following surgery, the degree of postoperative discomfort and sleep disturbance was assessed. When the VAS score was higher than 4, the analgesic drug (Apotel 1 gr) was given. Patients in both groups had their initial request times for analgesics noted and compared in terms of minutes. Bradycardia (HR < 50), hypotension (a 20% drop from baseline), dizziness, hypoxemia (SpO2 < 90%), shivering, nausea, and vomiting were among the side effects that patients were monitored for and correctly treated.

Statistical Analysis

The sample size of 40 patients in each group was established using Thema Nicholson *et al*.,[15] taking into account the power (probability) test of 80% and the 95% confidence interval ($\alpha = 0.05\%$ and $\beta = 10\%$). Descriptive features were presented using frequency charts, tables, and descriptive statistics such as mean and standard deviation. The mean pain at recovery, 4, 8, 12, 18, and 24 hours following surgery, was compared using the repeated measures test for normal data. The Kolmogorov–Smirnov test was used to determine whether the data were normal. In addition, nonnormal data were subjected to the Friedman test. The Chi-square test was employed in this study to look into qualitative factors like gender. Additionally, an independent *t*-test was used on normal data for quantitative variables in two groups. The Mann–Whitney test was applied to data that were not normal. SPSS software version 23 was used to evaluate the results, and a *P* value of less than 0.05 was deemed significant.

Results

According to Chi-square and t-tests, there was no statistically significant difference between the two groups' demographic data regarding age, gender, BMI (body mass index), duration of surgery, ASA class, surgical side, and mean propofol consumption ($P > 0.05$). The patients' demographic data in the two groups are demonstrated in Table 1.

Sleep Quality

The overall RCSQ score in both groups was not statistically significant on the night before surgery. However, on the night after surgery, sleep quality and the overall RCSQ score in patients who received dexmedetomidine + bupivacaine intra-articular and extra-articular (intervention group) were higher than those in patients who received just bupivacaine (control group), and this difference was statistically significant ($P < 0.001$) [Table2].

The mean arterial pressure and heart rate changes during the study are illustrated in Figures 2 and 3. According to the repeated measure one-way ANOVA test, there were no significant differences between the two groups regarding the hemodynamic variations ($P > 0.05$), except 4 hours after surgery when the mean arterial pressure in the intervention group was significantly lower than that in the control group ($P = 0.026$).

Only 4 hours after surgery, the MAP in the intervention group was significantly lower than that in the control group ($P = 0.026$).

There were no significant differences between the two groups regarding the heart rate variations ($P > 0.05$).

Pain management

The mean pain score in the intervention group at 8 and 12 hours after surgery was significantly lower than that in the control group, $P < 0.001$ and $P < 0.001$, respectively. However, in other studied times, the mean pain score in the control group was higher than that in the intervention group, but it was not statistically significant ($P > 0.05$) [Figure 4].

The mean pain score in the intervention group at 8 and 12 hours after surgery was significantly lower than that in the control group, $P < 0.001$ and $P < 0.001$, respectively.

According to Table 3, the analgesic consumption (Apotel) and analgesic requests in the intervention group were lower than those in the control group, and this difference was statistically significant ($P < 0.001$). Also, the time for the first analgesic request in the control group was lower than that in the intervention group ($P < 0.001$).

Hypotension, dizziness, and bradycardia were not observed in the intervention and control groups. Shivering was observed in three patients in the intervention group and two in the control group; however, it was not statically significant ($P = 0.089$). Seven patients in the control group and three patients in the intervention group had nausea, which was not statistically significant ($P = 0.226$).

Discussion

Surgical site infiltration can be used for minor superficial surgical procedures, administered in the subdermal and musculofascial planes, or instilled in a cavity (e.g., intra-articular administration for joint surgery).[16-18] Wound

Table 1: Patients' demographic information in both intervention and control groups

	Intervention group *n*=40 persons		Control group *n*=40 persons		*P*
Gender (F/M)	Male	Female	Male	Female	0.179
	25	15	28	12	
Age (year)	43.26±7.82		41.19±9.52		0.215
ASA class I and II	Class I	Class II	Class I	Class II	0.526
	10	30	14	26	
BMI (body mass index) (kg/m^2)	28.34±1.16		27.41±1.62		0.481
Duration of surgery (min)	129.77±11.43		132.19±10.53		0.449
Surgical side	Right Shoulder	Left Shoulder	Right Shoulder	Left Shoulder	0.237
	23	17	25	15	
Mean propofol consumption (mg/patient)	1265.44±150.72		1378.13±122.38		0.268

Values are presented as mean±SD or number. There were no significant differences between demographic data in the two groups ($P>0.05$)

Table 2: Patients' sleep quality using the Richards–Campbell Sleep Questionnaire (RCSQ)

RCSQ Items	Preoperative		*P*	Postoperative		*P*
	Control group	Intervention group		Control group	Intervention group	
Sleep depth	59.28±10.16	54.63±12.44	*P*=0.631	50.31±5.76	51.24±8.41	*P*<0.001
Sleep latency	72.42±15.35	68.74±23.18	*P*=0.147	61.22±9.57	64.54±12.47	*P*<0.001
Awakenings	68.29±11.48	70.89±9.52	*P*=0.481	52.41±8.38	63.72 ±7.28	*P*<0.001
Returning to sleep	73.49±10.63	75.58±8.82	*P*=0.237	65.29±8.55	70.35±8.14	*P*<0.001
Overall sleep quality	70.45±7.13	74.19±9.37	*P*=0.168	61.79±5.26	68.85±8.53	*P*<0.001

Values are presented as Mean±SD or number

Table 3: The analgesic consumption (Apotel) and analgesic requests in both intervention and control groups

Variables	Control group	Intervention group	*P*
Apotel consumption (gr)	44.18±2.57	31.77±3.18	*P*<0.001
Analgesic request			
2 times	1 patients (2.5%)	4 patients (10%)	*P*<0.001
3 times	7 patients (17.5%)	5 patients (12.5%)	
4 times	5 patients (12.5%)	2 patients (5%)	
5 times	4 patients (10%)	2 patients (5%)	
Time for first analgesia request (min)	82.53±4.27	103.25±6.15	*P*<0.001

Values are presented as mean±SD or number

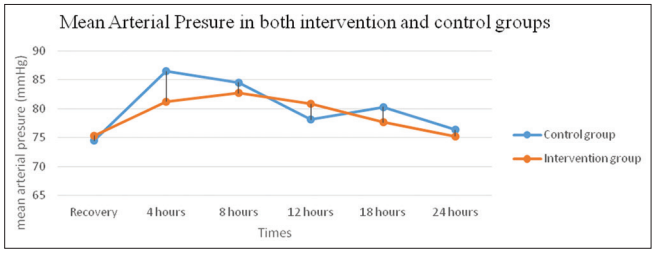

Figure 2: Mean arterial pressure variations in intervention and control groups at recovery, 4, 8, 12, 18, and 24 hours after surgery

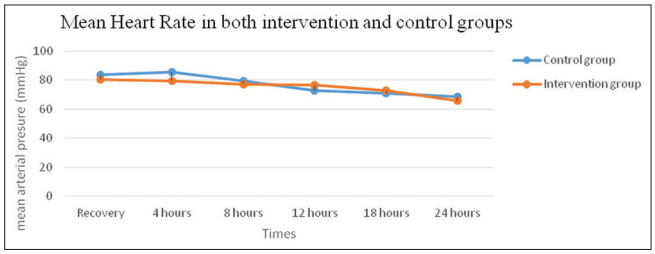

Figure 3: Mean heart rate variations in intervention and control groups at recovery, 4, 8, 12, 18, and 24 hours after surgery

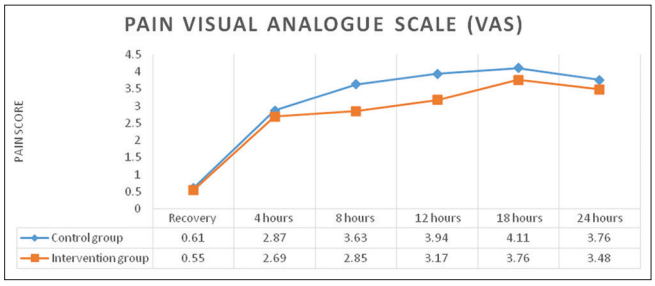

Figure 4: Mean pain score in intervention and control groups at recovery, 4, 8, 12, 18, and 24 hours after surgery

infiltration is contraindicated only by infection at the injection site, local anesthetic allergy, and patient refusal.[19] Surgical site infiltration requires knowledge of anatomy and the source of pain from surgical procedures. Rotator cuff repair surgery is considered an orthopedic procedure that induces severe pain.[20] Therefore, effective multimodal postoperative pain management is essential for all patients after rotator cuff surgery.

In our study, there were no significant differences between the two groups regarding the hemodynamic variations ($P > 0.05$), except 4 hours after surgery when the mean arterial pressure in the intervention group was significantly lower than that in the control group ($P = 0.026$). Khaled R. Al-Zaben *et al*.[21] compared caudal bupivacaine alone with bupivacaine plus two doses of dexmedetomidine (1 μg and 2 μg) for postoperative analgesia in pediatric patients undergoing infraumbilical surgery. The two dexmedetomidine groups had a significant reduction in the mean heart rate and blood pressure when compared to the control group at 20- and 30-minute time points after performing the caudal block. There were no significant differences in the hemodynamic values between the three groups during the PACU stay. However, two patients in group BD2 (dexmedetomidine 2 μg) developed bradycardia and hypotension. Zu¨leyha K. Bengısun *et al*.[22] added 0.5 mg/mL dexmedetomidine to levobupivacaine for interscalene block for postoperative pain management after arthroscopic shoulder surgery; patients experienced a stable hemodynamic status during and after surgery without any bradycardia and hypotension. Cihangir Biçer *et al*.[23] compared a combination of dexmedetomidine to bupivacaine in postoperative pain relief among patients undergoing thoracotomy. In the group in which patients received a combination of dexmedetomidine

and bupivacaine, the heart rate and MAP were lower, but this was not clinically significant. These results, to some extent, were consistent with our findings.

Our trial demonstrated a significant reduction in pain scores at 8 and 12 hours after surgery in the intervention group. However, in other studied times, the mean pain score in the intervention group was lower than that in the control group, but it was not statistically significant. Furthermore, the analgesic consumption and analgesic requests in the intervention group were lower than those in the control group, and this difference was statistically significant. In the Cihangir Bicer *et al.* study,[23] adding dexmedetomidine to bupivacaine reduced postoperative pain scores and morphine consumption in thoracotomy patients who received ultrasonography-guided paravertebral blockade. Also, VAS scores with rest and upon movement were significantly lower in group BD (bupivacaine + dexmedetomidine) compared to group B (bupivacaine). Eman A Ismail *et al*.[24] investigated the intrathecal versus intra-articular dexmedetomidine as an adjuvant to bupivacaine on postoperative pain following knee arthroscopy; the study revealed that dexmedetomidine administration decreased pain scores for 4 hours in both the intrathecal and intra-articular groups, compared to only 2 hours in the control patient group. Furthermore, there was a significant reduction in pain scores for 6 hours in the intra-articular group. Also, the time to the first postoperative analgesia request and total meperidine requirement was significantly lower in the intra-articular and intrathecal groups than in the control group. Another trial conducted in Egypt[25] illustrated that the addition of dexamethasone or dexmedetomidine to a solution of bupivacaine 0.25% provided better analgesia and decreased analgesic consumption than using bupivacaine alone in arthroscopic knee surgery. These results were consistent with our clinical trial findings. Nevertheless, in a study,[26] the interscalene brachial plexus block was more effective than intra-articular local anesthetic injection for postoperative analgesia in arthroscopic shoulder surgery. In a recent trial in Turkey,[27] intra-articular dexmedetomidine alone had a weaker effect than intra-articular levobupivacaine on postoperative pain relief after an arthroscopic partial meniscectomy, whereas adding dexmedetomidine to intra-articular levobupivacaine increased the duration and quality of postoperative analgesia without any side effect. These studies differed from our trial regarding applied drugs and adjuvants.

Our investigation revealed that on the night after surgery, sleep quality and the overall RCSQ score in patients who received dexmedetomidine + bupivacaine intra-articular and extra-articular (intervention group) were significantly higher than those in patients who received just bupivacaine (control group). Nicholas N DePhillipo *et al*.[15] evaluated the high incidence of acute self-reported sleep disturbances in patients following arthroscopic-assisted knee surgery; results showed that surgical variables, including the severity of the surgery, weekly postoperative pain level, and weekly hours of postoperative physical therapy, were not significant independent predictors of acute postoperative sleep disturbances. However, a recent review study[28] compared postoperative sleep disorders and their potential impacts on surgical outcomes; the study demonstrated that the development of postoperative sleep disturbance is multifactorial and significantly related to the surgical inflammatory response, the severity of surgical trauma, pain, anxiety, the use of anesthetics, and environmental factors such as nocturnal noise and light levels. Yue-Ming Sun *et al*.[29] tested the effect of low-dose dexmedetomidine infusion on nighttime sleep quality in postoperative ICU patients with invasive ventilation. Their trial illustrated that patients in the dexmedetomidine group tended to have a longer total sleep time, a higher sleep efficiency, and a lower arousal index, but the differences were not statistically significant. A study compared the surgery time to sleep disturbance.[30] It revealed that morning and afternoon surgeries significantly impact sleep function in patients undergoing general anesthesia, while afternoon surgery severely impacts sleep function. All operations in our trial were performed in the morning at 8:30.

Complications in the present study were minor and trivial. Hypotension, dizziness, and bradycardia were not observed. Shivering was observed in three patients in the intervention group and two in the control group; however, it was not statically significant ($P = 0.089$). Seven patients in the control group and three patients in the intervention group had nausea, which was not statistically significant. In the Eman A. Ismail *et al*. study,[24] there were no significant differences in the incidence of postoperative nausea and vomiting between patients who received dexmedetomidine intrathecal and intra-articular with the control group in knee arthroscopy surgery. Finally, new clinical approaches with the integration of clinical knowledge and experience to generalize the results of evidence-based clinical studies will have an essential role in the treatment and survival of patients.[31-33]

Conclusion

Our clinical trial demonstrated that administering 0.1% bupivacaine and dexmedetomidine 1 μg/kg intra-articular and extra-articular before surgical wound closure effectively reduced the pain intensity and analgesic consumption with low complications. Also, it maintained patients' hemodynamic stability and enhanced sleep quality (due to the excellent postoperative analgesia) without significant adverse effects.

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Study limitation

The limitation of our study was the lack of serum dose measurement of dexmedetomidine during surgery, so the evaluation of the systemic effect of dexmedetomidine after local absorption was unpredictable.

Ethical approval

Before the trial started, all participating patients signed an informed consent form. Ethical approval was obtained from the Research and Ethics Committee (IR.UMSU.REC.1397.388) of the Urmia University of Medical Sciences, Urmia, Iran.

Data availability

All relevant data are included in the article. Additional information is available from the corresponding author upon reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sarker K, Sethi J, Mohanty U. Comparative clinical effects of spinal manipulation, core stability exercise, and supervised exercise on pain intensity, segmental instability, and health-related quality of life among patients with chronic nonspecific low back pain: A randomized control trial. J Nat Sci Biol Med 2020;11:27-34.
2. Jiang M, Liu S, Deng H, Liang X, Bo Z. The efficacy and safety of fast track surgery (FTS) in patients after hip fracture surgery: A meta-analysis. J Orthop Surg Res 2021;16:1-24.
3. Mousavi S, Taghavi S, Abbasalizadeh F, Vazifekhah S, Naghavi-Behzad M. Changes in fetal circulation after maternal corticosteroid administration: A systematic review. Int J Womens Health Reprod Sci 2019;7:156-62.
4. Sane S, Vash RA, Rahmani N, Talebi H, Golabi P, Kalashipour F, *et al*. Comparing the effects of pregabalin and clonidine on postoperative pain in tonsillectomy: A randomized, double-blind, prospective clinical trial. Rev Recent Clin Trials 2022;17208-15.
5. Sane S, Mahdkhah A, Golabi P, Hesami SA, Kazemi Haki B. Comparison the effect of bupivacaine plus magnesium sulfate with ropivacaine plus magnesium sulfate infiltration on postoperative pain in patients undergoing lumbar laminectomy with general anesthesia. Br J Neurosurg 2024;38:256-9.
6. Musavi S, Nikniaz L, Hoseinifard H, Hamzehzadeh A, Vazifekhah S. Do corticosteroids affect prenatal biophysical parameters? A systematic review and meta-analysis. Int J Womens Health Reprod Sci 2020;8:259-64.
7. Golmohammadi M, Sane S, Ghavipanjeh Rezaei S, Hosseini R, Alwaily ER, Hussien BM, *et al*. Investigating the effect of dexmedetomidine in controlling postoperative emergence agitation in children under sevoflurane anesthesia. Anesthesiol Res Pract 2024;2024:6418429.
8. Rafiei MR, Khani AK, Kheradmand B, Abosaoda MK, Rasulova I, Khordad O, *et al*.. Effectiveness of Adding Dexamethasone to Lidocaine in Upper Limbs Nerve Blocks: A Systematic Review. J Perianesth Nurs. 2024:S1089-9472(24)00088-1.
9. Fahim Safah A, Alwan Abid T. Effects of ketorolac, xylazine, and bupivacaine multimodal analgesia on goats. Arch Razi Inst 2022;77:661-8.
10. Sane S, Shokouhi S, Golabi P, Rezaeian M, Kazemi Haki B. The effect of dexmedetomidine in combination with bupivacaine on sensory and motor block time and pain score in supraclavicular block. Pain Res Manag 2021;2021:8858312.
11. Koehler D, Marsh JL, Karam M, Fruehling C, Willey M. Efficacy of surgical-site, multimodal drug injection following operative management of femoral fractures: A randomized controlled trial. J Bone Joint Surg Am 2017;99:512-9.
12. Gueserse M, Zali A, Hassanzadeh S, Hatami M, Ahadi M. A comparative study of the effectiveness of acceptance and commitment therapy and transcranial direct current stimulation on anxiety, depression, and physical symptoms of individuals suffering from chronic pain. Int J Body Mind Cult 2022;9:11-21.
13. Sane S, Joshaghani F, Alizadeh G, Gholamveisi B, Golabi P. Comparison of the effect of dexmedetomidine with remifentanil on pain after lumbar laminectomy in patients under general anesthesia. Med J Tabriz Univ Med Sci 2021;43:311-22.
14. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Richards-campbell sleep questionnaire (RCSQ). InSTOP, THAT and one hundred other sleep scales. New York, NY: Springer; 2011. p. 299-302.
15. Nicholson T, Maltenfort M, Getz C, Lazarus M, Williams G, Namdari S. Multimodal pain management protocol versus patient controlled narcotic analgesia for postoperative pain control after shoulder arthroplasty. Arch Bone Jt Surg 2018;6:196-202.
16. Joshi GP, Machi A. Surgical site infiltration: A neuroanatomical approach. Best Pract Res Clin Anaesthesiol 2019;33:317-24.
17. Alasady MS, Kanj A, Kanj AEH. Evaluation the outcomes of using iliac bone graft for reconstruction of traumatic orbital floor fractures. J Popul Ther Clin Pharmacol 2022;29:e71-8.
18. Barazanchi AWH, MacFater WS, Rahiri JL, Tutone S, Hill AG, Joshi GP, *et al*. Evidence-based management of pain after laparoscopic cholecystectomy: A Prospect review update. Br J Anaesth 2018;121:787-803.
19. Saul D, Roch J, Lehmann W, Dresing K. Infiltration anesthesia. Oper Orthop Traumatol 2020;32:4-12.
20. Toma O, Persoons B, Pogatzki-Zahn E, Van de Velde M, Joshi GP; PROSPECT Working Group Collaborators. PROSPECT guideline for rotator cuff repair surgery: Systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2019;74:1320-31.
21. Al-Zaben KR, Qudaisat IY, Abu-Halaweh SA, Al-Ghanem SM, Al-Mustafa MM, Alja'bari AN, *et al*. Comparison of caudal bupivacaine alone with bupivacaine plus two doses of dexmedetomidine for postoperative analgesia in pediatric patients undergoing infra-umbilical surgery: A randomized controlled double-blinded study. Pediatr Anesth 2015;25:883-90.
22. Bengisun ZK, Ekmekci P, Akan B, Köroglu A, Tüzüner F. The effect of adding dexmedetomidine to levobupivacaine for interscalene block for postoperative pain management after arthroscopic shoulder surgery. Clin J Pain 2014;30:1057-61.
23. Biçer C, Ünalan EN, Aksu R, Önal Ö, Güneş I. Addition of dexmedetomidine to bupivacaine in ultrasonography-guided paravertebral blockade potentiates postoperative pain relief among patients undergoing thoracotomy. Rev Brasil Anestesiol 2019;69:144-51.
24. Ismail EA, Sayed JA, Bakri MH, Mahfouz RZ. Comparison of intrathecal versus intra-articular dexmedetomidine as an adjuvant to bupivacaine on postoperative pain following knee arthroscopy: A randomized clinical trial. Korean J Pain 2017;30:134-41.
25. Moeen SM, Ramadan IK, Elkady HA. Dexamethasone and dexmedetomidine as an adjuvant to intraarticular bupivacaine for postoperative pain relief in knee arthroscopic surgery: A randomized trial. Pain Physician 2017;20:671-80.
26. Aksu R, Biçer C, Ülgey A, Bayram A, Günes I, Güney A, *et al*. Comparison of interscalene brachial plexus block and intra-articular local anesthetic administration on postoperative pain management in arthroscopic shoulder surgery. Rev Brasil Anestesiol 2015;65:222-9.
27. Avcı O, Özdemir Kol İ, Gündoğdu O, Öztemur Z, Erşan İ. Effect of adding dexmedetomidine to intra-articular levobupivacaine on postoperative pain following arthroscopic meniscus surgery: A prospective, double-blind, randomized, placebo- controlled, clinical trial. Acta Orthop Traumatol Turc 2021;55:316-20.
28. Rampes S, Ma K, Divecha YA, Alam A, Ma D. Postoperative sleep disorders and their potential impacts on surgical outcomes. J Biomed Res 2020;34:271-80.
29. Li L, Wang R, Jia Y, Rong R, Xu M, Zhu T. Exosomes derived from mesenchymal stem cells ameliorate renal ischemic-reperfusion injury through inhibiting inflammation and cell apoptosis. Front Med (Lausanne) 2019;6:269.
30. Hou H, Wu S, Qiu Y, Song F, Deng L. The effects of morning/afternoon surgeries on the early postoperative sleep quality of patients undergoing general anesthesia. BMC Anesthesiol 2022;22:1-8.

31. Movaghar R, Abbasalizadeh S, Vazifekhah S, Farshbaf-Khalili A, Shahnazi M. The effects of synbiotic supplementation on blood pressure and other maternal outcomes in pregnant mothers with mild preeclampsia: A triple-blinded randomized controlled trial. BMC Womens Health 2024;24:80.
32. Boroumand F, Ghayur S, Gharaaghaji R, Vazifekhah S. Efficacy of prophylactic use of metformin in prevention of gestational diabetes mellitus in nondiabetic obese pregnant women. J Obstet Gynecol Cancer Res 2022;7:524-9.
33. Karami T, Hoshyar H, Tavana AM. Comparing caudal block and penile block using rectal acetaminophen in postoperative analgesia of hypospadias repair: A randomized clinical trial study. Int J Surg Open 2021;29:9-13.