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SHOULDER

Dexmedetomidine combined with interscalene brachial plexus block has a synergistic effect on relieving postoperative pain after arthroscopic rotator cuff repair

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Abstract

Purpose Interscalene brachial plexus block (ISB) is one of the most commonly used regional blocks in relieving postoperative pain after arthroscopic rotator cuff repair. Dexmedetomidine (DEX) is an alpha 2 agonist that can enhance the effect of regional blocks. The aim of this study was to compare the effects of DEX combined with ISB with ISB alone on postoperative pain, satisfaction, and pain-related cytokines within the first 48 h after arthroscopic rotator cuff repair.

Methods Fifty patients with rotator cuff tears who had undergone arthroscopic rotator cuff repair were enrolled in this single center, double-blinded randomized controlled trial study. Twenty-five patients were randomly allocated to group 1 and received ultrasound-guided ISB using a mixture of 1 ml (100 μg) of DEX and 8 ml of 0.75% ropivacaine preemptively. The other 25 patients were allocated to group 2 and underwent ultrasound-guided ISB alone using a mixture of 1 ml of normal saline and 8 ml of ropivacaine. The visual analog scale (VAS) for pain and patient satisfaction (SAT) scores were checked within 48 h postoperatively. The plasma interleukin (IL)-6, -8, -1β, cortisol, and substance P levels were also measured within 48 h, postoperatively.

Results Group 1 showed a significantly lower mean VAS score and a significantly higher mean SAT score than group 2 at 1, 3, 6, 12, and 18 h postoperatively. Compared with group 2, group 1 showed a significantly lower mean plasma IL-6 level at 1, 6, 12, and 48 h postoperatively and a significantly lower mean IL-8 level at 1, 6, 12, 24, and 48 h postoperatively. The mean timing of rebound pain in group 1 was significantly later than that in group 2 (12.7 h > 9.4 h, $p = 0.006$).

Conclusions Ultrasound-guided ISB with DEX in arthroscopic rotator cuff repair led to a significantly lower mean VAS score and a significantly higher mean SAT score within 48 h postoperatively than ISB alone. In addition, ISB with DEX showed lower mean plasma IL-6 and IL-8 levels than ISB alone within 48 h postoperatively, with delayed rebound pain.

Level of evidence I.

Trial Registration 2013-112, ClinicalTrials.gov Identifier: NCT02766556.

Keywords Interscalene brachial plexus block · Postoperative pain · Arthroscopic rotator cuff repair · Pain-related cytokine · Rebound pain · Dexmedetomidine

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Jung-Taek Hwang and Ji Su Jang are co-first authors, and equally contributed to this work.

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Introduction

Shoulder arthroscopic operations can be performed in in- or out-patient settings, but it may induce severe pain in the early postoperative period [17, 32, 33]. Therefore, it is important to control excessive postoperative pain by decreasing the pain to a tolerable level for the early return of patients to activities of daily living [35]. There are several regional blocks that can be used to relieve postoperative pain. Interscalene brachial plexus blocks (ISBs) are one of the most powerful regional blocks for shoulder operations, but they have a relatively short duration of effect [33, 51]. Suprascapular nerve blocks (SSNBs) are the most commonly used method for controlling postoperative shoulder pain, and axillary nerve blocks (ANBs) have recently been adopted as a type of regional block for shoulder pain control and are frequently used in combination with SSNB [14, 32, 49].

Dexmedetomidine (DEX), a selective agonist of α_2-adrenergic receptors, can be an effective adjuvant to local anesthetics for peripheral nerve blocks [22]. Preclinical and clinical studies have described a prolonged duration of analgesia when DEX was added to bupivacaine, levobupivacaine, or ropivacaine for peripheral perineural blocks [6-9, 20, 38, 42, 55].

The alterations in pain-related cytokines after arthroscopic rotator cuff repair under ISB combined with DEX have not been studied. Therefore, the present study was designed to test the hypothesis that DEX added to ropivacaine for ISB in elective shoulder operations would enhance the duration and effect of analgesia compared with ropivacaine alone and to assess its influence on serum interleukin (IL)-6, cortisol, IL-1β, IL-8, and substance P levels.

Materials and methods

Fifty patients with a rotator cuff tear who had undergone arthroscopic rotator cuff repair between August 2014 and April 2015 were enrolled in this study. All procedures were approved by the Institutional Review Board of Chuncheon Sacred Heart Hospital and carried out in accordance with the Declaration of Helsinki (IRB number: 2013-112), and a clinical trial registration was performed. All of the patients provided written informed consent to participate in the study. Rotator cuff tears were diagnosed by preoperative magnetic resonance imaging (MRI), and the size of the rotator cuff was confirmed at the time of surgery. The indication for surgery was a symptomatic full-thickness rotator cuff tear or a > 50% thickness partial-thickness rotator cuff tear in cases of failed conservative therapy [33]. Among the patients, 25 were randomly allocated to group 1 and received ISB with ropivacaine and DEX. The remaining 25 patients were allocated to group 2 and received ISB with ropivacaine and normal saline.

The study inclusion criteria were as follows: (1) defined rotator cuff tear on preoperative MRI, which indicated repair; (2) acceptable arthroscopic surgery, including rotator cuff repair; (3) patients > 20 years; and (4) acceptable routine regional blocks and patient-controlled analgesia (PCA). The exclusion criteria involved patients who: (1) did not undergo arthroscopic rotator cuff repair; (2) stopped PCA before 48 h postoperatively due to side effects; (3) had a concomitant operation for a Bankart lesion; (4) had a history of shoulder operation or fracture; (5) had a concomitant neurological disorder around the shoulder; (6) underwent conversion to open surgery from the arthroscopy; (7) had contraindications for the routine regional blocks used in this study; or (8) had an known allergy or hypersensitivity against ropivacaine or dexmedetomidine, including other amino-amide local anesthetics or α_2-adrenoceptor agonists.

Data collection and outcome measures

The visual analog scale (VAS) pain score, American Shoulder and Elbow Surgeons Shoulder Score, Constant score, height, weight, and plasma cortisol, IL-6, IL-8, IL-1β, and substance P levels were checked preoperatively, and ISB was performed preemptively under ultrasound guidance at the end of surgery. PCA was set at a fixed dose (0.05 μg/kg loading dose and 0.03 μg/min/kg continuous dose of fentanyl) to remove the effect of varying amounts of PCA [32, 33]. The VAS pain and patient satisfaction (SAT) scores were checked at 1, 3, 6, 12, 18, 24, 36, and 48 h postoperatively by an independent orthopedic resident who was blinded to whether the patient received DEX during the surgery. The VAS pain score was based on a scale from 0 to 10, where 0 indicated no pain and 10 indicated severe pain [32, 33]. The SAT score also ranged from 0 to 10, where 0 indicated unsatisfactory and 10 indicated very satisfactory [32, 33]. Plasma cortisol, IL-6, IL-8, IL-1β, and substance P levels were checked at 1, 6, 12, 24, and 48 h, postoperatively. The blood analysis was performed by laboratory staff who were blinded to the study. A 3-ml blood sample was retrieved from the peripheral vein of the contralateral upper limb or both lower limbs per sampling, and 3.8% sodium citrate (Sigma, St. Louis, MO, USA) was immediately added to the blood collection as an anticoagulant. The blood was processed and stored at 4 °C. The whole blood was centrifuged at 3000 rpm for 10 min. The plasma was separated from the blood cell layer and stored at − 40 °C. The frozen plasma had been thawed to 4 °C before the levels of blood markers were checked using several kits (Cortisol Parameter Assay

Kit, Human IL-6 Quantikine ELISA Kit, Human CXCL8/IL-8 Quantikine ELISA Kit, Human IL-1 beta/IL-1F2 Quantikine ELISA Kit, and Substance P Parameter Assay Kit; R&D SYSTEMS, Minneapolis, Minnesota, USA). The precision of the five blood markers is as follows: cortisol: intra-assay 5.4–9.2, interassay 9.3–21.2; IL-6: intra-assay 1.6–4.2, interassay 3.3–6.4; IL-8: intra-assay 5.4–6.5; IL-1β: intra-assay 3.0–7.5, interassay 5.7–8.4; and substance P: intra-assay 3.5–8.4, interassay 9.4–15.1 coefficient of variation (CV; %). The primary outcome measure was VAS, and the secondary outcome measures were SAT and the levels of plasma cortisol, IL-6, IL-8, IL-1β, and substance P. Postoperative rebound pain was confirmed if there was an increase in the VAS pain score between 1 and 48 h, postoperatively [25, 33].

Interventions

Double-blinded randomization was performed as follows. The 64 patients who met the inclusion criteria were randomly assigned to 1 of 2 groups depending on treatment. Randomization was performed with a computer random sequence generator by an independent nurse who prepared the syringe for the ISB treatment according to the group assignment. The patient and all of the medical staff who participated in the surgery were blinded to the assignments. Four patients without rotator cuff tears were excluded after the surgery. Two patients were excluded due to a history of ipsilateral operation history. One patient was excluded due to the early termination of PCA before 48 h postoperatively. One patient was excluded due to concomitant open reduction and internal fixation for ipsilateral os acromiale. One patient was excluded due to concomitant ipsilateral operation for a Bankart lesion. Four patients were excluded due to the omission of blood sampling or hemolysis of the blood sample. One patient was excluded, because she was unable to receive the ISB due to an enlarged thyroid. Thus, in total, 50 patients were included. Twenty-five patients were in group 1, and the remaining 25 patients were in group 2 (Fig. 1).

ISB was performed preemptively immediately after general anesthesia was induced by one anesthesiologist under ultrasound guidance (S-Nerve™, SonoSite, Bothell, WA, USA) once the patient was placed in the supine position. Nerves were stimulated with a commercially available nerve stimulator (Pajunk®, Geisingen, Germany). A thin layer of sterile ultrasound transmission gel (Sung Heung Corp., Pucheon, Kyungki-do, Republic of Korea) was placed between the ultrasound linear transducer and the skin

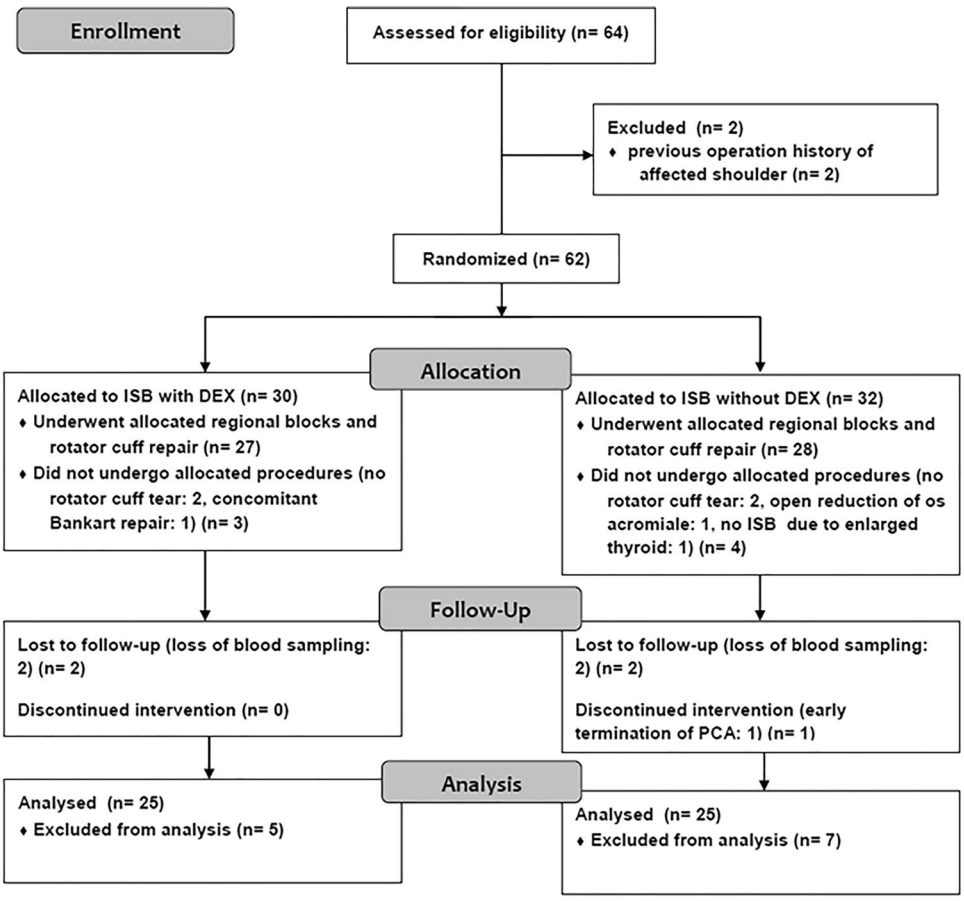

Fig. 1 Flow diagram. *ISB* interscalene brachial plexus block, *DEX* dexmedetomidine

immediately after preparing the skin with povidone–iodine solution [33]. The superior, middle, and inferior trunks of the brachial plexus were identified approximately 2 cm above the clavicle. A 50-mm 22-gauge needle (Uni-Plex NanoLine, Pajunk®, Geisingen, Germany) was introduced percutaneously using the out-of-plane technique. The needle was placed beside each trunk in succession, and the mixture of ropivacaine with DEX or saline (3 ml) was injected into each site. For group 1, a mixture of 8 ml of ropivacaine and 1 ml (100 µg) of DEX was used, and for group 2, a mixture of 8 ml of ropivacaine and 1 ml of normal saline was used. The needle was retracted slightly if a motor response < 0.2 mA was triggered. If contractions continued, a negative aspiration test was performed, and ropivacaine was injected slowly. Then, we turned the current back up to 1.0 mA after the injection. Ropivacaine was not injected during stimulation at an intensity of < 0.2 mA to avoid an intraneural injection [33, 50].

Operative treatment

All of the patients underwent arthroscopic rotator cuff repair and subacromial decompression. All of the procedures were performed by one surgeon. Four routine arthroscopic portals (anterior, posterior, lateral, and posterolateral) were used during the surgery. Arthroscopic subacromial decompression was performed with acromioplasty, followed by the removal of spurs after the bursectomy in all patients. The suture bridge technique was used for rotator cuff repair with 5.0-mm Bio-Corkscrew suture anchors (Arthrex, Naples, FL, USA) and a 4.75-mm Bio-SwiveLock device (Arthrex). Tendon-to-tendon sutures were occasionally used for small to medium tears located around the musculotendinous junction [32, 45]. Tenotomy or tenodesis of the long head of the biceps, distal clavicle resection, and anterior capsulectomy were performed simultaneously based on concomitant diseases. The indication of distal clavicle resection is symptomatic acromioclavicular arthritis, and the indication for anterior capsulectomy is adhesive capsulitis. Adhesive capsulitis was defined as passive forward elevation < 100° and passive external rotation at the side < 30° [32, 33, 43]. The operation time was the duration between the first skin incision and suture of the operative wound.

Postoperative rehabilitation

A shoulder-immobilizing sling with an abduction pillow was prescribed to each patient postoperatively, with instructions to maintain the shoulder at 30°–40° of internal rotation and 20° abduction. Postoperative rehabilitation was individualized according to the size of the tear and the tissue quality of the torn rotator cuff. All of the patients were allowed passive forward elevation using a pulley 48 h postoperatively, immediately after PCA had been removed [32, 33, 44].

Statistical analysis

Fifty patients (25 patients in each group) would provide a statistical power of 80% with a two-sided α level of 0.05 to detect a significant difference in VAS at 12 h postoperatively, assuming an effect size of 0.84 [mean difference, 1.85; standard deviation (SD), 2.21]. This calculation was based on the mean and SD of VAS observed in a pilot study of 20 patients taken at 12 h postoperatively. The normally distributed data between the groups were analyzed using independent sample t test. Otherwise, the nonparametric Mann–Whitney U test was used. Probable factors that may have affected rebound phenomenon characteristics were analyzed by univariate logistic regression. The statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

The demographic data, such as the mean age, body mass index (BMI), and symptom duration, were similar between the two groups (Table 1). In addition, there were no significant differences in the operative data between the two groups (Table 2). Although single row repair and side-to-side tendon repair were performed 3 times in group 1 only, there was no statistically significant difference between the two groups.

Group 1 showed a significantly lower mean VAS and a significantly higher mean SAT than group 2 at 1, 3, 6, 12, and 18 h postoperatively (VAS: 1.2 < 2.1, 1.2 < 2.4, 1.6 < 4.5, 4.2 < 6.1, and 4.5 < 5.5 ($p = 0.017$, $p = 0.015$, $p < 0.001$, $p = 0.003$ and $p = 0.040$); SAT: 8.3 > 7.6, 8.4 > 7.6, 7.8 > 5.6, 6.2 > 4.6, and 6.2 > 5.4 ($p = 0.034$, $p = 0.032$, $p < 0.001$, $p = 0.001$, and $p = 0.049$), respectively) (Table 3). Compared with group 2, group 1 showed a significantly lower mean plasma IL-6 level at 1, 6, 12, and 48 h postoperatively (7 < 10, 15 < 25, 20 < 33, and 13 < 19) and a significantly lower mean IL-8 level at 1, 6, 12, 24, and 48 h postoperatively (12 < 13.0, 11 < 13, 11 < 14, 11 < 13, and 12 < 15). Moreover, compared with group 2, group 1 showed a significantly lower mean plasma cortisol level at 6 h postoperatively (116.9 < 143.0) and a significantly lower plasma substance P level at 1 h postoperatively (112 < 128) (Table 4). All of the patients in group 1 and group 2 showed rebound pain one time. The mean timing of rebound pain in group 1 was significantly later than that in group 2 (12.7 h > 9.4 h, $p = 0.006$), and the mean level of rebound pain of the two groups was not significantly different (4.1 < 4.8, n.s.)

Table 1 Demographic data

Factors	Value			
	Group I	Group II	Confidence interval of the difference	*p* value
Number	25	25		
Age (years)[a]	55.6 ± 7.8 (43–70)	61.9 ± 9.0 (49–77)	− 11.1 to (− 1.5)	n.s
Gender (male:female)	19:6	16:9	− 0.1 to 0.4 (if male = 1, female = 0)	n.s
Dominant:nondominant	20:5	15:10	− 0.1 to 0.5 (if dominant = 1, nondominant = 0)	n.s
Symptom duration (months)[a]	6.2 ± 10.0 (0.25–33.0)	5.4 ± 5.8 (10.0–24.0)	− 3.8 to 5.5	n.s
Preoperative height (cm)[a]	164.2 ± 9.2 (147.0–177.0)	158.6 ± 7.8 (142.0–170.0)	0.7 to 10.4	n.s
Preoperative weight (kg)[a]	68.5 ± 13.2 (42.0–89.0)	67.5 ± 8.0 (56.0–83.0)	− 5.3 to 7.2	n.s
Preoperative BMI (kg/m^2)[a]	25.2 ± 3.1 (17.9–31.1)	26.9 ± 3.2 (20.9–32.8)	− 3.5 to 0.1	n.s
Preoperative VAS[a]	5.8 ± 2.0 (2.0–9.0)	6.2 ± 1.9 (4.0–10.0)	− 1.5 to 0.7	n.s
Preoperative ASES[a]	36.5 ± 10.3 (12.0–61.0)	40.6 ± 16.4 (3.3–65.0)	− 11.9 to 3.8	n.s
Preoperative constant[a]	59.1 ± 8.2 (42.5–74.0)	56.7 ± 7.9 (43.1–71.5)	− 2.2 to 6.9	n.s
Preoperative cortisol (ng/ml)	27.0 ± 9.7 (12.2–49.5)	30.3 ± 14.9 (14.0–71.0)	− 10.5 to 3.8	n.s
Preoperative IL-6 (pg/ml)	4.3 ± 1.7 (2.0–8.2)	3.9 ± 1.2 (2.2–6.4)	− 0.4 to 1.2	n.s
Preoperative IL-8 (pg/ml)	10.4 ± 2.7 (7.3–18.3)	10.6 ± 2.3 (7.3–16.5)	− 1.6 to 1.2	n.s
Preoperative IL-1β (pg/ml)	3.7 ± 0.7 (2.3–5.3)	3.5 ± 0.9 (2.2–6.2)	− 0.2 to 0.7	n.s
Preoperative SP (pg/ml)	120.5 ± 27.4 (29.74–142.63)	123.1 ± 20.8 (59.4–146.7)	− 16.4 to 11.2	n.s

The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

BMI body mass index, *VAS* visual analog scale pain score, *ASES* american shoulder and elbow surgeons score, *Constant* constant score, *IL* interleukin, *SP* substance P

[a]Factors are presented as the mean ± standard deviation with the range in parentheses. Symptom duration: the duration between symptom onset and operation

(Table 5). The mean timing of rebound pain was correlated with the combined DEX administration in the univariate logistic regression ($p = 0.010$, odds ratio = 1.223). However, the mean level of rebound pain did not show a significant correlation with the combined DEX administration (n.s., odds ratio = 0.753). All of the rebound pain occurred between 3 and 36 h postoperatively.

Discussion

The most important finding of the present study was that the combination of ultrasound-guided ISB with DEX tended to decrease the postoperative VAS and SAT scores after arthroscopic shoulder surgery compared to those of ISB alone within the first 48 h postoperatively. Pain is a major factor influencing the duration of hospital stays, and postoperative pain control is important for early rehabilitation and the early return of patients to activities of daily living [32, 33]. Several methods can be used for controlling postoperative pain after shoulder surgery. PCA can decrease some of the postoperative pain, but it may induce several side effects, such as nausea, vomiting, and somnolence [57]. A continuous analgesic infusion pump is an effective method for relieving postoperative shoulder pain. However, leakage, occasional equipment malfunction, and infection can happen [5, 33, 39]. Several regional blocks, including ISB, SSNB, and ANB, can be used [14, 23, 25, 32–35]. ISB is an efficacious method, but may lead to pneumothorax or phrenic nerve palsy and has a shorter duration of effect than SSNB [31, 33, 35, 56]. ISB can be performed using a single injection or continuous injections with a catheter [23, 31, 33, 51]. A randomized controlled trial showed that compared with single-injection ISB, continuous ISB leads to significantly shorter hospital stays; however, the catheter may dislocate during continuous ISB, and patients frequently feel uncomfortable [37, 51].

In this study, the combination of ultrasound-guided ISB with DEX tended to decrease postoperative VAS scores and increase postoperative SAT scores after arthroscopic shoulder surgery compared to those of ISB alone within the first 48 h postoperatively. DEX added to ropivacaine for ISB increased the duration of the nerve block. The mechanism by which α_2-adrenergic receptor agonists produce analgesia and sedation is not fully understood but is likely multifactorial. Peripherally, α_2 agonists produce analgesia by reducing the release of norepinephrine and causing α_2 receptor-independent inhibitory effects on nerve fiber action potentials.

Table 2 Operative data

Factors	Value			
	Group I	Group II	Confidence interval of the difference	*p* value
Number	25	25		
Operation time (minute)[a]	76 ± 21 (40–120)	83 ± 18 (55–120)	− 19.1 to 4.5	n.s
RCT size (cm)[a]	2.1 ± 1.4 (1.0–6.0)	2.4 ± 1.3 (1.0–5.0)	− 1.1 to 0.5	n.s
Suture bridge repair	22	25	− 0.3 to 0.0	n.s
Single row repair	1	0	0.0 to 0.1	n.s
Tendon to Tendon repair	2	0	0.0 to 0.2	n.s
SC lesion				
Debridement	3	4	− 0.2 to 0.2	n.s
Repair using suture anchor	2	1	− 0.1 to 0.2	n.s
Tendon to Tendon repair	0	0		n.s
LHB lesion				
Debridement	5	1	0.0 to 0.3	n.s
Tenotomy	1	4	− 0.3 to 0.1	n.s
Tenodesis	3	3	− 0.2 to 0.2	n.s
ADCR	1	2	− 0.2 to 0.1	n.s
Anterior capsulotomy	5	5	− 0.2 to 0.2	n.s
Amount of fentanyl in PCA (ug)	7920 ± 1132 (3631–7694)	5840 ± 691 (4841–7175)	− 459.2 to 620.4	n.s

Debridement was performed for fraying or spontaneous rupture of LHB. Fraying was defined as a LHB lesion less than 50%. Tenodesis or tenotomy was performed in cases with LHB dislocation, subluxation, or tear involving more than 50%

Anterior capsulotomy was performed for adhesive capsulitis.The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

RCT rotator cuff tear, *SC* subscapularis, *LHB* long head of biceps, *ADCR* arthroscopic distal clavicle resection, *ADCR* was performed for symptomatic AC arthritis, *AC* acromioclavicular joint, *pCA* patient-controlled analgesia

[a]Factors are presented as the mean ± standard deviation with the range in parentheses. Operation time was the duration between the skin incision and suture

Centrally, α_2 agonists produce analgesia and sedation by inhibiting the release of substance P in the nociceptive pathway at the level of the dorsal root neuron and by activating α_2 adrenoceptors in the locus coeruleus [1, 10, 22, 38].

Pain-related blood markers include proinflammatory cytokines, anti-inflammatory cytokines, cortisol, substance P, etc. [3, 4, 18, 21, 26, 28, 36, 47]. Cytokines influence the activity, differentiation, proliferation, and survival of immune cells, as well as regulate the production and activity of other cytokines that can increase (proinflammatory) or decrease (anti-inflammatory) the inflammatory response. Proinflammatory cytokines include IL-1, -2, -6, -7, and -8, and tumor necrosis factor (TNF), and anti-inflammatory cytokines include IL-4, -10, and -13, and transforming growth factor (TGF)-β [13, 14, 16, 18, 28, 30, 40, 52]. It has also been reported that salivary and plasma cortisol levels are closely related to stress or pain [16, 26]. Substance P has been thought to be related to pain and stem cell recruitment [27, 36]. Pain and the immune system influence each other, making it difficult to determine whether blocking nociception contributes to a reduction in the production of proinflammatory cytokines or vice versa, with a reduction in the formation of proinflammatory cytokines resulting in less severe pain [53].

The mean physiological blood levels of the blood markers are as follows: cortisol: 12.6 μg/ml; IL-6: 0.5–5.1 pg/ml; IL-8: 7.526–29.3 pg/ml; IL-1β: 0.12–16 pg/ml; and substance P: 18 pg/ml [2, 11, 12, 19, 24, 29, 41, 48]. The mean physiological blood levels are lower than those in the present study, because the operation caused pain. The mean plasma IL-6 level in patients without any nerve block after arthroscopic rotator cuff repair was 24.3 pg/ml [54]. This value is located between those of groups 1 and 2 in the present study. The mean plasma IL-6 and IL-1β levels in patients who experienced only narcosis were 2.04 and 38.53 pg/ml, respectively [58]. According to these values, the mean blood level of IL-6 was lower and the mean level of IL-1β was higher than those of the two groups in the present study.

Rebound pain has been reported in several studies in which regional blocks, such as ISB, SSNB, and ANB, were used to control pain after arthroscopic shoulder surgery [17, 25, 32, 33, 35]. One study showed that ANB combined with SSNB causes fewer rebound phenomena than that of SSNB alone [32]. Another study suggested that the combination

Table 3 The scores associated with pain according to postoperative time

Postoperative time	Group I	Group II	Confidence interval of the difference	*p* value
(A) VAS according to postoperative time (h)a				
1	1.2 ± 1.2 (0.0–4.0)	2.1 ± 1.4 (0.0–5.0)	− 1.6 to (− 0.2)	0.017
3	1.2 ± 1.2 (0.0–4.0)	2.4 ± 2.0 (0.0–8.0)	− 2.1 to (− 0.3)	0.015
6	1.6 ± 1.5 (0.0–5.0)	4.5 ± 3.0 (0.0–9.0)	− 4.2 to (− 1.5)	< 0.001
12	4.2 ± 2.5 (0.0–9.0)	6.1 ± 2.2 (1.0–9.0)	− 3.3 to (− 0.6)	0.003
18	4.5 ± 1.7 (0.0–8.0)	5.5 ± 1.5 (3.0–8.0)	− 1.9 to (− 0.1)	0.040
24	3.3 ± 1.3 (1.0–6.0)	3.7 ± 1.5 (1.0–8.0)	− 1.2 to 0.4	n.s
36	2.1 ± 1.0 (0.0–4.0)	2.8 ± 1.7 (1.0–8.0)	− 1.5 to 0.1	n.s
48	1.4 ± 0.8 (0.0–3.0)	2.0 ± 1.4 (1.0–7.0)	− 1.3 to 0.1	n.s
(B) SAT according to postoperative time (h)[b]				
1	8.3 ± 0.9 (6.0–10.0)	7.6 ± 1.3 (5.0–10.0)	0.1 to 1.3	0.034
3	8.4 ± 0.9 (6.0–10.0)	7.6 ± 1.6 (3.0–10.0)	0.1 to 1.6	0.032
6	7.8 ± 1.2 (5.0–10.0)	5.6 ± 2.3 (2.0–10.0)	1.2 to 3.3	< 0.001
12	6.2 ± 1.4 (4.0–9.0)	4.6 ± 1.7(2.0–9.0)	0.6 to 2.4	0.001
18	6.2 ± 1.4 (3.0–9.0)	5.4 ± 1.2 (3.0–7.0)	0.1 to 1.5	0.049
24	7.3 ± 1.0 (6.0–9.0)	6.7 ± 1.2 (5.0–9.0)	0.0 to 1.2	n.s
36	7.9 ± 0.8 (7.0–9.0)	7.7 ± 0.9 (6.0–9.0)	− 0.3 to 0.7	n.s
48	8.7 ± 0.6 (8.0–10.0)	8.4 ± 0.9 (6.0–9.0)	− 0.1 to 0.7	n.s

[a]VAS: visual analogue scale pain score. The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

[b]SAT: patient's satisfaction. The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

of ISB and SSNB tended to delay the mean time of rebound pain and subsequently reduced mean rebound pain severity compared to that of ISB alone [23]. In the present study, the mean time of rebound pain occurred later with the combination of ultrasound-guided ISB and DEX than that with the ultrasound-guided ISB alone, but the mean level of rebound pain was not significantly different between the two groups.

This study had some limitations. First, the VAS and SAT scores were subjective. However, all previous studies on preemptive regional blocks for postoperative pain control used these subjective scoring systems. Second, this study does not include a control group that underwent rotator cuff repair without an interscalene block at all. However, if we included a control group that underwent arthroscopic rotator cuff repair without ISB, this control group would not receive any benefits for postoperative pain relief using the regional block. To avoid the moral problem and facilitate the recruitment of participants, the two groups were determined to be ISB only and ISB with DEX.

There are several merits in the present study. First, no previous studies have been performed on the effect of DEX combined with ultrasound-guided ISB for relieving postoperative pain after arthroscopic rotator repair compared to ISB alone using pain-related blood markers. Therefore, adequate blood markers can be selected for evaluating pain and may be utilized for grading the pain objectively. The selected blood markers for pain can be used as a parameter to determine the amount of narcosis. Using blood markers, the problem of narcotic addiction can be reduced [46]. Second, the present study was a double-blinded randomized controlled trial in which a power analysis was performed. Third, one anesthesiologist conducted all of the ultrasound-guided ISBs using nerve stimulation and one orthopedic surgeon who specialized in shoulder arthroscopic surgery performed all the surgeries. Finally, PCA was set to a low fixed dose to remove the effect of differing quantities of the analgesic. DEX combined with ISB showed a synergistic effect in relieving postoperative pain in arthroscopic rotator cuff repair. Based on the results of the present study, evidence on objective blood pain markers might be obtained.

Conclusions

Ultrasound-guided ISB with DEX in arthroscopic rotator cuff repair showed a significantly lower mean VAS score and a significantly higher mean SAT score within 48 h postoperatively than ISB alone. In additional ISB with DEX

Table 4 The plasma level of pain-related cytokines according to postoperative time

Postoperative time	Group I	Group II	Confidence interval of the difference	*p* value
(A) Cortisol (ng/ml) according to postoperative time (h)[a]				
1	117 ± 45 (39–248)	143 ± 72 (56–421)	− 60.2 to 8.1	n.s
6	105 ± 44 (13–211)	142 ± 39 (91–251)	− 60.9 to (− 13.7)	0.003
12	117 ± 45 (31–206)	121 ± 47 (45–256)	− 30.9 to 21.7	n.s
24	53 ± 30 (15–168)	58 ± 30 (14–161)	− 22.2 to 12.2	n.s
48	51 ± 37 (10–173)	60 ± 43 (5–228)	− 32.2 to 13.5	n.s
(B) IL-6 (pg/ml) according to postoperative time (h)[b]				
1	7 ± 3 (3–20)	10 ± 5 (5–30)	− 5.8 to (− 0.6)	0.002
6	15 ± 6 (5–28)	25 ± 15 (7–65)	− 16.6 to (− 3.5)	0.006
12	20 ± 8 (6–36)	33 ± 21 (8–87)	− 22.1 to (− 4.0)	0.010
24	21 ± 8 (6–40)	30 ± 19 (9–78)	− 17.7 to (− 0.6)	n.s
48	13 ± 9 (5–50)	19 ± 12 (5–52)	− 12.4 to 0.0	0.039
(C) IL-8 (pg/ml) according to postoperative time (h)[c]				
1	12 ± 3 (8–19)	13 ± 3 (9–20)	− 3.0 to 0.1	0.015
6	11 ± 2 (8–16)	13 ± 3 (10–19)	− 4.1 to (− 1.1)	0.001
12	11 ± 2 (7–17)	14 ± 3 (9–20)	− 5.0 to (− 2.1)	< 0.001
24	11 ± 2 (9–17)	13 ± 2 (9–19)	− 3.7 to (− 1.3)	< 0.001
48	12 ± 2 (9–16)	15 ± 3 (9–25)	− 4.4 to (− 1.5)	< 0.001
(D) IL-1β (pg/ml) according to postoperative time (h)[d]				
1	4 ± 1 (2–9)	4 ± 1 (1–9)	− 0.7 to 0.9	n.s
6	4 ± 2 (2–9)	3 ± 1 (2–5)	− 0.3 to 1.5	n.s
12	4 ± 1 (2–7)	4 ± 1 (2–6)	− 0.6 to 0.6	n.s
24	4 ± 1 (2–7)	4 ± 1 (2–8)	− 0.5 to 1.0	n.s
48	4 ± 1 (2–8)	4 ± 1 (2–6)	− 0.7 to 0.5	n.s
(E) Substance P (pg/ml) according to postoperative time (h)[e]				
1	112 ± 29 (44–152)	128 ± 20 (80–157)	− 30.1 to (− 1.7)	0.035
6	112 ± 31 (23–158)	115 ± 25 (22–141)	− 18.6 to 13.1	n.s
12	116 ± 23 (80–184)	115 ± 14 (80–135)	− 10.3 to 11.4	n.s
24	121 ± 18 (77–159)	113 ± 25 (38–137)	− 4.5 to 20.4	n.s
48	111 ± 26 (39–155)	116 ± 16 (69–138)	− 16.4 to 8.1	n.s

[a]The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

[b]IL-6: interleukin 6. The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

[c]IL-8: interleukin-8. The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

[d]IL-1β: interleukin-1β. The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

[e]The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

showed lower mean plasma IL-6 and IL-8 levels than ISB alone within 48 h postoperatively, with delayed rebound pain.

Table 5 Characteristics of rebound pain according to the groups

	Group I	Group II	Confidence interval of the difference	*p* value
Mean size of rebound pain (VAS)	4.1 ± 1.9 (1.0–8.0)	4.8 ± 1.2 (2.0–7.0)	− 1.6 to 0.2	n.s
Mean timing of rebound pain (h)	12.7 ± 3.6 (6.0–18.0)	9.4 ± 4.5 (3.0–18.0)	1.0 to 5.7	0.006

The above analysis was performed using Mann–Whitney *U* test or *t* test for indifferent samples according to the normality of data to evaluate the differences between the mean values of the group I and group II. $p < .05$

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Chuncheon Sacred Heart Hospital (IRB number: 2013-112) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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