

# Combined suprascapular nerve block and axillary nerve block approach vs. peri-articular infiltration analgesia for postoperative pain management following arthroscopic shoulder surgery: a randomized clinical trial

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**Abstract. – OBJECTIVE:** Postoperative pain following shoulder surgery is a devastating situation. Several approaches, including regional nerve blocks such as combined suprascapular nerve block and axillary nerve block (SSNB+ANB) and peri-articular infiltration (PAI) analgesia, have been investigated to manage postoperative pain. This study aimed to compare the effects of PAI and SSNB+ANB on postoperative pain scores and analgesic consumption after arthroscopic shoulder surgery.

**PATIENTS AND METHODS:** A single-center prospective, randomized interventional study with a two-arm parallel design was performed. Sixty patients with arthroscopic shoulder surgery were randomized to SSNB+ANB (n=30) and PAI (n=30) group. Postoperative pain scores, analgesic requirements, and complications were evaluated in the postoperative anesthesia recovery unit and during the postoperative 24 hours.

**RESULTS:** The age of patients in Group PAI was significantly higher than in Group SSNB+ANB ( $p<0.001$ ). Groups were similar, considering demographic and clinical characteristics ( $p>0.05$ ). The length of anesthesia and surgery was significantly longer in Group PAI ( $p=0.009$  and  $p=0.025$ ). Although there was no significant difference in the amount of change in pain scores for postoperative 24 hours ( $p=0.537$ ), postoperative pain scores were significantly higher in Group SSNB+ANB group than Group PAI during postoperative 24 hours except for the 12th-hour evaluation ( $p<0.05$ ). Postoperative opioid requirement and rescue analgesic medications were significantly higher in Group SSNB+ANB ( $p<0.001$  and  $p=0.001$ ). The number of postoperative nausea and vomiting attacks was similar ( $p=0.317$ ).

**CONCLUSIONS:** PAI seems to be a more feasible and practical analgesic approach for managing postoperative pain after arthroscopic shoulder surgery regarding pain score and cumulative analgesic requirement.

## Key Words:

Shoulder arthroscopy, Suprascapular nerve block, Axillary nerve block, Peri-articular infiltration, Analgesia, Postoperative pain.

## Introduction

Shoulder surgery is characterized by relatively high intraoperative and postoperative pain<sup>1,2</sup>. Several regional nerve blocks have decreased intraoperative and postoperative pain severity and consecutive analgesic requirements<sup>1</sup>. Although interscalene brachial plexus block has been established as the most reliable analgesic technique, the paralysis of the phrenic nerve – associated with the use of interscalene brachial plexus block resulting in diaphragmatic paralysis – emerges as a significant complication<sup>1,3-7</sup> along with other less frequent side effects including the weakness of the arm, hoarseness of voice, brachial plexus neuropathy, rebound pain, and Horner's syndrome<sup>1,5</sup>. The search for other safe and alternative approaches involving nerve blocks for the anesthesia and analgesia management of arthroscopic shoulder procedures continues<sup>8</sup>.

The combination of suprascapular nerve block and axillary nerve block (SSNB+ANB) has been recently proposed as an alternative anesthetic and postoperative analgesic modality in this patient population<sup>1,2,6</sup>. These two nerve blocks cause the loss of the sensory innervation of the shoulder. SSNB+ANB is advantageous to the interscalene brachial plexus block since it does not lead to respiratory dysfunction due to phrenic nerve palsy or other serious complications.

Postoperative pain following arthroscopic shoulder surgery is primarily why these patients start

physical therapy immediately after the surgery<sup>9</sup>. Therefore, any reduction in postoperative pain is essential to promote rehabilitation and increase patient satisfaction<sup>2</sup>. Opioid medications are commonly used to reduce postoperative pain; however, they have significant drawbacks, including side effects and possibly leading to dependency<sup>10</sup>. Hence, the search for alternative methods that will provide safer and prolonged postoperative analgesia while at the same time reducing the reliance on opioids is still ongoing<sup>7,10-13</sup>. In parallel, several studies<sup>4,5</sup> have investigated new local anesthetic-based and opioid-sparing techniques as potential alternatives to opioids.

Peri-articular infiltration (PAI) analgesia, one of these potential alternatives, has been used recently for shoulder surgery<sup>4</sup>. PAI includes the direct injection of local anesthetic to the sites of surgical trauma and around the shoulder joint<sup>4</sup>. The results of the studies on the safety and analgesic efficacy of PAI are contradictory, especially compared to the studies on the safety and analgesic efficacies of interscalene brachial plexus and erector spinae blocks and SSNB+ANB<sup>5,10,14-18</sup>. To date, no study assessed the efficacies of the PAI and SSNB+ANB techniques. The objective of this study is to assess the efficacies of SSNB+ANB and PAI techniques in the pain management of patients who underwent arthroscopic shoulder surgery in terms of postoperative pain scores, postoperative analgesic usage, and patient satisfaction comparatively.

## Patients and Methods

### Research Design

This study was designed as a single-center (a tertiary hospital), single-blind, prospective, randomized interventional study featuring a two-arm parallel design. The local Ethical Committee approved the study protocol (Tekirdağ Namik Kemal University Research Ethics Committee, Date: 23/02/2021, 2021.43.02.06), which was carried out under the principles of the Declaration of Helsinki. The study was registered with the ID number NCT04855019 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). The recommendations of the Consolidated Standards of Reporting Trials (CONSORT) were followed in the research design and the study's findings (available at: <https://clinicaltrials.gov/ct2/show/NCT04855019>).

### Population and Sample

The study population comprised adult patients who underwent arthroscopic shoulder surgery.

The patient enrollment started on the 20<sup>th</sup> of May 2021. The criteria to be met for inclusion in the study were determined as follows: a) being >18 years old, b) patients who will undergo elective shoulder arthroscopy surgery, and c) having been given either 1 or 2 for the American Society of Anesthesiologists (ASA) score. On the other hand, patients with neuropathy, known drug allergies, regular opioid use for any reason, anticoagulant therapy, and inability to respond to visual analog scale (VAS) were excluded from the study. The patients included in the study were informed about anesthesia and postoperative pain management modalities. They were also informed that they could withdraw from the study. Written informed consent was obtained from all patients who volunteered to participate in the study. The sixty patients included in the study were then randomly assigned into two groups, with 30 patients. The patients in the first group were scheduled to have SSNB +ANB and postoperative pain management modality before the arthroscopic shoulder surgery, whereas the patients in the second group were scheduled to have PAI.

### Interventions

A pre-anesthetic evaluation was performed on all patients. General anesthesia was induced using 1 to 2 mg/kg propofol, 1 µg/kg fentanyl, and 0.3 to 0.6 mg/kg rocuronium. Anesthesia was maintained with sevoflurane in a mixture of 50:50 air/oxygen and 0.1 µg/kg remifentanyl per minute. Prophylactic antibiotics were given before and after the surgery, combined with anti-emetics in cases where necessary.

Ultrasound-guided SSNB+ANB was performed on the patients in Group 1 as described in the literature<sup>19-21</sup>. Accordingly, 20 ml 0.50% bupivacaine was used to perform SSNB and ANB sequentially. A total of 20 ml 0.25% bupivacaine was injected pre-operatively into the peri-articular area of the patients in Group 2 as described in the literature<sup>15</sup>. The local anesthetic agents extensively infiltrated the surgical site. The infiltration of all affected tissues within 2.5 cm from the surface of the surgical area was used<sup>15</sup>.

### Follow-Up

All patients were initially followed in the post-anesthesia care unit (PACU) and transferred to the clinical wards. Patient-controlled analgesia (PCA) was initiated immediately with a bolus dose of 20 mg tramadol and a lockout time of 10 minutes for 24 hours. 1 g paracetamol was

administered intravenously as a rescue analgesic medication at a maximum of four doses with six hours in between each dose during the postoperative follow-up period to patients with a visual analog scale (VAS) score of 4 or more or upon patients' request.

All patients were discharged during the first morning following the first 24 hours postoperatively.

### **Variables**

Demographic data (age, gender), body mass index (BMI), the type of surgery, the duration of anesthesia and the surgery, and the type of intraoperative complications were recorded. The VAS scores assigned for postoperative pain in the PACU and then at the clinical wards during the postoperative first, fourth, eighth, 12<sup>th</sup>, and 24<sup>th</sup> hours were recorded. The total amount of opioid dosage was measured using the PCA application. In addition, the number of rescue analgesic drug requirements was calculated and recorded. The overall satisfaction level of the patients in terms of quality of pain relief was measured after the postoperative 24<sup>th</sup> hour and recorded as satisfied, ambivalent, or unsatisfied. One of the researchers, blinded to the group allocation, assessed the postoperative outcomes, including the VAS scores and the satisfaction levels.

### **Outcomes**

The study's primary outcomes were the change in the postoperative VAS scores assigned for pain and the total opioid consumption during the postoperative first 24 hours. The secondary outcomes were the frequencies of postoperative nausea and vomiting (PONV) attacks.

### **Sample Size**

The sample size was initially determined as 46 cases, with 23 cases in each group, to test the statistical significance of a one-point decrease in the postoperative VAS scores from the baseline to the end of the PACU period between the groups. The margins of error and power were determined at 5% and 90%, respectively. The sample size was determined as 60 cases, with 30 cases in each group, considering a drop-out rate of 30%.

The power of the study was calculated as 99% based on the descriptive statistics obtained from the postoperative VAS scores of 30 patients in each group measured during the follow-up control at the postoperative 24<sup>th</sup> hour.

### **Statistical Analysis**

Descriptive statistics were expressed using mean  $\pm$  standard deviation values in the case of continuous variables that were determined to conform to the normal distribution and median and minimum-maximum values in the case of continuous variables that were determined not to conform to the normal distribution. Categorical variables were expressed as numbers and percentages. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to determine whether the numerical variables conform to the normal distribution.

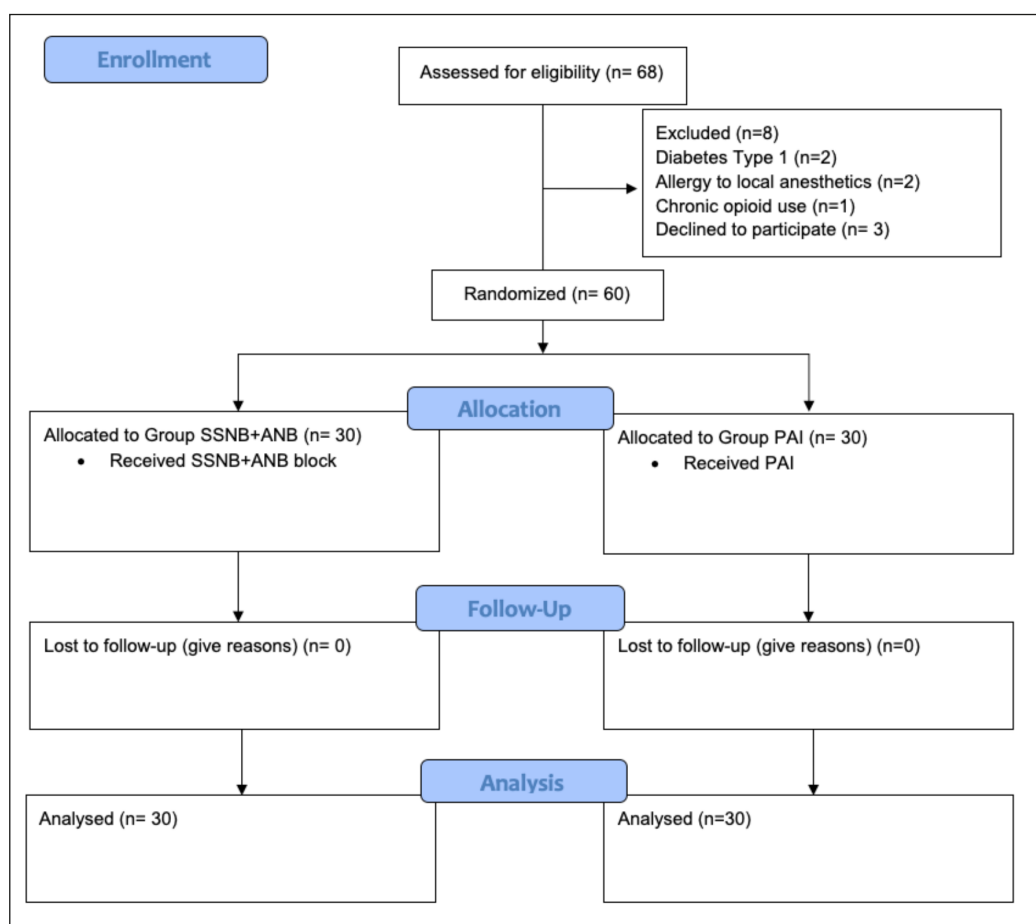
The independent samples *t*-test was used to compare two independent groups with numerical variables (age, BMI, total opioid dosage for PCA) that were determined to conform to the normal distribution. On the other hand, the Mann-Whitney U test was used to compare two independent groups with numerical variables that were determined not to conform to the normal distribution. The Pearson's chi-squared test was used to compare the differences between categorical variables in 2x2 tables. Lastly, the Fisher-Freeman-Halton test was used to compare the categorical variables between the groups in RxC tables.

For statistical analysis, Jamovi project (2022) version 2.2.5.0 Computer Software (Retrieved from: <https://www.jamovi.org>) and JASP version 0.16 (Retrieved from: <https://jasp-stats.org>) software packages were used. In all statistical analyses, the significance level (*p*-value) was set at 0.05.

## **Results**

The CONSORT flow diagram is documented in Figure 1. There were 30 patients in each group. The patients in Group 2 (the PAI Group) were significantly older than the patients in Group 1 (the SSNB+ANB Group) ( $54.9 \pm 7.3$  vs.  $45.9 \pm 6.5$  years, respectively;  $p < 0.001$ ). Most of the patients in both groups, 22 (73.3%) patients in Group 1 and 18 (60.0%) in Group 2, had ASA grade 1. There was no significant difference between the groups regarding gender, BMI values, and ASA grades (Table I).

Stand-alone rotator cuff repair was the most common surgical procedure used in both groups (40.0% and 36.7% in Group 1 and Group 2, respectively). 26 (86.7%) and 23 (76.7%) patients underwent stand-alone arthroscopic rotator cuff repair or rotator cuff repair combined with oth-



**Figure 1.** The CONSORT flow diagram of the study.

er surgical procedures in Group 1 and Group 2, respectively. There was no significant difference between the groups in terms of the distribution of the surgical procedures ( $p=0.062$ ). The median duration of the anesthesia and surgery was longer in Group 2 than in Group 1 ( $p=0.009$  and  $p=0.025$ ). Complications developed in two and three patients in Group 1 and Group 2, respectively ( $p=0.999$ ).

Postoperative outcomes regarding pain and postoperative nausea/vomiting are shown in Table II.

The median VAS scores for pain were significantly higher in Group 1 than in Group 2 in all assessments conducted in the first 24 hours postoperatively, except for the 12<sup>th</sup> hour assessment (Figure 2). However, there was no significant difference in the change in VAS scores for pain during the postoperative first 24 hours ( $p=0.537$ ). The total opioid doses for PCA were  $172.3 \pm 38.6$  mg and  $107.0 \pm 27.9$  mg in Group 1 and Group 2, respectively, indicating a significant differ-

ence between the groups ( $p<0.001$ ). There was also a significant difference between the groups in the number of rescue analgesia requirements ( $p=0.001$ ). Most patients, that is, 60.0% of the patients in Group 1 and 70.0% in Group 2, were satisfied with postoperative pain management, and there was no significant difference between the groups in terms of the distribution of the patients' satisfaction levels ( $p=0.697$ ). We detected no significant difference in the frequency of PONV attacks between the groups ( $p=0.317$ ).

## Discussion

This study demonstrated that PAI is more efficacious than SSNB+ANB regarding improved postoperative pain scores, reduction in postoperative opioid consumption, and rescue analgesia requirement. Although there was no significant difference between the two groups regarding patients' satisfaction levels and the amount of change in the VAS scores for pain, PAI might be

preferred due to its safety and feasibility. To the best of the knowledge of this study's authors, this study is the first study to date that comparatively assessed the efficacies of the PAI and SSNB+ANB techniques in postoperative pain management following arthroscopic shoulder surgery.

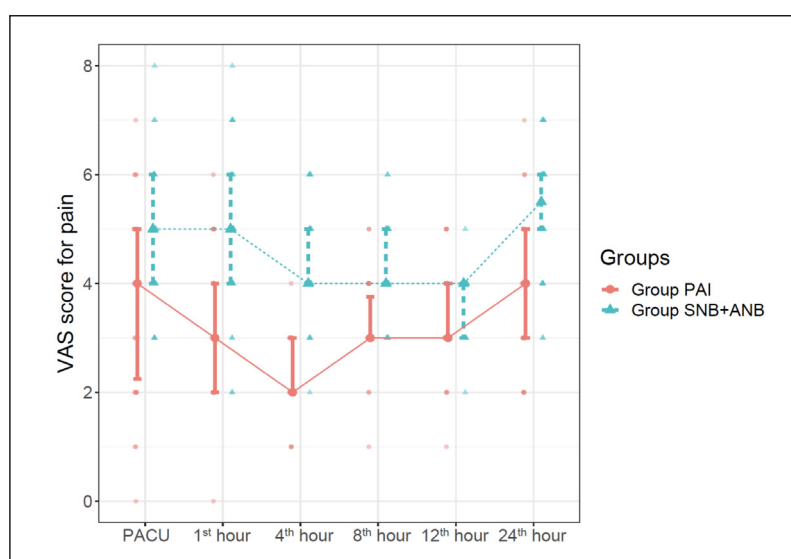
The combined use of SSNB with ANB is defined as the shoulder block<sup>6,22</sup>. Several studies<sup>6,8,23-25</sup> are available in the literature that compared SSNB+ANB with other anesthetic approaches in shoulder surgery. Saini et al<sup>6</sup> and Pani et al<sup>8</sup> compared SSNB+ANB with interscalene block in one of these studies. They did not find any significant difference between the efficacies of the two approaches in terms of postoperative pain; however, they stated that SSNB +ANB approach was more advantageous as it leads to fewer undesirable effects. In

contrast, Neuts et al<sup>23</sup> and Dhir et al<sup>24</sup> determined that the SSNB+ANB approach was inferior to the interscalene block in analgesia and opioid requirement. It was stated that the SSNB+ANB approach is advantageous over other approaches due to lower incidences of complications, such as dyspnea and discomfort. Similar outcomes were reported in other studies<sup>26</sup>. Therefore, the optimum postoperative pain management after shoulder surgery is still debated. The findings of this study indicated that PAI is associated with lower pain scores that lasted up to the postoperative 24<sup>th</sup> hour, less opioid consumption, and lower numbers of rescue analgesia. Thus, it has been concluded that the PAI technique is advantageous over other complicated analgesic interventional techniques in the context of shoulder surgery.

**Table I.** Demographic and clinical characteristics of the study groups.

	Groups		p
	Group SNB+ANB (n=30)	Group PAI (n=30)	
<b>Age (year)<sup>†</sup></b>	45.9 ± 6.5	54.9 ± 7.3	<b>&lt;0.001*</b>
<b>Sex<sup>‡</sup></b>			
Male	17 (56.7)	22 (73.3)	0.279***
Female	13 (43.3)	8 (26.7)	
<b>BMI (kg/m<sup>2</sup>)<sup>†</sup></b>	29.1 ± 2.4	30.4 ± 4.3	0.148*
<b>ASA grade<sup>‡</sup></b>			
I	22 (73.3)	18 (60.0)	0.262***
II	7 (23.3)	10 (33.3)	
III	0 (0.0)	2 (6.7)	
IV	1 (3.3)	0 (0.0)	
<b>Surgical procedures<sup>‡</sup></b>			
Rotator cuff repair	12 (40.0)	11 (36.7)	0.062***
Rotator cuff repair + decompression	4 (13.3)	10 (33.3)	
Rotator cuff repair + biceps tenodesis	6 (20.0)	1 (3.3)	
Rotator cuff repair + stabilization	4 (13.3)	1 (3.3)	
Arthroscopic labrum repair of shoulder	2 (6.7)	1 (3.3)	
Decompression	1 (3.3)	1 (3.3)	
Bankart repair	1 (3.3)	5 (16.7)	
<b>Duration of anesthesia (hr)<sup>§</sup></b>	2.0 [1.5- 2.5]	2.5 [2.0- 2.5]	<b>0.009**</b>
<b>Operation time (hr)<sup>§</sup></b>	1.5 [1.0- 2.0]	2.0 [1.5- 2.0]	<b>0.025**</b>
<b>Complications<sup>‡</sup></b>	2 (6.7)	3 (10.0)	0.999
<b>Type of complication<sup>‡</sup></b>			
Cardiopulmonary	0 (0.0)	2 (66.7)	N/A
Musculoskeletal	2 (100.0)	1 (33.3)	

†: mean ± standard deviation, ‡: n (%), §: median [min-max]. BMI: body mass index, ASA: American Society of Anesthesiologists, N/A: not applicable. \*: Independent samples *t*-test. \*\*: Mann-Whitney U test. \*\*\*: Pearson's Chi-square test/Fisher Freeman Halton test.



**Figure 2.** Graphical representation of postoperative VAS scores for pain measured during the follow-up period while in the hospital. VAS: visual analog scale; PACU: postoperative anesthesia.

Several authors<sup>10,14,16</sup> compared PAI with the interscalene block in various arthroscopic shoulder surgeries. They found that interscalene block provided better results in the early postoperative period, whereas PAI provided adequate pain control starting from day 1 to day 3 post-operatively<sup>10,14,16</sup>. PAI is advantageous over other techniques because the incidences of side effects such as nausea and temporary arm numbness are relatively low in the case of PAI<sup>4</sup>. We detected no significant differences in the number of PONV attacks and complications between the groups in the current study. The low number of events in each category might be the reason for insignificance. Bojaxhi et al<sup>18</sup> investigated the synergistic effect of the local infiltration analgesia on the interscalene block with different approaches. They found that continuous interscalene block was more effective in decreasing opioid consumption and postoperative pain than single-shot interscalene block with local infiltration analgesia. Bjørnholdt et al<sup>15</sup> compared local infiltration analgesia with continuous interscalene brachial plexus block in patients with a primary shoulder replacement. They infiltrated the surgical site extensively with ropivacaine. The 24-hour opioid consumption was significantly higher in the local infiltration analgesia group. There was no significant difference between the groups in opioid consumption during the following three days. They concluded that local infiltration analgesia might not be recommended for shoulder replacement surgery, given the high pain scores associated with its use.

In this study, the PAI approach was more effective in reducing postoperative pain than the SSNB+ANB approach. In addition, using PAI significantly reduced the amount of opioid requirement and the number of rescue analgesia. The discrepancies between the results on the efficacies of the analgesic approaches used for postoperative pain management can be attributed to the fact that the application of approaches requires a high level of training and experience and different anatomic localization, e.g., the knee vs. the shoulder, and different types of surgeries, e.g., shoulder replacement vs. arthroscopic interventions<sup>15</sup>. Therefore, prospective studies are needed to shed light on these discrepancies.

The outcomes of PAI have been evaluated in a systematic review and meta-analysis by Yung et al<sup>4</sup>. They found that PAI was associated with lesser postoperative pain scores and a lesser amount of postoperative opioid analgesic medications. Thus, they concluded that PAI is more efficacious than interscalene brachial plexus block analgesia. However, the non-inferiority testing of PAI over the interscalene block was inconclusive. They attributed the inconclusive outcomes to the heterogeneity of the results<sup>4</sup>. Another popular option for postoperative pain management following shoulder surgery has been SSNB+ANB. However, there are some inherent procedural risks of SSNB+ANB, including pneumothorax and nerve damage<sup>4</sup>. PAI's use as a practical analgesic approach in shoulder surgery has not yet been supported with high-level evidence. This study's

**Table II.** Postoperative outcomes in the study groups.

	Groups		p
	Group SSNB+ANB (n=30)	Group PAI (n=30)	
<b>VAS score for pain<sup>§</sup></b>			
PACU	5.0 [3.0 - 8.0]	4.0 [0.0 - 7.0]	0.006**
1 <sup>st</sup> hour	5.0 [2.0 - 8.0]	3.0 [0.0 - 6.0]	<0.001**
4 <sup>th</sup> hour	4.0 [2.0 - 6.0]	2.0 [1.0 - 4.0]	<0.001**
8 <sup>th</sup> hour	4.0 [3.0 - 6.0]	3.0 [1.0 - 5.0]	<0.001**
12 <sup>th</sup> hour	4.0 [2.0 - 5.0]	3.0 [1.0 - 5.0]	0.118**
24 <sup>th</sup> hour	5.5 [3.0 - 7.0]	4.0 [2.0 - 7.0]	<0.001**
Δ 24 <sup>th</sup> hour - PACU	0.0 [-33.3 - 66.7]	0.0 [-16.7 - 47.5]	0.537**
<b>Total opioid dose for PCA (mg)<sup>†</sup></b>	172.3 ± 38.6	107.0 ± 27.9	<0.001*
<b>Number of rescue analgesia<sup>‡</sup></b>	1.0 [0.0 - 3.0]	1.0 [0.0 - 2.0]	0.001**
<b>Patient satisfaction<sup>‡</sup></b>			
Satisfied	18 (60.0)	21 (70.0)	0.697***
Unsatisfied	6 (20.0)	5 (16.7)	
Ambivalent	6 (20.0)	4 (13.3)	
<b>PONV attacks<sup>§</sup></b>	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	0.317**

†: mean ± standard deviation, ‡: n (%), §: median [min-max]. VAS: visual analog scale, PACU: postoperative anesthesia recovery unit, PCA: patient-controlled analgesia, PONV: postoperative nausea and vomiting. \*: Independent samples *t*-test. \*\*: Mann-Whitney U test. \*\*\*: Pearson's Chi-square test/Fisher Freeman Halton test.

authors hope that this study will fill the gap in that regard, and PAI will find widespread use.

Clinical conditions due to symptomatic acromioclavicular joints have been treated non-invasively *via* joint injections. Sabeti-Aschra et al<sup>27</sup> determined that intraarticular and peri-articular lidocaine hydrochloride and betamethasone injections have comparable efficacies. Various analgesic approaches using intra-articular, peri-articular, or wound infiltrating techniques were investigated in other studies<sup>17,22</sup>. In one of these studies, Ozkan et al<sup>22</sup> compared the efficacies of pre-procedural SSNB+ANB and post-procedural subacromial local infiltration in arthroscopic shoulder surgery. They found that SSNB+ANB resulted in lower pain scores and less opioid than post-procedural bupivacaine infiltration. Beaudet et al<sup>17</sup> reported similar postoperative outcomes favoring perioperative interscalene analgesia over intra-articular analgesia. Several authors<sup>17,28,29</sup> reported lower postoperative pain scores following shoulder surgery using continuous postoperative wound infiltration with ropivacaine. The discrepancies regarding the efficacies of infiltration analgesia approaches may originate from the differences in the analgesic medications used and the

dosages thereof, infiltration techniques, and anatomic sites used for infiltration. This study used the infiltration method described in the literature for PAI<sup>15</sup>. Standardization of the infiltration techniques may help reduce the discrepancies between the results of different studies.

Regarding the nerves innervating the shoulder area, 60-70% of the innervation of the shoulder joint is related to the suprascapular nerve, and the remaining 25-30% of the innervation is provided by the axillary nerve. Therefore, blocking two different nerves in the SSNB+ANB approach caused significant increases in the length of anesthesia compared to the interscalene block<sup>6</sup>. This study did not measure the time required to apply SSNB+ANB and PAI. However, the mean overall operation time was significantly longer in the PAI group compared to the SSNB+ANB group. Although it is impossible to accurately assess the timing of the analgesia procedures for pain management, the fact that PAI requires more time may be attributed to the operator's relatively lower level of experience.

### Limitations

There were some limitations to this study. First, the nerve blocks and the technique used for PAI

might be regarded as operator-dependent procedures. Although the interviewer bias was tried to be minimized through blinded investigators in assessing the postoperative outcomes, this study could not be conducted as a double-blind study given the inherent differences in the analgesic procedures. This issue may be a factor in sampling and selection bias. No control groups were included in this randomized study, as it would pose an ethical challenge.

## Conclusions

It was concluded that PAI is a more feasible and practical analgesic approach for managing postoperative pain after arthroscopic shoulder surgery in terms of pain score and cumulative analgesic requirement compared to SSNB+ANB.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Ethics Approval

The local Ethical Committee approved the study protocol (Tekirdağ Namık Kemal University Research Ethics Committee, Date: 23/02/2021, 2021.43.02.06), which was carried out under the principles of the Declaration of Helsinki.

## Informed Consent

Written informed consent was obtained from all patients who volunteered to participate in the study.

## Funding

None.

## Availability of Data and Materials

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' Contributions

Ayhan Şahin: substantial conception and design of the study. Onur Baran: substantial conception and design of the study. Mehmet Ümit Çetin: acquisition, analysis and interpretation of the data of the manuscript. Ahmet Gültekin: drafting the article, making critical revisions related to relevant intellectual content of the manuscript. Makbule Cavidan Arar: supervision, validation and final approval of the version of the article to be published.

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