



Effects of propofol-remifentanyl versus sevoflurane-remifentanyl on acute postoperative pain after total shoulder arthroplasty: a randomized trial

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Background: While some evidence indicates that propofol-based anesthesia has less postoperative pain than sevoflurane-based anesthesia, these results are controversial. We compared acute postoperative pain intensity and opioid consumption after total shoulder arthroplasty between propofol-remifentanyl (PR) and sevoflurane-remifentanyl (SR) anesthesia.

Methods: Among 48 patients undergoing shoulder arthroscopic surgery anesthetized with PR or SR, postoperative pain intensity was assessed at 30 minutes and at 2, 6, 12, and 24 hours. The total patient-controlled analgesia volume and number of patients requiring rescue analgesics were assessed.

Results: No significant difference in postoperative pain intensity was observed between the two groups. Postoperative opioid consumption and analgesic requirements were also comparable in the first 24 hours after surgery.

Conclusion: PR and SR anesthesia for shoulder arthroscopic surgery provide comparable postoperative analgesia results.

Keywords: Anesthesia; Propofol; Sevoflurane; Total shoulder arthroplasty

Introduction

Postoperative pain management is the main challenge for anesthesiologists and surgeons in patients undergoing shoulder arthroscopic surgery. Inadequate control of postoperative pain is associated with prolonged recovery, increased healthcare costs, and increased risks of undesirable surgical outcomes [1]. Various pharmacotherapeutics, including opioids, nonsteroidal anti-inflammatory drugs, gabapentinoids, and regional nerve blocks, have been used alone or in combination to prevent postoperative pain.

Previous studies have shown that an anesthetic regimen may ac-

tivate peripheral nociceptive neurons or suppress nociceptive signal propagation. Recent studies have demonstrated that the effect on postoperative pain of propofol-based anesthesia is superior to that of sevoflurane-based anesthesia [2,3]; however, other studies have not corroborated the superiority of propofol for treating postoperative pain [4,5].

This study aimed to compare acute postoperative pain intensity and opioid consumption after total shoulder arthroplasty (TSA) between patients receiving propofol-remifentanyl (PR) and sevoflurane-remifentanyl (SR) anesthesia.

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Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2016-12-009-001). Informed consent was obtained from all patients.

1. Study design

This prospective, randomized, double-blind study enrolled 48 patients aged 18 to 65 years with American Society of Anesthesiologists (ASA) physical status (PS) classification I or II undergoing TSA. The exclusion criteria were routine use of analgesics, history of neurologic or psychological disease, body mass index of $> 35 \text{ kg/m}^2$, and intake of any sedatives or analgesics within 24 hours before surgery. This study was registered at ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT04333992>).

The patients were assigned to either the PR or SR group using computer-generated randomization. Standardized monitoring was performed in the operating room. In the PR group, anesthetic induction was achieved with initial propofol and remifentanyl target concentrations of $4 \text{ }\mu\text{g/mL}$ and $3 \text{ to } 4 \text{ ng/mL}$, respectively, using target-controlled infusion (TCI) devices (Orchestra Base Primea, Fresenius Vial, Brézins, France) and rocuronium 0.8 mg/kg . After intubation, anesthesia was maintained with a fixed target concentration of propofol $2 \text{ to } 4 \text{ }\mu\text{g/mL}$ and remifentanyl $2 \text{ to } 3 \text{ ng/mL}$ to maintain an acceptable hemodynamic response and bispectral index (BIS) values of 40 to 60. In the SR group, anesthesia was induced with thiopental 5 mg/kg and an initial target remifentanyl concentration of $3 \text{ to } 4 \text{ ng/mL}$ using TCI and rocuronium 0.8 mg/kg . Anesthesia was maintained with 1.5% to 2.5% end-tidal concentration of sevoflurane in 50% oxygen with air, and remifentanyl $2 \text{ to } 3 \text{ ng/mL}$ was continuously infused to maintain acceptable hemodynamics and BIS values of 40 to 60. Propofol or sevoflurane with remifentanyl administration was stopped at the end of surgery. Ketorolac 30 mg was administered intravenously (IV) for postoperative pain control and ramosetron 0.3 mg was administered IV for antiemetic prophylaxis. Residual neuromuscular blockade was reversed with pyridostigmine 0.2 mg/kg and glycopyrrolate 0.01 mg/kg IV. The patients were then transferred to the postanesthesia care unit (PACU).

Postoperative pain intensity was assessed using a numerical rating scale (NRS: 0, no pain to 10, worst pain) at 30 minutes and at 2, 6, 12, and 24 hours. When the NRS score was > 4 or when the patient requested analgesics, fentanyl $50 \text{ }\mu\text{g}$ was administered IV. In addition, patient-controlled analgesia (PCA) was infused immediately after PACU arrival. The PCA device was set to deliver 0.38

$\mu\text{g/kg/hr}$ of fentanyl as a basal infusion rate and $20 \text{ }\mu\text{g}$ on demand with a 15-minute lockout time [6]. If the pain was poorly controlled, additional fentanyl ($50 \text{ }\mu\text{g}$) was administered. The total PCA volume and number of patients requiring rescue analgesics were recorded. The incidence of postoperative nausea and vomiting (PONV) and use of rescue antiemetics were also recorded 24 hours after surgery. Ramosetron 0.3 mg was administered when the patients experienced vomiting or required antiemetics. Other adverse events such as respiratory depression, headache, and dizziness were also recorded. All anesthetic procedures and study assessments were performed by an anesthesiologist who was blinded to the group assignments and study protocols.

2. Statistical analyses

We estimated the sample size using the NRS score (at 30 minutes postoperatively) from our preliminary study [2]. The mean \pm standard deviation (SD) of NRS score was 7.0 ± 0.6 in the PR group and 7.6 ± 0.78 in the SR group. Thus, based on a power of 80% and an α error of 5% , 23 patients were required in each group. Therefore, 52 patients were enrolled to compensate for potential dropouts. Statistical analyses were performed using IBM SPSS ver. 23 (IBM Corp., Armonk, NY, USA). Continuous data were analyzed using *t*-tests and are expressed as mean \pm SD, whereas categorical data were analyzed using the chi-square test or Fisher exact tests as appropriate and are expressed as number (%). A *p*-value of < 0.05 was considered statistically significant.

Results

Among the 52 patients screened for eligibility, data from 48 of them were analyzed; three patients refused to participate and one did not meet the inclusion criteria.

There were no significant differences between the two groups with respect to age, sex, ASA PS classification, height, weight, or duration of surgery (Table 1). The pain NRS did not significantly differ at any time point, but the magnitude of the pain scores was lower in the PR group than in the SR group (Table 2). Regarding the use of postoperative analgesics, no difference was observed between the two groups in terms of fentanyl consumption via PCA. Likewise, the total dose of rescue drugs did not differ significantly; however, the SR group showed a tendency for higher postoperative analgesic use than the PR group (Table 3). The incidence of PONV and need for antiemetics did not differ between the groups (Table 4). No significant differences were observed in postoperative adverse events such as headache, dizziness, and respiratory depression (Table 4).

Table 1. Demographic and baseline characteristics

Characteristic	PR group	SR group	p-value
No. of patients	24	24	
Age (yr)	58.4 ± 9.9	58.4 ± 9.0	0.544
Sex, male:female	15:9	16:8	> 0.999
ASA PS classification, I:II	16:8	14:10	0.766
Height (cm)	164.6 ± 7.5	164.5 ± 8.6	0.326
Weight (kg)	65.8 ± 9.5	66.6 ± 9.3	0.988
Duration of surgery (min)	135.2 ± 47.5	122.5 ± 51.2	0.960

Values are presented as number or mean ± standard deviation.
PR, propofol-remifentanyl; SR, sevoflurane-remifentanyl; ASA, American Society of Anesthesiologists; PS, physical status.

Table 2. Postoperative pain intensity during the first 24 hours after surgery

Time	Pain score		p-value ^{a)}
	PR group (n = 24)	SR group (n = 24)	
30 min	6.79 ± 1.14	7.12 ± 1.03	0.295
2 hr	5.37 ± 1.27	5.91 ± 1.05	0.117
6 hr	3.20 ± 1.41	3.95 ± 1.26	0.059
12 hr	1.75 ± 0.73	1.95 ± 0.62	0.296
24 hr	0.95 ± 0.46	1.08 ± 0.40	0.327

Values are presented as mean ± standard deviation.
PR, propofol-remifentanyl; SR, sevoflurane-remifentanyl.

^{a)}Statistically significant at $p < 0.05$.

Table 3. Cumulative fentanyl consumption and rescue analgesics during the first 24 hours after surgery

Variable	PR group (n = 24)	SR group (n = 24)	p-value ^{a)}
Total dose of PCA (μg)	595.0 ± 176.1	672.6 ± 92.0	0.064
Rescue analgesics needed	13 (54.2)	19 (79.2)	0.066
Total dose of rescue fentanyl (μg)	47.9 ± 54.1	75.0 ± 46.6	0.070

Values are presented as mean ± standard deviation or number (%).
PR, propofol-remifentanyl; SR, sevoflurane-remifentanyl; PCA, patient-controlled analgesia.

^{a)}Statistically significant at $p < 0.05$.

Table 4. Reported side effects during the first 24 hours after surgery

Side effect	PR group (n = 24)	SR group (n = 24)	p-value ^{a)}
PONV	3 (12.5)	3 (12.5)	> 0.999
Rescue antiemetics needed	1 (4.2)	2 (8.3)	> 0.999
Headache	1 (4.2)	0 (0)	> 0.999
Dizziness	0 (0)	0 (0)	> 0.999
Respiratory depression	0 (0)	0 (0)	> 0.999

Values are presented as number (%).
PR, propofol-remifentanyl; SR, sevoflurane-remifentanyl; PONV, postoperative nausea and vomiting.

^{a)}Statistically significant at $p < 0.05$.

Discussion

In this study, we did not observe a significant difference in postoperative pain intensity between PR and SR anesthesia. Postoperative opioid consumption and analgesic requirements were also comparable in the first 24 hours after surgery, demonstrating that there was no benefit in choosing one general anesthetic over the other for patients undergoing TSA.

TSA is a surgical procedure used to improve the functional outcomes of glenohumeral arthritis [7]. Most patients experience substantial postoperative pain; thus, adequate control of acute postoperative pain contributes to early recovery by maintaining motor function and reducing the risk of developing chronic pain [8]. A multimodal approach to postoperative pain management has been applied, including pharmacologic and nonpharmacologic adjuvants such as opioids administered IV local analgesic infiltration, and peripheral nerve block [9,10]. The present study aimed to assess the effects of propofol and sevoflurane as general anesthetics on postoperative pain in patients undergoing TSA.

Previous studies have investigated the effects of propofol- and inhalation-based anesthesia on postoperative pain. While some studies have shown less postoperative pain after propofol anesthesia [2,3], Cheng et al. [2] demonstrated that maintenance with propofol provided better postoperative analgesia and less morphine consumption than isoflurane. In a study by Li et al. [3], propofol anesthesia was associated with less postoperative pain than sevoflurane anesthesia in patients who underwent gynecological laparoscopies, while others have reported no beneficial effects on pain control. Fassoulaki et al. [4] showed that there was no difference in the intensity of pain after surgery and in morphine requirements between the sevoflurane and propofol groups of their study. Pokkinen et al. [5] showed that the choice of anesthetic (sevoflurane or propofol) had no effect on postoperative pain and oxycodone use. Comparing the two agents, there is some evidence supporting the mixed effects of propofol or sevoflurane on acute postoperative pain. The antinociceptive properties of propofol include neuronal suppression of the dorsal horn by interaction with GABAA and glycine receptors, which leads to decreased transmission of noxious stimuli [11,12]. In particular, the pain-relieving properties of propofol have been demonstrated in combination with opioids [13,14]. However, the proposed pronociceptive properties of propofol include the activation of potential ion channels [15]. The analgesic effects of sevoflurane can be explained by the suppression of sensory stimuli transmission at anesthetic concentrations [16,17]. Hao et al. [18] reported reduced Fos-immunopositive neurons in the dorsal horns of the sevoflurane group, suggesting that sevoflurane possesses analgesic effects. However, volatile anes-

thetics such as isoflurane intensify pain sensitivity by inhibiting nicotinic receptors in the spinal cord and, thus, hinder norepinephrine release [19]. The results of the present study are comparable to those reported previously. We found no significant differences in pain intensity and post-opioid consumption at any time point, although we did observe a lower magnitude of pain scores and use of postoperative analgesics in the PR group than in the SR group.

The use of intraoperative opioids is important for achieving balanced anesthesia. Remifentanil, an ultra-short-acting opioid, is widely used in general anesthesia to provide hemodynamic stability, anesthetic-sparing, and rapid cognitive effects [20,21]. However, remifentanil-induced hyperalgesia (RIH) is challenging in postoperative pain management. The possible mechanism of RIH is attributed to a pain-facilitating system involving rapid and prolonged upregulation of *N*-methyl-D-aspartate (NMDA) receptors [22,23]. However, inhalational or intravenous anesthetics might modulate postoperative hyperalgesia by inhibiting NMDA receptor function [24–26]. Shin et al. [27] showed that remifentanil hyperalgesia was induced during SR anesthesia but not during PR anesthesia. Moreover, they found that RIH was activated by a high dose (4 ng/mL with TCI) but not a low dose (1 ng/mL with TCI) of remifentanil. The better postoperative analgesic effects of propofol can be attributed to the direct activation of R-aminobutyric acid type A receptors by propofol, which inhibits NMDA receptors and modulates calcium ion channels [28]. In the present study, we used intraoperative remifentanil (3–4 ng/mL) and observed a comparable postoperative analgesic pattern in both groups, which suggests that we could not identify a potent antagonistic interaction between propofol and remifentanil that might affect NMDA receptor activation.

Without prophylaxis, the use of inhalational anesthetics and opioids may increase the risk of PONV by 30% [29]. In the present study, however, we did not observe any difference in PONV incidence between the two groups, indicating that ramosetron might have affected prophylaxis.

This study had several limitations. First, in addition to the anesthetic regimen, postoperative pain can be affected by many factors including patient anxiety, mood, and genetic differences in response to analgesics. We did not assess these parameters preoperatively. Second, the pain scores after TSA were high; thus, the anesthetic regimen might have been underpowered to detect significant differences in early analgesic effects. Third, we did not evaluate the long-term analgesic effects of the two general anesthetics. Further studies with follow-up times longer than 24 hours postoperatively are required to investigate this effect. Finally, we set the intraoperative remifentanil level at 3 to 4 ng/mL in both groups, but the total dose of remifentanil was not included. Based on the re-

sults of a comparable postoperative analgesic pattern in both groups, we postulate that there was no antagonistic interaction between propofol and remifentanil. However, assessment of intraoperative remifentanil use might be needed for more precise comparison.

In conclusion, the postoperative analgesic effects were comparable between PR and SR as anesthetic regimens in patients who underwent TSA.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Data curation: all authors; Formal analysis: EKC, DyK; Methodology: DyK; Visualization: SK; Resources: EKC, SK; Software: SK, DyK; Supervision: EKC; Writing-original draft: EKC, SK; Writing-review & editing: EKC, SK, DyK.

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