

Remifentanil infusion versus propofol and remifentanil patient controlled sedation/analgesia for moderate sedation during interventional radiological procedures: A prospective randomized trial

Sule Arican, Gamze Sarkilar, Ruhiye Reisli, Seref Otelcioglu

Necmettin Erbakan University Medical of Faculty, Department of Anaesthesiology, Konya, Turkey

Copyright © 2018 by authors and Annals of Medical Research Publishing Inc.

Abstract

Aim: The use of intravenous sedation and analgesia during interventional radiological procedures is increasing. Sedation and analgesia should minimize patients' negative psychological reactions caused by fears and anxiety. Also they should relieve pain and provide patients a safe and comfortable environment.

The aim of this study was to compare the efficacy and safety of two drugs and methods used for moderate sedation during radiological procedures.

Material and Methods: Sixty patients, with American Society of Anesthesiologists scores (ASA) I-II-III, undergoing interventional radiology procedures were included in this study. The patients were administered remifentanil bolus (0.2 µg.kg⁻¹) followed by remifentanil infusion (0.05 µg.kg⁻¹.min⁻¹) in Group R, 2.5mL loading dose (25 mg propofol–25 µg remifentanil) and a 1mL bolus dose (10 mg propofol–10 µg remifentanil) via patient-controlled analgesia/sedation (PCAS) device in Group PR. All the patients' sedation levels were assessed with the Ramsey Sedation Scale (RSS), pain levels were assessed with Visual Analog Scale (VAS). Their recoveries were assessed with the modified Aldrete score (MAS) at 5 min intervals.

Results: Although a significant difference was noted between the groups for RSS values at 5, 10, 20, 25, and 30th minutes during the procedure (P<0.05), there was no significant difference in VAS, anxiety levels and MAS (P > 0.05).

Conclusion: Both propofol–remifentanil PCAS and remifentanil infusion provide sufficient moderate sedation.

Keywords: Remifentanil; propofol; sedation; interventional radiology

INTRODUCTION

Nowadays the implementation of sedation and/or analgesia outside the operating room has increased in accordance with the rise in prevalence and diversity of interventional radiological procedures.

Moderate sedation/analgesia is a drug-induced depression of consciousness with adequate spontaneous ventilation, patient airway, and maintained cardiovascular functions, in which the patient responds purposefully to the verbal and light tactile stimulation (1). Moderate sedation provides a low risk of serious adverse events with all currently available agents (2). Medication used in moderate sedation should have minimum side effects, it should depress the patient's consciousness level in a controlled manner, and it should have inactive metabolites, and should not necessitate resedation (3,4).

Patient-controlled analgesia (PCA) is the possible pain

management modality used for interventional procedures (5). The patient-controlled analgesia/sedation (PCAS) is an effective and safe method (6). Sedatives, opioids, and local anesthetics are used alone or in combination during interventional procedures. They have synergistic effects when used together (5).

Although there are several studies in the literature reporting that administering propofol in combination with an opioid leads to moderate sedation there are very few studies on opioid effects alone.

This study aimed to compare remifentanil infusion and propofol–remifentanil PCAS methods used to provide ideal sedation in patients undergoing radiological procedures.

MATERIAL and METHODS

The study was conducted with the approval of Faculty Ethics Committee (Ref. no. 2009/357). This study

Received: 08.04.2018 Accepted: 24.05.2018 Available online: 28.05.2018

Corresponding Author: Ugur Ekici, Istanbul Gelişim University, Health Sciences Colleges, Department of Health Administration, Istanbul, Turkey, E-mail: opdrugurekici@hotmail.com

included 60 patients between 18 and 70 years of age who had ASA I-II-III and were undergoing interventional radiology procedures for diagnostic and treatment purposes. Written informed consent was obtained from all participants included in the study. Patients who had allergic reaction to medications to be used, patients with serious cardiovascular and respiratory system diseases, obesity, sleep apnea syndrome, high risk of pulmonary aspiration, or pregnancy, patients who were unable to grasp the meaning of PCAS, and unaccompanied patients were excluded from the study.

We used G Power Software to determine the sample size. We calculated that a total of 56 patients (28 patients for each group) would be needed to compare the two groups with 90% power, 5% type I error level, and 25% effect size for the test. Sixty patients were enrolled to account for the possibility of exclusion.

Patients who were scheduled to undergo painful interventional radiological procedures under local anesthesia were randomly assigned into either the remifentanyl (Ultiva; GlaxoSmithKline, Italy) infusion group (Group R; n=30) or the remifentanyl-propofol (Propofol; Fresenius Kabi, Sweden) PCAS group (Group PR; n=30) according to a computer-generated randomization list. Premedication was not performed in any of the cases. An ante-cubital vein was cannulated for intravenous infusions and drug administration.

In group R, remifentanyl was diluted in 0.9% physiological saline (concentration of 40 µg.mL⁻¹) and administered at 0.2 µg.kg⁻¹ bolus dose, followed by a 0.05 µg.kg⁻¹.min⁻¹ infusion. Meanwhile, in group PR, a mixture of 10 µg.mL⁻¹ remifentanyl and 10 mg.mL⁻¹ propofol was administered via a PCAS device. In the PCAS device the initial loading dose was set at 2.5 mL (25 mg propofol – 25 µg remifentanyl) and the bolus dose was set at 1 ml (10 mg propofol–10 µg remifentanyl) (Fig. 1). The lockout time was not set. The patients from Group PR were instructed about using the PCAS (Abbott Pain Manager; Abbott Laboratories, Chicago, IL, USA) device during the preanesthetic evaluation.

Baseline hemodynamic values were recorded before the procedure. Electrocardiogram (ECG), peripheral oxygen saturation (SpO₂), noninvasive arterial pressure, respiratory rate (RR), Visual Analog Scale (VAS) (0=no pain; 10=severe pain), and Ramsey sedation score (RSS) (1=anxious and agitated; 2=cooperative; 3=responding to verbal commands; 4=responding to minor stimulation; 5=responding to deep stimulation; and 6=no response to stimulation) values were recorded every 5 minutes during the procedure. The presence of anxiety in patients was noted as "yes" or "no."

All patients were informed about VAS prior to the procedure. VAS scores were assessed as follows: 1–3, mild pain; 4–7, moderate pain; and score >7, severe pain. A sufficient sedation level for this study was determined as 2–3 according to RSS. Patients were asked to indicate

the severity of pain during the procedure.

The patients were given 2 l/min oxygen via a face mask then the radiologist administered local anesthetics (2% prilocaine at 3 mg/kg dose) to all patients subcutaneously in addition to intravenous sedation and analgesia.

When VAS scores were ≥4, 10 µg remifentanyl as an intravenous bolus dose in group R and 10 µg remifentanyl–10 mg propofol from PCAS devices in Group PR were administered. In both the groups, patients who's RSS was 1 received 1 mg dose of midazolam (Dormicum, Roche, Germany) for additional sedation. Naloxone hydrochloride and flumazenil were available during all the procedures. An experienced radiologist carried out all of the procedures.

During the procedure and in the recovery room, heart rate (HR), mean arterial pressure (MAP) and SpO₂ was recorded at 5-minute intervals after getting basal values.

Hypotension, bradycardia, desaturation, apnea, nausea, vomiting, euphoria, and shivering were recorded as intraoperative and postoperative complications.

If the saturation decreased <90%, oxygen given via the face mask was increased at a rate of 4 L.min⁻¹ in both the groups, the infusion was stopped in group R, and 1 minute lockout time was set in Group PR. The patient was awakened with tactile stimulation or with a loud noise.

Patients who developed bradycardia were treated with 0.5 mg atropine. The patients who developed hypotension and did not respond to the increased fluid infusion were treated with 5–10 mg ephedrine. Metoclopramide, which is an antiemetic drug, was planned for the treatment of nausea and vomiting.

Drug infusion was continued until the end of the procedure. After the procedure, the patients were taken to the recovery room, and noninvasive arterial pressure, HR, SpO₂, and modified Aldrete scores (MAS) were measured and recorded (7). The patient vital signs were measured at 5-minute intervals while patients were awake (MAS=10) for at least 30 minutes in the recovery room.

Prior to discharge, the patients were asked to grade their satisfaction of the applied anesthesia technique by using a 6-point satisfaction scale (0=very poor; 1=poor; 2=moderate; 3=good; 4=very good; 5=excellent). At the end of the process the same scale was used to assess the satisfaction of the radiologists. Then, the patients were discharged with a companion.

Statistical analysis

Statistical analyses were performed with SPSS 14.0. Data were submitted to a frequency distribution analysis by Kolmogorov–Smirnov's test. Values displaying normal distribution were expressed as the mean ± SD and values with skew distribution were expressed as median (interquartile range). Differences between numeric variables were tested with independent samples t or Mann–Whitney U tests where appropriate. Categorical

variables were assessed with Pearson's chi-square test or Fisher's exact test. P value of <0.05 was considered statistically significant.

RESULTS

The present study included 60 patients (ASA I-II-III) who underwent interventional radiological procedures. The patients were divided into two groups of 30 patients each. No significant difference was found in the demographic variables of 60 patients who underwent interventional radiological procedures under moderate sedation (P > 0.05) (Table 1).

Table 1. Demographic characteristics of patients

	Group R (n=30)	Group PR (n=30)	P
Age (years)	53.6±12.2	49.3±15.4	0.077
Weight (kg)	76.0±10.4	71.1±9.6	0.064
Gender, male	13 (43.3)	16 (53.3)	0.079
ASA			0.075
I	6 (20)	7 (23.3)	
II	15 (50)	16 (53.4)	
III	9 (30)	7 (23.3)	

Data are given mean±standard deviation or number (%)
ASA, American Society of Anesthesiologists

The duration of the procedure was 31.8±9.7 minutes in group R and 33.2±10.2 minutes in Group PR (P > 0.05). The

distribution of applied radiological procedures according to the groups is summarized in Table 2. No significant difference was observed between the group distributions of applied procedures (P > 0.05).

Table 2. The distribution of radiological procedures according to groups

	Group R (n=30)	Group PR (n=30)
Cerebral angiography	2 (6.6)	3 (10)
Placing tunneled catheter	6 (20)	9 (30)
Percutaneous hepatic cyst drainage	15 (50)	11 (36.6)
Splenic artery chemoembolization	1 (3.3)	1 (3.3)
Percutaneous transhepatic biliary drainage	2 (6.6)	2 (6.6)
Hepatic tumor ablation	2 (6.6)	1 (3.3)
The renal artery chemoembolization	2 (6.6)	3 (10)

Data are given as number (%)

No significant difference was found in HR, MAP, and RR (P > 0.05), while SpO2 was found to be significant difference at 5, 10, and 15 minutes during the procedure and 30 minutes in the recovery room between the two groups (P < 0.05) (Fig. 2). SpO2 was <90% in one patient in Group R.

The comparison of RSS values between the groups showed a significant difference at 5, 10, 20, 25, and 30th minutes (P < 0.05) (Fig. 3). During the procedure, mean RSS scores were 2.4 (2.0/2.6) in Group R and 2.3 (2.0/2.8) in Group PR.

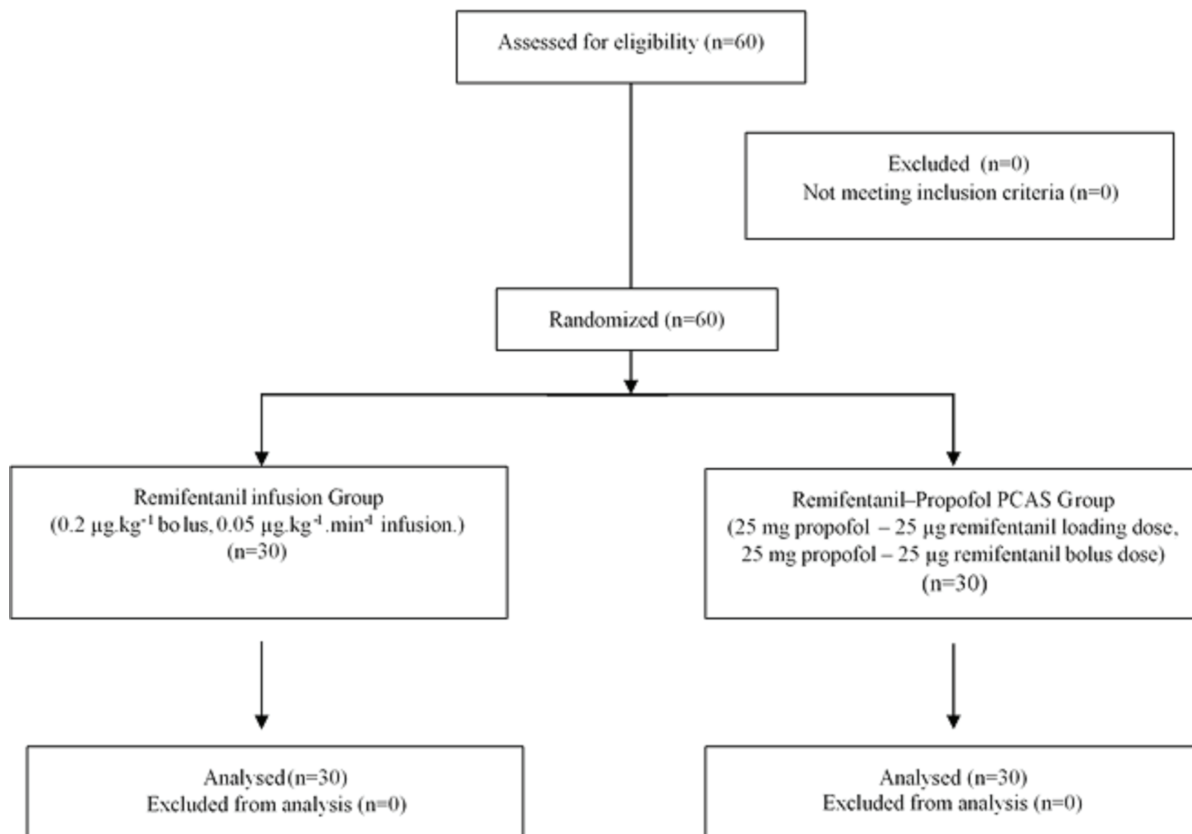


Figure 1. Flow diagram of the study

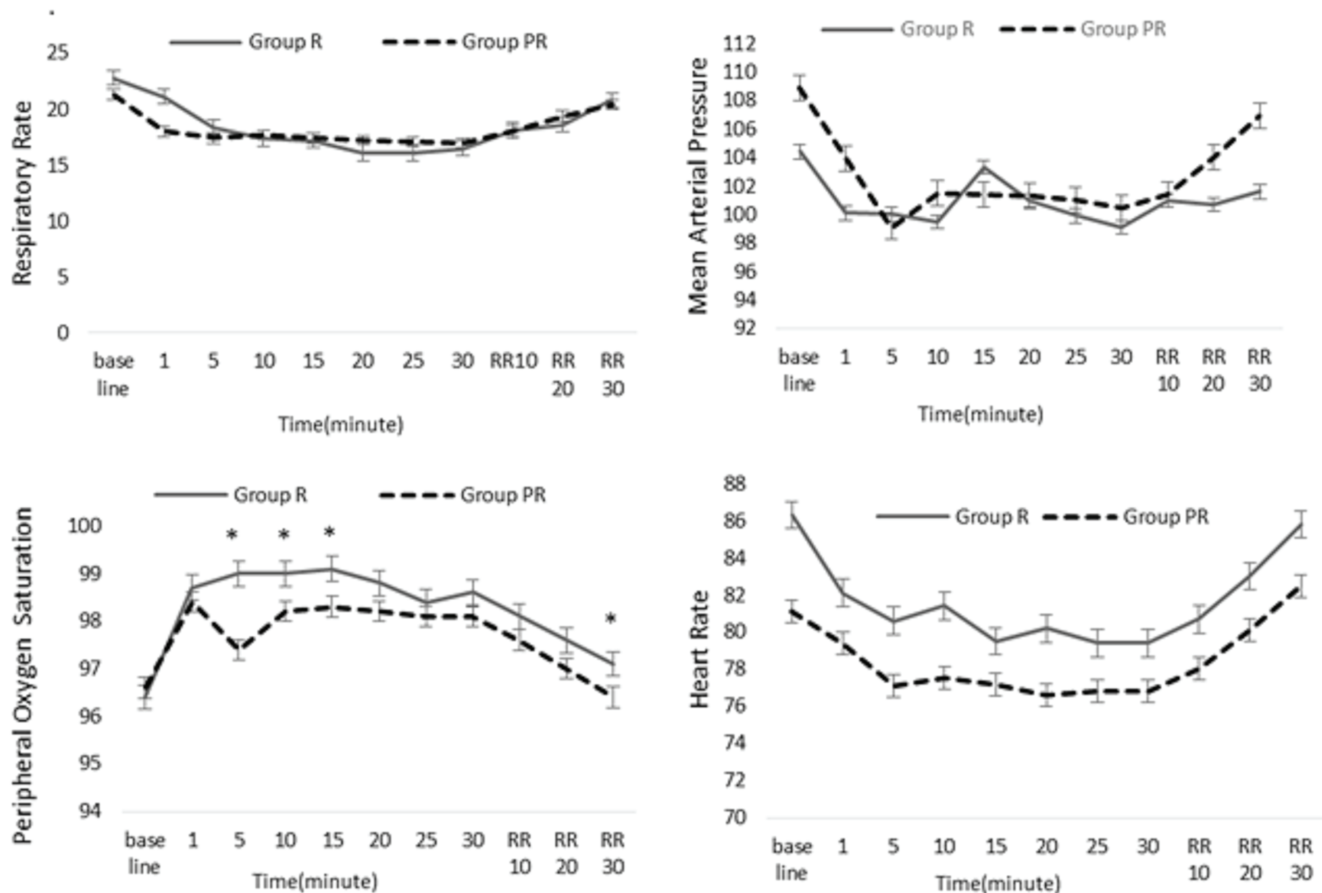


Figure 2. Mean values for respiratory rate, mean arterial pressure, peripheral oxygen saturation and heart rate recorded during procedures and recovery room. (RR; Recovery room difference between Group R and Group PR was statistically significant $p < 0.05$)

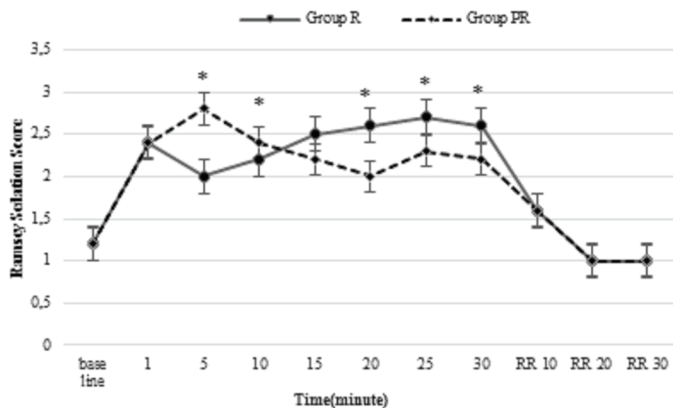


Figure 3. Mean values for Ramsey sedation score recorded during procedures and recovery room. (RR; Recovery room *difference between Group R and Group PR was statistically significant $p < 0.05$),

No significant difference was found in VAS ($P > 0.05$). Five patients in Group R were treated with 10 µg remifentanyl during the procedure because of pain. Seven patients in Group R while only one patient in Group PR required additional 1 mg midazolam ($P < 0.05$).

Dose of remifentanyl in the group R was 143 µg, while it was 45 µg in the group PR. Significant difference was observed between the groups for dose of remifentanyl ($P < 0.05$)

Anxiety levels were 1 before the procedure and 0 after

drug administration in both the groups. No significant difference was observed between the groups for anxiety levels ($P > 0.05$).

MAS was 10 in both the groups at 15 minutes in the recovery room. No significant difference was observed between the groups for MAS ($P > 0.05$).

In Group R, patient satisfaction was classified as good in 23.3%, very good in 33.3% and excellent in 43.4% of the patients although in Group PR those numbers were 10%, 30% and 60%, respectively. In Group R, radiologist satisfaction was defined as good in 16.7%, very good in 33.3% and excellent in 50% of the radiologists although those numbers became 10%, 23.3% and 66.7%, respectively, in Group PR. No significant difference was observed between the groups for patient and radiologist satisfaction ($P > 0.05$). Three patients in Group R experienced side effects such as nausea and they were treated with metoclopramide. One of them experienced vomiting.

DISCUSSION

Training, experience, preoperative plan and assessment on administering sedatives and analgesics, and careful monitoring of the patient during and after any interventional procedure increase the reliability of that

procedure (8). The method of use and administration for short-acting anesthetic agents is important, especially in the case of outside the operating room procedures.

Propofol is the most preferred agent because of easy titration, fast onset sedation and recovery, less residual effects after cessation, and lower nausea/vomiting rates (5). Opioids are widely used in painful procedures, but rarely as a single agent. Remifentanyl is a less known agent for outside the operating room procedures. Its effects start rapidly, lasting 3–10 minutes without considering the infusion period after a continuous infusion (9). The use of remifentanyl is safe; it is efficient as a potent very short-lived analgesic during painful interventional radiological procedures (9,10).

A study conducted by Akcobay et al. (11) showed a low dose remifentanyl infusion with a bolus injection at intervals to provide better analgesia than propofol and sufficient sedation/amnesia. A study performed by Joo et al. (12) compared propofol–remifentanyl PCAS and remifentanyl PCA. Propofol–remifentanyl PCAS was found to decrease the need for additional sedative and remifentanyl. Compared with propofol infusion, propofol–remifentanyl PCAS decreased the need for propofol without causing deep sedation (13).

In this study, the mean dose of remifentanyl in the remifentanyl infusion group was 143 µg, while it was only 45 µg in the propofol–remifentanyl PCAS group. According to RSS, patients given 2–3 points were included in the moderate sedation group. The average sedation score was 2.4 in the remifentanyl infusion group and 2.3 in the propofol–remifentanyl PCAS group. Anxiety scores were also similar. The moderate sedation target was acquired using both the methods and drug doses. The need for additional sedative/analgesic (7/5 patient) increased in the remifentanyl group, and only one patient needed sedation in the PCAS group. This was presumed to be related to the synergistic effect caused by the usage of both the drugs together.

Adverse events are lowered by moderate sedation during interventional radiological procedures. Hypotension is the major adverse cardiovascular event (14).

Cardiovascular depression is one of the most significant side effects of propofol causing vasodilatation and decreased systemic vascular resistance and preload. Reduction in blood pressure is more distinct considering old patients with myocardial depression and dehydration (15). Cardiovascular side effects of opioid usage include bradycardia and hypotension (16). In accordance with the literature, this study demonstrated reduced heart rate and average blood pressure means compared with baseline values in both the groups. Reductions were similar and clinically insignificant.

Oxygen desaturation is a common problem during moderate sedation. Propofol may cause airway obstruction in susceptible cases even with moderate sedation (15). It may also cause apnea and oxygen

desaturation even with common doses because of its strong respiratory depressant effects (16). Opioids cause less respiratory depression when used as a single agent than in combinations with propofol and midazolam (17). Administering propofol–remifentanyl PCAS reduces respiratory depression and airway intervention rates (18).

Factors such as obesity, history of apnea, and snoring problem leading to airway obstruction may cause desaturation. Oxygen administered via nasal cannula (2 L) is mostly sufficient. Encouraging deep breath and recuperative chin lift–jaw thrust maneuvers for head positioning can be employed in cooperative patients (19).

This study excluded patients with obesity, history of apnea, possible airway obstruction, and risk factors concerning airway safety. Only one patient in the Group R was compensated for desaturation (<90%) by increasing oxygen to 4 L and via recuperative maneuvers for head positioning. Both methods and dose adjustments employed in this study were considered suitable in terms of airway safety.

A study performed by Joo et al. (12) compared propofol–remifentanyl PCAS and remifentanyl PCA. Propofol–remifentanyl PCAS was found to decrease nausea–vomiting incidence, and increase patient satisfaction. However, temporary apnea and desaturation rates were higher.

The most significant gastrointestinal side effects of opioids are nausea and vomiting (16). In this study, nausea was seen in three patients with a remifentanyl infusion and none with propofol–remifentanyl PCAS. In the PCAS group, this may be caused by lower total remifentanyl dose and antiemetic effects of propofol. Incidences of nausea and vomiting may be declined by administering opioids as PCAS as well as in combination with propofol.

Patients may not be able to press the button or have distress due to insufficient sedation and/or analgesia during the procedures. This rate has been reported to be 3%–16% and mostly caused by procedures with too much pain or prolonged duration, inability to stand still, noncooperation, and insufficient explanation (20). Patients can be calmed down by telling them that they will be monitored continuously and interfered by their physicians if needed. Additionally, patient satisfaction and pain should be assessed separately as patients may be highly satisfied notwithstanding the pain they experience during the procedure. A prospective study conducted by Mueller et al. (21) on interventional radiological procedures found experienced patients to have less anxiety and pain regarding surgical procedures. As mentioned earlier, patient understanding and cooperation are other factors increasing satisfaction and affecting the need for sedation/analgesia. Inability to press the button and pain anxiety was encountered in the PCAS group. Patients were harmonized by their physicians telling them that they would be monitored continuously and interfered if needed. Patient and radiologist satisfaction were high

and similar in this study, although the need for analgesia and sedatives was higher in the remifentanil infusion group.

The study by Joo et al. (12) found the median times (4 minutes) to reach an Aldrete score ≥ 9 to be similar for both the PCAS remifentanil and propofol–remifentanil groups. Patients were discharged from the hospital after 67 minutes in the remifentanil group and 64 minutes in the propofol–remifentanil group. At 15 minutes, their MAS were approximately 10 in both the groups; therefore, the patients were discharged and accompanied by their companion after 30-minute observation.

This study has several limitations. First, drug concentrations vary significantly and are highly indefinite in PCA studies. Lockout intervals and individualized doses with proper monitoring are needed to prevent apnea and oxygen desaturation, especially in the case of remifentanil–propofol combination (12). Second, additional monitoring devices were not used. Especially end-tidal carbon dioxide monitoring with capnography in the spontaneously breathing patients undergoing sedation for early identification of hypoxia is important (22). Thus patient safety will increase in non-operating room.

CONCLUSION

In conclusion, although remifentanil infusion as a single agent and propofol–remifentanil PCAS have similar hemodynamic profile, sedation levels, and patient/physician satisfaction, PCAS can be preferred owing to decrease the incidence of nausea/vomiting and the need for additional analgesic and sedatives.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was conducted with the approval of Faculty Ethics Committee (Ref. no. 2009/357).

REFERENCES

- American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002;96(4):1004–17.
- McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc* 2008;67(6):910–23.
- Haytural C, Aydın B, Demir B, Bozkurt E, Parlak E, Dişibeyaz S, et al. Comparison of Propofol, Propofol-Remifentanil, and Propofol-Fentanyl Administrations with Each Other Used for the Sedation of Patients to Undergo ERCP. *Biomed Res Int*. 2015;465465.
- Karaman S, Akarsu T, Fırat V. Epidural anestezide bilinçli sedasyon; remifentanil ve propofol karşılaştırması. *Türk Anesteziyoloji ve Reanimasyon Derneği Dergisi*. 2005;33(2):313-20.
- Moran TC, Kaye AD, Mai AH, Bok LR. Sedation, analgesia, and local anesthesia: a review for general and interventional radiologists. *Radiographics* 2013;33(2):47-60.
- Agostoni M, Fanti L, Arcidiacono PG, Gemma E, G Strini Torri G, Testoni PA. Midazolam and pethidine versus propofol and fentanyl patient controlled sedation/analgesia for upper gastrointestinal tract ultrasound endoscopy: a prospective randomized controlled trial. *Dig Liver Dis* 2007;39(11):1024-9.
- McGrath B, Chung F. Postoperative recovery and discharge. *Anesthesiology Clin N Am* 2003;21(2):367-86.
- Johnson S. Sedation and analgesia in the performance of interventional procedures. *Semin Intervent Radiol* 2010;27(4):368-73.
- Parashchanka A, Schelfout S, Coppens M. Role of novel drugs in sedation outside the operating room: dexmedetomidine, ketamine and remifentanil. *Curr Opin Anaesthesiol* 2014;27(4):442-7.
- Park NS, Bae JI, Park AW, Won JH, Lee HS. Safety and effectiveness of analgesia with remifentanil for percutaneous transhepatic biliary drainage. *AJR Am J Roentgenol* 2009;192(5):1430-3.
- Akcaboy ZN, Akcaboy EY, Albayrak D, Altınoren B, Dikmen B, Gogus N. Can remifentanil be a better choice than propofol for colonoscopy during monitored anesthesia care? *Acta Anaesthesiol Scand* 2006;50(6):736-1.
- Joo HS, Perks WJ, Kataoka MT, Errett L, Pace K, Honey RJ. A comparison of patient-controlled sedation using either remifentanil or remifentanil-propofol for shock wave lithotripsy. *Anesth Analg* 2001;93(5):1227-32.
- Mazanikov M, Udd M, Kylanpää L, Mustonen H, Lindström O, Farkkila M, et al. Patient-controlled sedation with propofol and remifentanil for ERCP: a randomized, controlled study. *Gastrointest Endosc* 2011;73(29):260–6
- Arepally A, Oechsle D, Kirkwood S, Savader SJ. Safety of conscious sedation in interventional radiology. *Cardiovasc Intervent Radiol* 2001;24(3):185-90.
- Tuite C, Rosenberg EJ. Sedation and analgesia in interventional radiology. *Semin Intervent Radiol* 2005;22(2):114–20.
- Shabanie A. Conscious sedation for interventional procedures: a practical guide. *Tech Vasc Interv Radiol* 2006;9(2):84–8.
- Eberl S, Polderman JA, Preckel B, Kalkman CJ, Fockens P, Hollmann MW. Is 'really conscious' sedation with solely an opioid an alternative to every day used sedation regimes for colonoscopies in a teaching hospital? Midazolam/fentanyl, propofol/alfentanil, or alfentanil only for colonoscopy: a randomized trial. *Tech Coloproctol* 2014;18(8):745–52.
- Mandel JE, Lichtenstein GR, Metz DC, Ginsberg GG, Kochman ML. A prospective, randomized, comparative trial evaluating respiratory depression during patient-controlled versus anesthesiologist-administered propofol-remifentanil sedation for elective colonoscopy. *Gastrointest Endosc* 2010;72(1):112–3.
- Olsen JW, Borger RL, Doshi SK. Moderate sedation: what radiologists need to know. *AJR Am J Roentgenol* 2013;201(59):941–6.
- Patatas K, Koukkoulli A. The use of sedation in the radiology department. *Clin Radiol* 2009;64(8):655–63.
- Mueller PR, Biswal S, Halpern EF, Kaufman JA, Lee MJ. Interventional radiologic procedures: patient anxiety, perception of pain, understanding of procedure, and satisfaction with medication—a prospective study. *Radiology* 2000;215(3):684–8.
- Srinivasa V, Kodali BS. Capnometry in the spontaneously breathing patient. *Curr Opin Anaesthesiol* 2004;17(6):517–20.