Randomized controlled trial of the Effect of General Anesthetics on postoperative recovery after minimally Invasive Nephrectomy (REGAIN trial)

Hyun-Kyu Yoon
Seoul National University Hospital
Hyerin Kim
Seoul National University Hospital
Susie Yoon
Seoul National University Hospital
Jeong-Hwa Seo
Seoul National University Hospital
Won Ho Kim
Seoul National University Hospital
Ho-Jin Lee (zenerdiode03@gmail.com)
Seoul National University Hospital

Research Article

Keywords: Anesthetics, general, Anesthesia, Inhalation, Anesthesia, Intravenous, Enhanced recovery after surgery, Perioperative medicine, Postoperative Period

Posted Date: March 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1413541/v1

Abstract

Background: We compared the effect of general anesthetics on postoperative quality of recovery between propofol-based total intravenous anesthesia (TIVA) and inhalation anesthesia.

Methods: In this randomized, single-blinded trial, 150 patients undergoing robot-assisted or laparoscopic nephrectomy for renal cancer were randomly allocated to either the TIVA or desflurane anesthesia (DES) group. Postoperative recovery was evaluated using the Korean version of the Quality of Recovery-15 questionnaire (QoR-15K) at 24 h, 48 h, and 72 h postoperatively. A generalized estimating equation (GEE) was performed to analyze longitudinal QoR-15K data. Opioid consumption, pain severity, the occurrence of postoperative nausea and vomiting, and quality of life at three weeks after discharge were also compared.

Results: Data were analyzed for 70 patients in each group. The TIVA group showed a significantly higher QoR-15K score at 24 and 48 h postoperatively (24 h: DES, 96 [IQR: 77–109] vs. TIVA, 104 [IQR: 82–117], median difference 8 [95% CI: 1–15], $p = 0.029$; 48 h: DES, 110 [IQR: 95–128] vs. TIVA, 125 [IQR: 109–130], median difference 8 [95% CI: 1–15], $p = 0.022$), however not at 72 h ($p = 0.400$). During the entire study period, the GEE revealed significant effects of group (adjusted mean difference 6.2, 95% CI: 0.39–12.1, $p = 0.037$) and time ($p < 0.001$) on postoperative QoR-15K scores, without group-time interaction ($p = 0.051$). However, there were no significant differences at other time points and in other postoperative outcomes, except opioid consumption, during the first 24 h postoperatively.

Conclusions: Propofol-based TIVA showed only a transient and marginal improvement in postoperative recovery compared to desflurane anesthesia, which would have been difficult to lead to significant differences in other postoperative outcomes.

Trial registration: Clinicaltrials.gov, NCT04447105 (date of registration: June 25, 2020)

Introduction

General anesthetic techniques, which are divided into inhalation and intravenous anesthesia, can affect postoperative recovery. The most well-known difference between the two techniques may be the decrease in postoperative nausea and vomiting (PONV) for propofol-based total intravenous anesthesia (TIVA) compared with inhalation anesthesia (Gan et al., 2020). Previous studies have also reported that the use of propofol-based TIVA yields better outcomes than inhalation anesthesia in terms of postoperative morbidity (Ishii et al., 2016; H.-J. Lee et al., 2019; Qiu, Choi, Wong, Irwin, & Cheung 2016). Further, propofol-based TIVA may be associated with improvements in oncologic outcomes compared with inhalation anesthesia (Hasselager, Hallas, & Gögenur 2021). However, propofol-based TIVA has not yet been strongly recommended in perioperative guidelines due to the lack of strong evidence (Feldheiser et al., 2016; Gustafsson et al., 2019).

Standardized evidence-based anesthesia protocol can improve postoperative recovery and clinical outcomes (Grant et al., 2019). However, with the introduction of minimally invasive surgery and advances in perioperative medicine, the incidence of postoperative morbidity and duration of hospital stay have decreased significantly. Therefore, it is becoming increasingly difficult to identify whether treatments exert significant effects on postoperative outcomes using these traditional variables (Yoon et al., 2020). Furthermore, these variables have been reported to deviate greatly from patient-perceived postoperative recovery (Rajabiyazdi et al., 2021). In contrast, the Quality of Recovery-15 (QoR-15) questionnaire can provide a meaningful and overall assessment of patient-centered postoperative recovery (P. S. Myles 2018) and has been recommended as an endpoint in clinical studies investigating postoperative recovery (Kleif, Waage, Christensen, & Gögenur 2018; P. S. Myles et al., 2018).

This randomized controlled trial (RCT) aimed to investigate differences in postoperative quality of recovery after minimally invasive nephrectomy between two main general anesthesia techniques using the Korean version of QoR-15 (QoR-15K) (Yoon et al. 2020). We hypothesized that propofol-based TIVA would improve early postoperative recovery compared to inhalation anesthesia.

Methods

This prospective, randomized, single-blinded trial was approved by the relevant institutional review board (IRB) (2003-177-1113). Before patient enrollment, the study protocol was registered with ClinicalTrials.gov (NCT04447105). This study was performed in accordance with Good Clinical Practice Guidelines and Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz, Altman, & Moher 2010). The study adhered to the tenets outlined in the Declaration of Helsinki, and all patients provided written informed consent. Enrollment occurred at Seoul National University Hospital in South Korea between June 2020 and July 2021.

Patient selection

We screened adult patients (age: 19 to 80 years) with renal cancer scheduled to undergo elective minimally invasive nephrectomy for study eligibility. Patients with the following features were excluded: 1) American Society of Anesthesiologists (ASA) physical status ≥ III, 2) history of allergic reaction to anesthetics or analgesics included in the protocol of this study, 3) history of chronic pain defined as having taken analgesics or anticonvulsants for more than 3 months, 4) requirement of mechanical ventilation ≥ 2 hours after surgery, 5) poorly controlled psychological diseases that precluded cooperation, and 6) difficulty understanding the informed consent process or questionnaires in the Korean language.

Randomization and blinding

After enrollment, block randomization (block size: 4 and 6) was used to randomly allocate patients to the propofol-based TIVA (TIVA group) or inhaled desflurane (DES group) groups at a 1:1 ratio using R software (Version: 3.6.1, R Development Core Team, Vienna, Austria). Randomization was conducted by an anesthesiologist who was not involved in this study. Patients and the outcome assessor were blinded

to group assignments, but the attending anesthesiologists could not be blinded due to the differences in intraoperative anesthetic techniques between the groups. Information regarding the allocation order stored in an opaque envelope was delivered to the attending anesthesiologists on the day of surgery.

Anesthetic management

Without premedication, anesthesia was induced with a 1.0–2.0 mg/kg bolus dose of propofol (Fresofol MCT 1%, Fresenius Kabi Korea Ltd, Korea) and maintained with desflurane (Suprane, Baxter Healthcare, Puerto Rico) in the DES group. In the TIVA group, anesthesia was induced and maintained with a target-controlled infusion (TCI) of propofol (Fresofol MCT 2%, Fresenius Kabi Korea Ltd, Korea) using an infusion pump (Orchestra®; Fresenius Vial, Brezins, France) using the Marsh pharmacokinetic model. Other than the anesthetics used to maintain general anesthesia, the following anesthetic management procedure was identical in both groups. During induction, 5 mg of dexamethasone and 0.075 mg of palonosetron were administered for PONV prophylaxis. Remifentanil was started using a TCI using the Minto pharmacokinetic model with a target of effect-site concentration 3.0 ng/mL, then was adjusted to maintain arterial pressure within 20% of baseline ward pressure. Rocuronium was used to maintain deep neuromuscular block under monitoring with acceleromyography. The bispectral index and mean arterial blood pressure were maintained within 40–60 and 60–90 mmHg, respectively. For early postoperative pain control, 1 g of intravenous (IV) acetaminophen was injected over 30 minutes at the point of insertion of the Jackson–Pratt drains. A loading dose of IV fentanyl (50 μg) was administered following skin closure for intravenous patient-controlled analgesia (IV-PCA). Patients were extubated after administration of sugammadex for the reversal of neuromuscular blockade, following which they were transferred to the post-anesthesia care unit (PACU).

Postoperative management in the PACU and ward

Patients in the PACU were permitted to utilize IV-PCA delivered via a semi-electronic infusion pump (AutoMed 3200, ACE Medical, Seoul, Republic of Korea). The bolus dose of fentanyl and lock-out interval were 20 mcg and 10 min, respectively, and there was no basal infusion. Patients were instructed to use IV-PCA when they had a numeric rating scale (NRS) pain score ≥ 3. If pain persisted at NRS ≥ 7 despite active use of IV-PCA (four times/hour), 50 μcg of IV fentanyl was administered as the first-line rescue analgesic. Rescue antiemetics were administered upon the patient's request or when they reported moderate to severe PONV. Such treatment involved the administration of 10 mg of metoclopramide in the PACU. In the ward, initial rescue antiemesis treatment involved the administration of 0.3 mg of ramosetron, followed by 10 mg of metoclopramide as the second rescue treatment when necessary. Water sips were permitted on the morning of postoperative day (POD) 1, and a liquid and soft-blended diet was initiated in stages on the same day. An oral extended-release tramadol 37.5 mg/acetaminophen 325 mg combination tablet was routinely administered at 12-hour intervals from the morning of POD 1 until discharge. During the first 8 h postoperatively, the initial rescue analgesic was 50 mcg of IV fentanyl and then 1 g of IV acetaminophen. After taking routine oral analgesic (the morning of POD 1), the initial rescue analgesic was 650 mg of oral acetaminophen, and an alternative rescue analgesic was 50 mcg of IV fentanyl. However, when the patient complained of PONV, 1 g of IV acetaminophen was administered

at the discretion of the attending physicians. Ward ambulation was also initiated on the morning of POD 1 after radical nephrectomy and 24 h after partial nephrectomy. The Foley catheter was removed at the start of ward ambulation. During the follow-up period (until POD 3), transdermal analgesic patches, IV opioids other than fentanyl, and oral analgesics other than the tramadol/acetaminophen combination tablet were not allowed.

Outcome measures

The day before surgery, the investigators asked the patients to complete the QoR-15K and the EuroQoL 5-dimension 5-level scale (EQ-5D-5L) to measure baseline status (Kim et al., 2016). The following baseline and intraoperative variables were recorded: sex, age, body mass index, the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM score) (Prytherch et al., 1998), ASA physical status, Apfel score (Apfel, Läärä, Koivuranta, Greim, & Roewer 1999), type of surgery (radical vs. partial), type of approach (laparoscopic vs. robot-assisted), estimated blood loss (mL), intraoperative crystalloid and colloid administration (mL/kg), intraoperative transfusion, operative time (min), and intraoperative remifentanil consumption (mcg). The primary outcome was the QoR-15K score measured at 24 h postoperatively. Secondary outcomes included the QoR-15K score measured at 48 h and 72 h postoperatively; the interval of fentanyl consumption during the first 24 h and 24–48 h postoperatively; resting and movement-evoked pain intensity using an 11-point NRS at 24, 48, and 72 h postoperatively; the occurrence of PONV at 24, 48, and 72 h postoperatively; and quality of life at three weeks after discharge as measured using the EQ-5D-5L in the outpatient clinic. Considering the confusion caused by certain points of the QoR-15K for respondents (Yoon et al. 2020), all QoR-15K questionnaires were completed under the investigator's guidance. We also compared the administration of rescue analgesics other than fentanyl, serum high-sensitivity C-reactive protein on POD 3, postoperative complications classified using the Clavien–Dindo classification during hospitalization evaluated at the time of discharge (Katayama et al., 2016), acute kidney injury diagnosed based on Kidney Disease: Improving Global Outcomes criteria (Thomas et al., 2015), and length of hospital stay between the two groups. All outcomes were evaluated by physicians that were not involved in this study and were blinded to the group assignment.

Statistical analysis

Based on our previous study (Yoon et al. 2020), we assumed a QoR-15K score of 95 ± 20 at 24 h after minimally invasive nephrectomy under inhalation anesthesia. Although we were planning to investigate a QoR-15K at 48 and 72 h postoperatively, we could not consider it in sample size calculation due to the lack of relevant data. Considering a QoR-15K score of 10 as minimal clinically important difference (MCID) at 24 h postoperatively (Barrington, Seah, Gotmaker, Lim, & Byrne 2019), the sample size calculation using G*Power (version 3.1.9; Franz Faul, University of Kiel, Germany) yielded 64 patients per group to achieve a two-tailed significance of 0.05 and a power of 80%. Considering the dropout rate of 15%, a total of 150 patients were required for enrolment.

Continuous variables are reported as the mean ± standard deviation or median [interquartile range (IQR)] and were compared using Student's *t*-test or the Mann-Whitney *U*-test according to the normality of the data. Categorical variables are reported as frequencies or percentages, and were compared using the chi-square test or Fisher's exact test based on their expected frequencies. The effect size and 95% confidence interval (CI) were also calculated.

We also performed a generalized estimating equation (GEE), which is more flexible than repeated-measures analysis of variance, to analyze repeated QoR-15K score measurements (Schober & Vetter 2018). If there was no significant interaction between group and time in the GEE, we calculated the adjusted mean difference of QoR-15K score between the two groups, excluding the interaction term from the model. If a significant interaction between group and time was observed in the GEE, then post hoc pairwise multiple comparisons using least squares mean with the Bonferroni correction were performed to calculate the adjusted mean difference of QoR-15K score between the two groups at each time point. The above analysis was also performed, with Bonferroni correction, for each dimension of the QoR-15K.

All tests were two-sided, and the level of statistical significance was set at $p < 0.05$. All statistical analyses were conducted using R software (Version: 3.6.1, R Development Core Team, Vienna, Austria).

Results

Among 246 eligible patients, 96 were excluded, following which the remaining 150 patients were randomly allocated to the TIVA or DES group (Fig. 1). During the study period, ten patients were additionally excluded due to cancellation of the operation on the day of surgery (n = 4), ASA Physical Status of III on the day of surgery (n = 1), requirement of mechanical ventilation after massive intraoperative bleeding (n = 1), refusal to complete the questionnaire after surgery (n = 3), and postoperative cognitive dysfunction (n = 1). In total, 140 patients were included in the final analysis. Table 1 summarizes the baseline characteristics of the included participants, which did not significantly differ between the TIVA and DES groups, except for the amount of remifentanil administered intraoperatively (median difference: 270 [IQR: 169 to 376] mcg, $p < 0.001$).

Table 1
Baseline and perioperative characteristics of the propofol-based total intravenous anesthesia (TIVA) and inhaled desflurane (DES) groups.

Characteristics	DES group (*N* = 70)	TIVA group (*N* = 70)
Demographic variables		
Age (years)	59.0 (48.0–65.0)	60.0 (53.0–67.0)
Female	21 (30.0)	27 (38.6)
BMI (kg/m^2)	26.0 (23.7–28.2)	24.7 (22.7–27.1)
Baseline medical status		
ASA physical status, I/II	21 (30.0)/49 (70.0)	15 (21.4)/55 (78.6)
Apfel score, 1/2/3/4	31 (44.3)/21 (30.0)/17 (24.3)/1 (1.4)	25 (35.7)/21 (30.0)/21 (30.0)/3 (4.3)
POSSUM		
Physiological score	19.5 (15.0–22.0)	19.5 (16.0–21.0)
Operative severity score	8.0 (8.0–9.0)	8.0 (8.0–9.0)
Preoperative serum hs-CRP (mg/dL)	0.1 (0.0–0.2)	0.1 (0.0–0.1)
Surgical variables		
Extent of surgery		
Radical	12 (17.1)	16 (22.9)
Partial	58 (82.9)	54 (77.1)
Type of surgery		
Laparoscopic	12 (17.1)	15 (21.4)
Robot-assisted	58 (82.9)	55 (78.6)
Intraoperative variables		
Duration of surgery (min)	90.0 (75.0–115.0)	90.0 (75.0–105.0)
Intraoperative remifentanil (mcg)	653 (500.0–1000.0)	978.5 (800.0–1200.0)
Estimated blood loss (ml)	130 (60–200)	100 (50–150)

Values are expressed as mean (SD), median (IQR), number (n), and number of patients (%).

ASA, American Society of Anesthesiologists; BMI, body mass index; N/A, not applicable; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity; pRBC, packed red blood cell.

Figure 2 **and Supplemental Tables S1–4** show the comparisons of QoR-15K scores between the two groups. Eight patients (TIVA group: n = 5, DES group: n = 3) were discharged before 72 h postoperatively; thus, they could not complete the QoR-15K at that point. The TIVA group showed significantly higher QoR-15K score at 24 and 48 h postoperatively (24 h: DES, 96 [IQR: 77–109] vs. TIVA, 104 [IQR: 82–117], median difference 8 [95% CI: 1–15], $p = 0.029$; 48 h: DES, 110 [IQR: 95–128] vs. TIVA, 125 [IQR: 109–130], median difference 8 [95% CI: 1–15], $p = 0.022$), however not at 72 h (DES group, 125 [IQR: 113–137] vs. TIVA group, 129 [IQR: 115–140], median difference 3 [95% CI: -3–8], $p = 0.400$). During the entire study period, the GEE revealed significant effects of group (adjusted mean difference 6.2, 95% CI: 0.39–12.1, $p = 0.037$) and time ($p < 0.001$) on postoperative QoR-15K scores, without group-time interaction ($p = 0.051$). Among the five dimensions of the QoR-15K, only the pain dimension was significantly better in the TIVA group than in the DES group during the study period (Table 2).

Table 2

Comparison of each dimension[a] of the Korean version of the Quality of Recovery-15 (QoR-15K) [a] between the propofol-based total intravenous anesthesia (TIVA) and inhaled desflurane (DES) groups via the generalized estimating equation (GEE).

	Adjusted mean difference[b]	Corrected 95% CI	*p* value
Physical comfort (0–50) during the study period	2.0	-0.3 to 4.2	0.087
Emotional state (0–40) during the study period	1.6	-0.7 to 4.0	0.168
Psychological support (0–20)			
24 h postoperatively	0.5	-0.6 to 1.7	0.813[c]
48 h postoperatively	1.0	0.1 to 2.1	0.021[c]
72 h postoperatively	0.4	-0.3 to 0.1	0.480[c]
Physical independence (0–20)			
24 h postoperatively	1.6	1.0 to 3.0	0.033[c]
48 h postoperatively	1.0	-1.4 to 3.4	0.930[c]
72 h postoperatively	-0.5	-2.7 to 1.8	> 0.999[c]
Pain (0–20) during the study period	1.5	0.3 to 3.0	0.013

CI, confidence interval.

[a] The QoR-15K consists of 15 short-form instrument items, and these items can be classified into the following five categories: physical comfort (5 items), emotional state (4 items), psychological support (2 items), physical independence (2 items), and pain (2 items). Each item is evaluated using an 11-point numerical rating scale (0–10), and a higher score means a better recovery.

[b] Adjusted mean differences are expressed as the TIVA group versus the DES group.

[c] A Bonferroni corrected $p < 0.05$ was considered statistically significant.

Table 3 shows the comparison of other postoperative outcomes between the two groups. Fentanyl consumption during the first 24 h postoperatively was significantly lower in the TIVA group than in the DES group (adjusted median difference − 140 mcg, corrected 95% CI: − 250 to − 30 mcg, Bonferroni corrected $p = 0.008$). However, no other postoperative outcomes differed between the two groups. One hundred four patients (74.3%) completed the EQ-5D-5L questionnaire three weeks after hospital discharge (Table 4). There was no significant difference in any item of the EQ-5D-5L before surgery and after hospital discharge between the two groups.

Table 3
Comparison of secondary outcomes between the propofol-based total intravenous anesthesia (TIVA) and inhaled desflurane (DES) groups.

	DES group (*N* = 70)	TIVA group (*N* = 70)	Median or % difference[a] (95% CI)	*p* value
NRS score, at rest (0–10)				
24 h postoperatively	3 (2–5)	3 (1–5)	-1 (-1 to 0)[c]	0.453[c]
48 h postoperatively	2 (1–3)	2 (1–3)	0 (-1 to 0)[c]	0.345[c]
72 h postoperatively [b]	2 (0–3)	1 (0–2)	0 (-1 to 0)[c]	0.234[c]
NRS score, movement-evoked (0–10)				
24 h postoperatively	7 (5–8)	7 (5–8)	0 (-1 to 1)[c]	> 0.999[c]
48 h postoperatively	5 (4–7)	5 (3–6)	0 (-1 to 0)[c]	0.480[c]
72 h postoperatively [b]	3 (2–5)	3 (2–5)	0 (-1 to 0)[c]	0.564[c]
Interval fentanyl consumption (mcg)				
< 24 h	500 (300–740)	355 (210–500)	-140 (-250 to -30)[c]	0.008[c]
24–48 h	170 (60–460)	120 (40–320)	-20 (-100 to 40)[c]	0.512[c]
Early IV-PCA stop due to opioid-related side effects before 48h postoperatively	11 (15.7)	9 (12.9)	-0.03 (-0.15 to 0.09)	0.629
Rescue analgesics				
< 24 h postoperatively	12 (17.1)	5 (7.1)	-0.10 (-0.23 to 0.03)[c]	0.201[c]
Intravenous acetaminophen	5 (7.1)	0 (0)		
Oral acetaminophen	3 (4.3)	4 (5.7)		
Intravenous fentanyl	4 (5.7)	1 (1.4)		
24–48 h postoperatively	6 (8.6)	5 (7.1)	-0.01 (-0.12 to 0.09)[c]	> 0.999[c]
Intravenous acetaminophen	2 (2.9)	2 (2.9)		
Oral acetaminophen	4 (5.7)	4 (5.7)		

	DES group (*N* = 70)	TIVA group (*N* = 70)	Median or % difference[a] (95% CI)	*p* value
Intravenous fentanyl	2 (2.9)	2 (2.9)		
48–72 h postoperatively	6 (8.6)	5 (7.1)	-0.01 (-0.13 to 0.10)[c]	> 0.999[c]
Intravenous acetaminophen	2 (2.9)	1 (1.4)		
Oral acetaminophen	4 (5.7)	4 (5.7)		
Postoperative nausea and vomiting				
< 24 h postoperatively	14 (20.0)	16 (22.9)	0.03 (-0.14 to 0.19)[c]	> 0.999[c]
24–48 h postoperatively	12 (17.1)	7 (10.0)	-0.07 (-0.21 to 0.07)[c]	0.645[c]
48–72 h postoperatively	5 (7.5)	10 (15.4)	0.07 (-0.05 to 0.20)[c]	0.507[c]
Duration of PACU stay (min)	40.0 (39.0–43.0)	40.0 (39.0–44.0)	0.0 (-1.0 to 1.0)	0.772
Serum hs-CRP on POD 3 (mg/dL)	7.0 (4.4–10.4)	6.0 (3.4–7.9)	-1.2 (2.6 to 0.2)	0.081
Postoperative complications, Clavien-Dindo classification, ≥ Class I	7 (10.0)	11 (15.7)	0.06 (-0.05 to 0.17)	0.311
Class I	2 (2.9)	4 (5.7)		
Class II	5 (7.1)	6 (8.6)		
Class IIIa	0 (0)	1 (1.4)		
Postoperative AKI	18 (25.7)	16 (22.9)	-0.03 (-0.17 to 0.11)	0.693
KDIGO Stage 1	10 (14.3)	12 (17.1)		
KDIGO Stage 2	6 (8.6)	3 (4.3)		
KDIGO Stage 3	2 (2.9)	1 (1.4)		
Length of hospital stay (days)	6 (6–6)	6 (6–6)	0 (0 to 0)	0.375
Values are expressed as mean (SD), median (IQR), and number of patients (%).				

	DES group (*N* = 70)	TIVA group (*N* = 70)	Median or % difference[a] (95% CI)	*p* value

AKI, acute kidney injury; CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; hs-CRP, high-sensitivity C-reactive protein; IV-PCA, intravenous patient-controlled analgesia; IQR, interquartile range; NRS, numeric rating scale; PACU, post-anesthesia care unit; POD, postoperative day.

[a] Median or % differences are expressed as the TIVA group versus the DES group.

[b] This included 67 patients in the DES group and 65 patients in the TIVA group.

[c] Bonferroni adjustments with corrections of the 95% confidence intervals were applied to multiple comparisons. A Bonferroni corrected $p < 0.05$ was considered statistically significant.

Table 4
Comparisons of EuroQol 5-dimension instrument with a five-level scale (EQ-5D-5L) scores on the day before surgery (preoperative) and at three weeks postoperatively (early post-discharge) between the propofol-based total intravenous anesthesia (TIVA) and inhaled desflurane (DES) groups.

	Preoperative			**Early post-discharge**		
	DES (N = 70)	**TIVA (N = 70)**	p **value**	**DES (N = 50)**	**TIVA (N = 54)**	p **value**
Mobility			0.552			0.419
No problems	63 (90.0)	64 (91.4)		35 (70.0)	39 (72.2)	
Slight problems	5 (7.1)	6 (8.6)		10 (20.0)	13 (24.1)	
Moderate problems	1 (1.4)	0		5 (10.0)	2 (3.7)	
Severe problems	1 (1.4)	0		0	0	
Extreme problems or unable	0	0		0	0	
Self-care			0.513			0.568
No problems	68 (97.1)	68 (97.1)		42 (84.0)	45 (83.3)	
Slight problems	2 (2.9)	1 (1.4)		7 (14.0)	8 (14.8)	
Moderate problems	0	1 (1.4)		1 (2.0)	0	
Severe problems	0	0		0	0	
Extreme problems or unable	0	0		0	1 (1.9)	
Usual activities			0.942			0.216
No problems	64 (91.4)	65 (92.9)		27 (54.0)	28 (51.9)	
Slight problems	5 (7.1)	4 (5.7)		17 (34.0)	24 (44.4)	
Moderate problems	1 (1.4)	1 (1.4)		6 (12.0)	2 (3.7)	
Severe problems	0	0		0	0	
Extreme problems or unable	0	0		0	0	
Pain/Discomfort			0.818			0.572
No problems	51 (72.9)	53 (75.7)		18 (36.0)	20 (37.0)	
Slight problems	17 (24.3)	16 (23.2)		24 (48.0)	29 (53.7)	

Values are expressed as number of patients (%).

IQR, interquartile range.

	Preoperative			Early post-discharge		
Moderate problems	2 (2.9)	1 (1.4)		8 (16.0)	5 (9.3)	
Severe problems	0	0		0	0	
Extreme problems or unable	0	0		0	0	
Anxiety/Depression			0.758			0.547
No problems	36 (51.4)	36 (51.4)		33 (66.0)	31 (57.4)	
Slight problems	30 (42.9)	28 (40.0)		12 (24.0)	14 (25.9)	
Moderate problems	4 (5.7)	5 (7.1)		5 (1.0)	9 (16.7)	
Severe problems	0	1 (1.4)		0	0	
Extreme problems or unable	0	0		0	0	
Visual analog scale, mm (0-100)	80 (70–90)	80 (80–90)	0.607	80 (70–85)	80 (70–80)	0.178
Values are expressed as number of patients (%).						
IQR, interquartile range.						

Discussion

The difference in postoperative quality of recovery between the two groups varied depending on the time after surgery. Although propofol-based TIVA significantly improved the quality of recovery at 24 and 48 h after minimally invasive nephrectomy compared with desflurane anesthesia, their effect size was smaller than the predefined MCID. Furthermore, this difference did not remain at 72 h postoperatively. There was no significant difference between the two groups in any other postoperative clinical outcomes, including quality of life, at three weeks after discharge.

Several studies have investigated the effect of general anesthetic techniques on postoperative recovery using the QoR-40 (De Oliveira, Bialek, Rodes, Kendall, & McCarthy 2017; Joe et al., 2021; W. K. Lee, Kim, Kang, Kim, & Lee 2015; Liu, Gu, Chen, & Shen 2019; Na, Jeong, Eum, Park, & Kim 2018; Niu et al., 2021; Park et al., 2020). An RCT including female patients undergoing thyroid surgery reported the superiority of propofol-based TIVA for early postoperative recovery, mainly due to the reduction in PONV (W. K. Lee et al. 2015). However, differences in patient characteristics and insufficient PONV prophylaxis made this result difficult to apply to other surgeries, and subsequent RCTs have yielded conflicting results (De Oliveira et al. 2017; Joe et al. 2021; Liu et al. 2019; Na et al. 2018; Niu et al. 2021; Park et al. 2020). Moreover, in most previous studies, outcomes were assessed only within POD 1, except in two recently published RCTs (Joe et al. 2021; Niu et al. 2021). One involving patients undergoing pancreatectomy reported that postoperative recovery was significantly better on POD 3 in the propofol-based TIVA group than in the

DES group (Joe et al. 2021). However, the clinical implications of a significant difference only on POD 3 may be debatable considering the relatively long length of hospital stay following pancreatectomy. Rather, this difference seen only on POD 3 might have resulted from the transient effect of type of general anesthetic techniques, similar to our result. Another recent RCT for laparoscopic hysterectomy reported no significant difference between the two techniques in terms of postoperative recovery (Niu et al. 2021). However, the study only included relatively young female patients, making the results difficult to generalize. Additionally, unlike this study, transient but significant improvement of early postoperative recovery in the TIVA group could accept the improvement of early postoperative recovery in the TIVA reported in several studies (W. K. Lee et al. 2015; Liu et al. 2019; Na et al. 2018; Park et al. 2020).

Our study differs from previous investigations in that we aimed to mitigate the impact of the antiemetic effect of propofol-based TIVA by implementing multimodal PONV prophylaxis in both groups, in accordance with recent guidelines (Gan et al. 2020). Furthermore, we included the patients undergoing minimally invasive cancer surgeries. Given the growing interest in the effects of anesthetic type on oncologic outcomes (Hasselager et al. 2021; Makito, Matsui, Fushimi, & Yasunaga 2020; Wall, Sherwin, Ma, & Buggy 2019), our study may provide additional meaningful information regarding anesthetic selection in the patients undergoing cancer surgeries. We also reduced the impact of confounding factors on postoperative recovery using a homogeneous sample of patients and a standardized perioperative protocol. Lastly, we used the QoR-15, which has higher clinical feasibility than the QoR-40 (Stark, Myles, & Burke 2013) and was the first validated measurement for postoperative recovery under the standardized criteria (Kleif et al. 2018). Therefore, our results may provide more reliable information regarding the effect of general anesthetic techniques on postoperative recovery.

The main perceived advantages of propofol-based TIVA compared to desflurane anesthesia in this study were its opioid-sparing effect and improvement of pain dimension in the QoR-15K. Propofol may improve postoperative pain through its anti-inflammatory and antioxidant effects and antagonistic effects at NMDA receptors, which can play an important role in pain signaling (Qiu et al. 2016; Shin et al., 2010). Several meta-analyses have supported the superiority of propofol-based TIVA for improving postoperative pain compared with inhalation anesthesia (Peng et al., 2016; Qiu et al. 2016; Schraag et al., 2018). However, since the analgesic effect of propofol-based TIVA can vary depending on the degree of surgical trauma and postoperative pain management, our results should be interpreted cautiously. In an aforementioned RCT that addressed laparoscopic hysterectomy outcomes, no differences in postoperative recovery were observed between propofol-based TIVA and sevoflurane anesthesia (Niu et al. 2021). In this study, the intensity of postoperative pain was low, indicating that propofol-based TIVA may not have induced a significant difference in postoperative pain outcomes. Additionally, regional analgesia—which was not included in our study—can negate the analgesic and opioid-sparing effects of propofol-based TIVA (Dam et al., 2021), which may further contribute to insignificant differences in QoR-15 scores between the two groups.

Our findings suggested that propofol-based TIVA improved postoperative recovery during the early postoperative period, which is also in line with the opinion of anesthesiologists who participated in a

relevant survey (79% somewhat to strongly agreed that TIVA leads to superior quality of recovery) (Lim, Braat, Hiller, & Riedel 2018). However, considering its transient and marginal effect during hospitalization and the time course of postoperative recovery in our patients, it may be difficult to show that propofol-based TIVA leads to significant improvements in other postoperative outcomes.

Our study has several limitations. First, as this study was a single-blinded RCT, some biases may have influenced our results. However, although attending anesthesiologists could not be blinded, the investigator who evaluated postoperative outcomes was completely blinded to the group allocation. Second, the sample size was calculated based on the QoR-15K score at 24 h postoperatively, according to our previous study (Yoon et al. 2020), although this was not sufficiently powered to detect significant differences in other outcomes. Additionally, we considered a QoR-15K score of 10 as the MCID, greater than the previously reported MCID of 8 for the QoR-15 (Paul S. Myles et al., 2016). In the planning stage of this study, we initially considered a QoR-15K score of 8 to be MCID based on the previous study (Paul S. Myles et al. 2016). However, considering the difference in QoR-15K scores between the two groups may decrease over time after surgery (W. K. Lee et al. 2015), we had set the MCID of 10 at 24 h postoperatively as the primary outcome, which was a greater value than 8. Thus, we recalculated the sample size before patient enrollment after the approval of IRB. Third, our study was conducted at a single tertiary university hospital and thus may not reflect perioperative management at other institutions. Fourth, there was a significant difference in the total amount of intraoperative remifentanil used between the two groups. The type of general anesthesia technique and amount of intraoperative remifentanil could have affected postoperative pain severity and opioid consumption (Shin et al. 2010). Although we assumed that this difference would have been due to the vasodilatory or analgesic effect of desflurane (Ryu et al., 2020; Ryu et al., 2018), we found it difficult to explain the mechanism behind this difference from our results. However, since there was no significant difference in postoperative pain severity, but rather, less postoperative opioid consumption in the TIVA group, the difference in intraoperative remifentanil amount would not have had a significant effect on our primary and secondary outcomes. Lastly, since we followed the conventional discharge criteria determined by attending surgeons, this may explain why a significant difference in postoperative recovery during the early postoperative period did not lead to significant differences in the length of hospital stay. Further research is required to investigate the clinical impact of these two anesthetic techniques under a discharge protocol adjusted according to the degree of postoperative recovery. Despite these limitations, to our best knowledge, this is the first study to evaluate the impact of general anesthetic techniques on the quality of postoperative recovery, as measured using the QoR-15K in patients undergoing minimally invasive cancer surgeries.

In conclusion, our findings indicate that propofol-based TIVA provides better early postoperative recovery at 24 and 48 h postoperatively than inhalation anesthesia. However, this transient and marginal improvement did not last until 72 h postoperatively. Additionally, this transient and slight improvement led to no significant differences in other postoperative outcomes, including quality of life, at the early discharge phase of our study. However, considering our modest sample size, further studies with sufficient power are needed to establish a standardized anesthetic technique to improve postoperative recovery.

Abbreviations

PONV
postoperative nausea and vomiting
TIVA
total intravenous anesthesia
QoR-15
Quality of Recovery-15
RCT
randomized controlled trial
QoR-15K
Korean version of QoR-15
IRB
institutional review board
CONSORT
Consolidated Standards of Reporting Trials
ASA
American Society of Anesthesiologists
TCI
target-controlled infusion
IV
intravenous
IV-PCA
intravenous patient-controlled analgesia, PACU:post-anesthesia care unit
NRS
numeric rating scale
POD
postoperative day
EQ-5D-5L
EuroQoL 5-dimension 5-level scale
POSSUM
Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
MCID
minimal clinically important difference
IQR
interquartile range
CI
confidence interval
GEE
generalized estimating equation

Declarations

Ethics approval and consetn to participate

Obtained

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contribution

HKY: Conception, design of the study, data curation, writing manuscript, visualization, HJL: Conception, design of the study, data curation, writing manuscript, project administration, supervision, SY: Formal analysis, writing manuscript, visualization, HK, JHS: Data curation, formal analysis, WHK: Formal analysis, writing-review & editing.

Acknowledgments

We would like to thank the Division of Statistics in the Medical Research Collaborating Centre at Seoul National University Hospital for helping with statistical analyses.

References

1. Apfel, C. C., Läärä, E., Koivuranta, M., Greim, C.-A., & Roewer, N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91(3):693–700.
2. Barrington, M. J., Seah, G. J., Gotmaker, R., Lim, D., & Byrne, K. Quality of recovery after breast surgery: a multicenter randomized clinical trial comparing pectoral nerves interfascial plane (pectoral nerves II) block with surgical infiltration. Anesth Analg. 2019;130(6):1559–67.

3. Dam, M., Hansen, C., Poulsen, T. D., Azawi, N. H., Laier, G. H., Wolmarans, M., et al. Transmuscular quadratus lumborum block reduces opioid consumption and prolongs time to first opioid demand after laparoscopic nephrectomy. Reg Anesth Pain Med. 2021;46(1):18–24. https://doi:10.1136/rapm-2020-101745.
4. De Oliveira, G. S., Bialek, J., Rodes, M. E., Kendall, M. C., & McCarthy, R. J. The effect of sevoflurane compared to propofol maintenance on post-surgical quality of recovery in patients undergoing an ambulatory gynecological surgery: A prospective, randomized, double-blinded, controlled, clinical trial. J Clin Anesth. 2017;43:70–4. https://doi:10.1016/j.jclinane.2017.10.001.
5. Feldheiser, A., Aziz, O., Baldini, G., Cox, B. P. B. W., Fearon, K. C. H., Feldman, L. S., et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand. 2016;60(3):289–334. https://doi:10.1111/aas.12651.
6. Gan, T. J., Belani, K. G., Bergese, S., Chung, F., Diemunsch, P., Habib, A. S., et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg. 2020;131(2):411–48. https://doi:10.1213/ANE.0000000000004833.
7. Grant, M. C., Roda, C. M. P., Canner, J. K., Sommer, P., Galante, D., Hobson, D., et al. The impact of anesthesia-influenced process measure compliance on length of stay: results from an enhanced recovery after surgery for colorectal surgery cohort. Anesth Analg. 2019;128(1):68–74.
8. Gustafsson, U. O., Scott, M. J., Hubner, M., Nygren, J., Demartines, N., Francis, N., et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. World J Surg. 2019;43(3):659–95. https://doi:10.1007/s00268-018-4844-y.
9. Hasselager, R. P., Hallas, J., & Gögenur, I. Inhalation or total intravenous anaesthesia and recurrence after colorectal cancer surgery: a propensity score matched Danish registry-based study. Br J Anaesth. 2021;126(5):921–30. https://doi:10.1016/j.bja.2020.11.019.
10. Ishii, K., Makita, T., Yamashita, H., Matsunaga, S., Akiyama, D., Toba, K., et al. Total intravenous anesthesia with propofol is associated with a lower rate of postoperative delirium in comparison with sevoflurane anesthesia in elderly patients. J Clin Anesth. 2016;33:428–31. https://doi:10.1016/j.jclinane.2016.04.043.
11. Joe, Y. E., Kang, C. M., Lee, H. M., Kim, K. J., Hwang, H. K., & Lee, J. R. Quality of Recovery of Patients Who Underwent Curative Pancreatectomy: Comparison of Total Intravenous Anesthesia Versus Inhalation Anesthesia Using the QOR-40 Questionnaire. World J Surg. 2021;45(8):2581–90. https://doi:10.1007/s00268-021-06117-0.
12. Katayama, H., Kurokawa, Y., Nakamura, K., Ito, H., Kanemitsu, Y., Masuda, N., et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surg Today. 2016;46(6):668–85.
13. Kim, S.-H., Ahn, J., Ock, M., Shin, S., Park, J., Luo, N., et al. The EQ-5D-5L valuation study in Korea. Qual Life Res. 2016;25(7):1845–52.

14. Kleif, J., Waage, J., Christensen, K. B., & Gögenur, I. Systematic review of the QoR-15 score, a patient-reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth. 2018;120(1):28–36. https://doi:10.1016/j.bja.2017.11.013.
15. Lee, H.-J., Bae, J., Kwon, Y., Jang, H. S., Yoo, S., Jeong, C. W., et al. General Anesthetic Agents and Renal Function after Nephrectomy. J Clin Med. 2019;8(10):1530. https://doi:10.3390/jcm8101530.
16. Lee, W. K., Kim, M. S., Kang, S. W., Kim, S., & Lee, J. R. Type of anaesthesia and patient quality of recovery: a randomized trial comparing propofol–remifentanil total i.v. anaesthesia with desflurane anaesthesia. Br J Anaesth. 2015;114(4):663–8. https://doi:10.1093/bja/aeu405.
17. Lim, A., Braat, S., Hiller, J., & Riedel, B. Inhalational versus Propofol-Based Total Intravenous Anaesthesia: Practice Patterns and Perspectives among Australasian Anaesthetists. Anaesth Intensive Care. 2018;46(5):480–7. https://doi:10.1177/0310057x1804600509.
18. Liu, T., Gu, Y., Chen, K., & Shen, X. Quality of recovery in patients undergoing endoscopic sinus surgery after general anesthesia: total intravenous anesthesia vs desflurane anesthesia. Int Forum Allergy Rhinol. 2019;9(3):248–54. https://doi:10.1002/alr.22246.
19. Makito, K., Matsui, H., Fushimi, K., & Yasunaga, H. Volatile versus Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery. Anesthesiology. 2020;133(4):764–73. https://doi:10.1097/aln.0000000000003440.
20. Myles, P. S. Measuring quality of recovery in perioperative clinical trials. Curr Opin Anaesthesiol. 2018;31(4):396–401. https://doi:10.1097/ACO.0000000000000612.
21. Myles, P. S., Boney, O., Botti, M., Cyna, A. M., Gan, T. J., Jensen, M. P., et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. Br J Anaesth. 2018;120(4):705–11. https://doi:10.1016/j.bja.2017.12.037.
22. Myles, P. S., Myles, D. B., Galagher, W., Chew, C., Macdonald, N., & Dennis, A. Minimal Clinically Important Difference for Three Quality of Recovery Scales. Anesthesiology. 2016;125(1):39–45. https://doi:10.1097/aln.0000000000001158.
23. Na, S. H., Jeong, K. H., Eum, D., Park, J. H., & Kim, M. S. Patient quality of recovery on the day of surgery after propofol total intravenous anesthesia for vitrectomy: A randomized controlled trial. Medicine (Baltimore). 2018;97(40):e12699. https://doi:10.1097/MD.0000000000012699.
24. Niu, Z., Gao, X., Shi, Z., Liu, T., Wang, M., Guo, L., et al. Effect of total intravenous anesthesia or inhalation anesthesia on postoperative quality of recovery in patients undergoing total laparoscopic hysterectomy: A randomized controlled trial. J Clin Anesth. 2021;73:110374. https://doi:10.1016/j.jclinane.2021.110374.
25. Park, J., Kim, M., Park, Y. H., Shim, J. W., Lee, H. M., Kim, Y. S., et al. Comparison of the effects of intravenous propofol and inhalational desflurane on the quality of early recovery after hand-assisted laparoscopic donor nephrectomy: a prospective, randomised controlled trial. BMJ Open. 2020;10(12):e039881. https://doi:10.1136/bmjopen-2020-039881.
26. Peng, K., Liu, H. Y., Wu, S. R., Liu, H., Zhang, Z. C., & Ji, F. H. Does Propofol Anesthesia Lead to Less Postoperative Pain Compared With Inhalational Anesthesia?: A Systematic Review and Meta-

analysis. Anesth Analg. 2016;123(4):846–58. https://doi:10.1213/ANE.0000000000001504.

27. Prytherch, D., Whiteley, M., Higgins, B., Weaver, P., Prout, W., & Powell, S. POSSUM and Portsmouth POSSUM for predicting mortality. Journal of British Surgery. 1998;85(9):1217–20.
28. Qiu, Q., Choi, S. W., Wong, S. S. C., Irwin, M. G., & Cheung, C. W. Effects of intra-operative maintenance of general anaesthesia with propofol on postoperative pain outcomes - a systematic review and meta-analysis. Anaesthesia. 2016;71(10):1222–33. https://doi:10.1111/anae.13578.
29. Rajabiyazdi, F., Alam, R., Pal, A., Montanez, J., Law, S., Pecorelli, N., et al. Understanding the meaning of recovery to patients undergoing abdominal surgery. JAMA surgery. 2021;156(8):758–65.
30. Ryu, K.-H., Hwang, S.-H., Shim, J.-G., Ahn, J.-H., Cho, E.-A., Lee, S.-H., et al. Comparison of vasodilatory properties between desflurane and sevoflurane using perfusion index: a randomised controlled trial. Br J Anaesth. 2020;125(6):935–42. https://doi:10.1016/j.bja.2020.07.050.
31. Ryu, K.-H., Song, K., Lim, T.-Y., Choi, W.-J., Kim, Y.-H., & Kim, H.-S. Does Equi–Minimum Alveolar Concentration Value Ensure Equivalent Analgesic or Hypnotic Potency? Anesthesiology. 2018;128(6):1092–8. https://doi:10.1097/aln.0000000000002158.
32. Schober, P., & Vetter, T. R. Repeated Measures Designs and Analysis of Longitudinal Data: If at First You Do Not Succeed-Try, Try Again. Anesth Analg. 2018;127(2):569–75. https://doi:10.1213/ANE.0000000000003511.
33. Schraag, S., Pradelli, L., Alsaleh, A. J. O., Bellone, M., Ghetti, G., Chung, T. L., et al. Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: a systematic review and meta-analysis. BMC Anesthesiol. 2018;18(1):1–9.
34. Schulz, K. F., Altman, D. G., & Moher, D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8(1):18. https://doi:10.1186/1741-7015-8-18.
35. Shin, S. W., Cho, A. R., Lee, H. J., Kim, H. J., Byeon, G. J., Yoon, J. W., et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. Br J Anaesth. 2010;105(5):661–7. https://doi:10.1093/bja/aeq257.
36. Stark, P. A., Myles, P. S., & Burke, J. A. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology. 2013;118(6):1332–40.
37. Thomas, M. E., Blaine, C., Dawnay, A., Devonald, M. A., Ftouh, S., Laing, C., et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015;87(1):62–73.
38. Wall, T., Sherwin, A., Ma, D., & Buggy, D. J. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. Br J Anaesth. 2019;123(2):135–50. https://doi:10.1016/j.bja.2019.04.062.
39. Yoon, S., Joo, H., Oh, Y. M., Lee, J., Bahk, J.-H., & Lee, H.-J. Validation and clinical utility of the Korean version of the Quality of Recovery-15 with enhanced recovery after surgery: a prospective observational cohort study. Br J Anaesth. 2020;125(4):614–21. https://doi:10.1016/j.bja.2020.06.040.

Figures

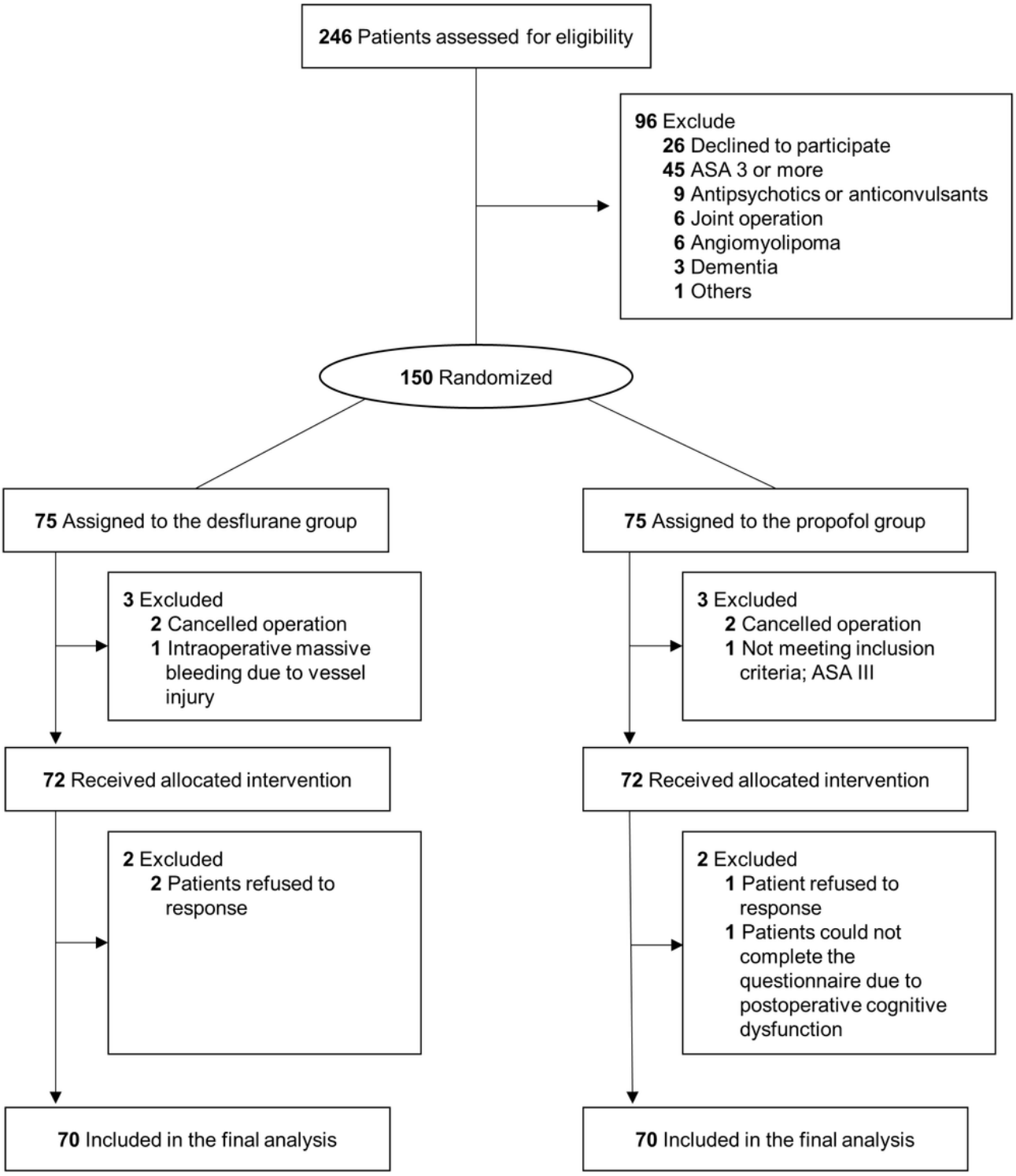

Figure 1

Consolidated Standards of Reporting Trials flow diagram.

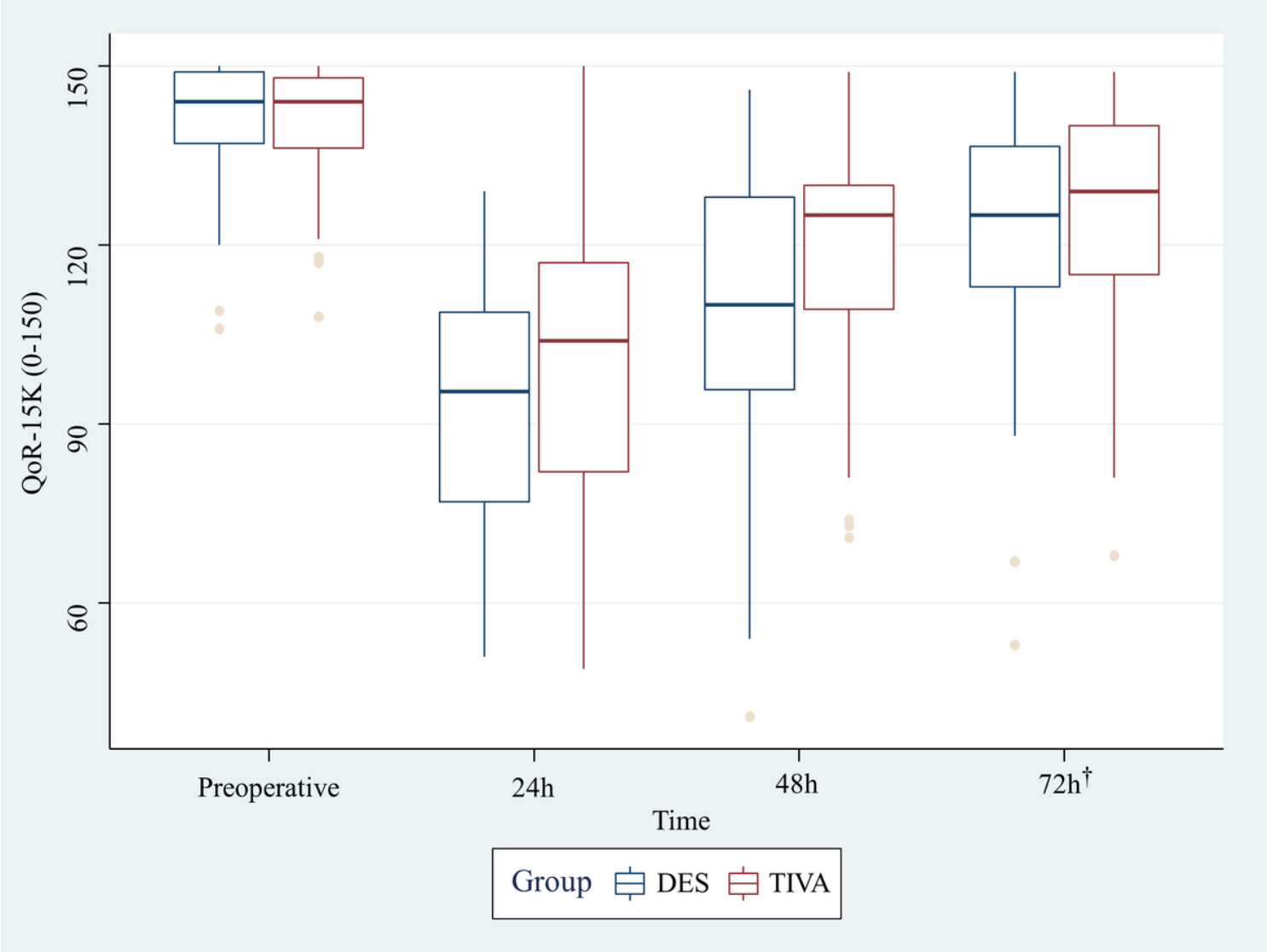

Figure 2

Comparison of scores on the Korean version of the Quality of Recovery-15 (QoR-15K) between the propofol-based total intravenous anesthesia (TIVA) and inhaled desflurane (DES) groups. Data are shown as the mean and standard deviation. GEE: generalized estimating equation. * Group, time, and group-time interaction were adjusted in the GEE model. †This included 67 patients in the DES group and 65 patients in the TIVA group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTableQORPM220228.docx