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Original Contribution

# Desflurane versus sevoflurane anesthesia and postoperative recovery in older adults undergoing minor- to moderate-risk noncardiac surgery – A prospective, randomized, observer-blinded, clinical trial

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## HIGHLIGHTS

- Older adults are at-risk for prolonged recovery after volatile anesthesia.
- The effect of desflurane versus sevoflurane on recovery is not entirely clear.
- Postoperative recovery was not significantly faster after desflurane anesthesia.
- PONV, delirium and cognitive dysfunction were similar between the groups.

## ARTICLE INFO

*Keywords:*
Desflurane
Sevoflurane
Minor noncardiac surgery
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Same-day surgery

## ABSTRACT

*Study objective:* The effect of volatile anesthetics on postoperative recovery in older adults is still not entirely clear. Thus, we evaluated the effect of desflurane versus sevoflurane anesthesia on speed of postoperative recovery in older adults eligible for same-day discharge. We further evaluated the incidence of postoperative nausea and vomiting (PONV), bispectral index (BIS) values, and S100—B concentrations.
*Design:* Single-center, prospective, observer-blinded, randomized clinical trial.
*Setting:* Operating room.
*Patients:* 190 patients ≥65 years of age and scheduled for minor- to moderate-risk noncardiac surgeries.
*Interventions:* Goal-directed administration of desflurane versus sevoflurane for maintenance of anesthesia with an intraoperative goal of BIS 50 ± 5.
*Measurements:* The primary outcome was the time to anesthesia recovery, which was defined as the time between arrival at the post-anesthesia care unit (PACU) and reaching criteria for discharge from PACU, based on modified Aldrete score ≥ 12 points. Modified Aldrete scores were assessed at PACU arrival and thereafter in five-minute intervals. PONV was evaluated during PACU stay and the first three postoperative days, BIS values were recorded during PACU stay, and S100—B values were measured before and after surgery, and on the second postoperative day.
*Main results:* 95 patients were randomized to receive desflurane, and 95 patients to receive sevoflurane. We did not observe a significant difference in median duration of postoperative recovery between the groups

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(desflurane: 0 min [0;0]; sevoflurane: 0 min [0;0]; $p = 0.245$). 77 patients (81.1%) in the desflurane group and 84 patients (88.4%) in the sevoflurane group already had Aldrete scores ≥12 points upon arrival at PACU ($p = 0.277$). There was also no significant difference in the incidences of PONV ($p = 0.606$), postoperative BIS values ($p = 0.197$), and postoperative maximum S100—B concentrations ($p = 0.821$) between the groups.
*Conclusions:* Despite previous reports, we did not observe significant faster recovery times after desflurane anesthesia. Both volatile anesthetics may be appropriate for same-day discharge in older adults.

## 1. Introduction

The number of surgical procedures with same-day hospital discharge in older adults has been steadily increasing over the last decade [1,2]. It is known that context-sensitive decrement times of volatile anesthetics are impaired in older adults, which is associated with prolonged recovery times after anesthesia [3–6]. In this context, it has been shown that early readiness for discharge from the post-anesthesia care unit is significantly associated with a lower incidence of postoperative complications requiring intervention on the ward and should thus be targeted [7].

A recent large, randomized trial has shown that maintenance of anesthesia with sevoflurane leads to a higher incidence of postoperative delirium in older adult patients undergoing major cancer surgery [8]. Although it is well known that volatile anesthetics differ in their pharmacokinetic characteristics [3–6], studies comparing their effects on postoperative recovery are still limited. In this context, time to extubation, opening of eyes and orientation is significantly faster after desflurane anesthesia as compared to sevoflurane anesthesia [9–13]. The differences in their clinical characteristics are due to their underlying pharmacokinetics, specifically the lower blood/gas partition coefficient of desflurane of 0.45 as compared to sevoflurane's coefficient of 0.65, which leads to a faster systemic elimination of desflurane [6]. Thus, it might be possible that faster recovery after desflurane anesthesia is associated with faster neurocognitive recovery and finally with a faster return to pre-anesthetic cognitive capacity [14,15]. In fact, previous studies comparing desflurane versus sevoflurane were relatively small with an average number of patients per study of approximately 100 patients [16], and were powered to detect only differences in emergence times, e.g. eye opening, but did not evaluate their influence on postoperative recovery [9–11,16]. More importantly, the choice of the anesthetic for maintenance of anesthesia in older adults is still mainly based on the preference of the attending anesthetists rather than on scientific evidence [17].

Therefore, we evaluated the primary hypothesis that maintenance of anesthesia with desflurane will result in a significantly shorter postoperative recovery – defined as reaching a modified Aldrete score ≥ 12 points – as compared to sevoflurane in older adults undergoing minor- to moderate-risk noncardiac surgery. Additionally, we compared incidences of postoperative nausea and vomiting (PONV), postoperative bispectral index (BIS) values, and postoperative maximum S100—B concentrations, which is a laboratory marker for blood-brain barrier impairment and has been shown to be significantly increased in patients with postoperative delirium [18]. It has further been shown that postoperative S100—B concentrations can be used as a possible risk-stratifier for the development of postoperative delirium [19]. Furthermore, we also compared the incidences of postoperative delirium and postoperative cognitive dysfunction within 30 days after surgery between the groups.

## 2. Materials and methods

### 2.1. Study design and participants

This prospective randomized, observer-blinded, single-center clinical trial was conducted at the Medical University of Vienna after approval by the local Institutional Review Board (Ethics Committee of the Medical University of Vienna, Registration number: 1111/2022) and registration at ClinicalTrials.gov (Registration number NCT05331027, Date of registration 15th April 2022) and at the European Clinical Trial Database (Registration number: EudraCT 2022–000556-11, Date of registration 9th February 2022). We obtained written informed consent from all patients before surgery. Patients, who met the following criteria were eligible for inclusion: (1) ≥ 65 years of age; (2) scheduled for elective minor- to moderate-risk noncardiac surgery with planned duration of surgery ≤2 h (defined in eAppendix 1 in the Online Supplement). Patients meeting one of the following criteria were excluded: (a) Emergency surgery; (b) Bariatric surgery; (c) Documented dementia or neurologic disorder; (d) Language, vision or hearing impairments that may compromise cognitive assessments; (e) Malignant hyperthermia; (f) Structural muscle disease.

### 2.2. Randomization and masking

We randomized patients shortly before induction of anesthesia at 1:1 ratio to maintenance of anesthesia with either desflurane or sevoflurane, respectively. We used a web-based randomization program (Randomizer, Medical University of Graz, Graz, Austria; https://www.meduniwien.ac.at/randomizer/web) using permutated blocks.

Patients randomly assigned to the desflurane group received desflurane for maintenance of anesthesia after endotracheal intubation with an intraoperative goal of a bispectral index (BIS) 50 ± 5 (Bispectral Index™, Medtronic©, Minneapolis, United States of America). Patients randomly assigned to the sevoflurane group received sevoflurane for maintenance of anesthesia after endotracheal intubation with an intraoperative goal of a bispectral index (BIS) 50 ± 5.

The attending anesthesiologist was not blinded to the allocated group. Study personnel involved in randomizations and intraoperative study procedures were not involved in outcome assessment. Blinded study personnel performed postoperative visits of study participants, which included drawing of blood samples as well as phone follow-ups. Both patients and blinded study personnel were not informed about the randomized allocation. They further had no access to electronic anesthesia documentation. We trained all study personnel for the assessments of our study specific outcomes.

### 2.3. Anesthesia protocol

We avoided preoperative anxiolytic medication in study patients. All patients were monitored with an ECG, non-invasive blood pressure, $SpO_2$ and BIS before induction of anesthesia. We standardized anesthesia according to the study protocol as follows: induction of anesthesia: bolus administration of 1 $\mu g.kg^{-1}$.body $weight^{-1}$ (BW) remifentanil, 1 $mg.kg^{-1}.BW^{-1}$ propofol, and 0.6 $mg.kg^{-1}.BW^{-1}$ rocuronium. One minute after induction, we performed an evaluation of BIS values. Intubation was performed if BIS values were lower than 60. If BIS values were higher than 60, we administered a second bolus of 0.5 $mg.kg^{-1}.BW^{-1}$ propofol before intubation. All patients received 4 mg of dexamethasone for PONV prophylaxis.

We performed maintenance of anesthesia according to the allocated randomized group using desflurane or sevoflurane in a mixed oxygen carrier gas using a fresh gas flow rate of 0.5 $L.min^{-1}$. Continuous infusion of remifentanil starting with a rate of 0.1 $\mu g.kg^{-1}.min^{-1}$, was used for maintaining intraoperative analgesia. If heart rate increased by 20%

within five minutes and no changes in blood pressure or BIS values were observed, we increased the rate of remifentanil infusion by 0.05 $\mu g.kg^{-1}.min^{-1}$. No additional boli of remifentanil were administered after induction of anesthesia. Patients did not receive local or regional anesthesia in addition to general anesthesia.

We set tidal volume between 6 and 8 mL lean body weight to maintain end-tidal $CO_2$ within 35-40 mmHg in all patients. Intraoperative vasopressor and fluid management was performed at the discretion of the attending anesthesiologist to maintain a minimum mean arterial pressure of 65 mmHg according to clinical standard of care. All patients were actively warmed using convective warming to maintain normothermia. We avoided administration of atropine, scopolamine, and clonidine during surgery.

According to our study protocol, we stopped the administration of volatile agent and discontinued infusion of remifentanil at the end of skin closure. We further administered 1000 mg paracetamol in all patients. Thereafter, the fresh gas flow rate with 100% oxygen was set to the maximum. All patients received 200 mg sugammadex for complete reversal of muscle relaxation. If reversal of muscle relaxation was insufficient (Train of Four stimulation <x90%), a second dose of 200 mg sugammadex was administered. Patients having general or gynecologic surgery received 0.05 $mg.kg^{-1}.BW^{-1}$ piritramide after extubation. Patients having endoscopic urologic surgery received 0.025 $mg.kg^{-1}.BW^{-1}$ piritramide after extubation. Patients were extubated according to clinical extubation criteria.

In the PACU, nurses administered 0.05 $mg.kg^{-1}.BW^{-1}$ piritramide when the numeric pain rating scale (NRS) was ≥4 according to standard clinical care. Study associated NRS score assessments were performed every 10 min by blinded study investigators. A NRS score of 0 indicates no pain, a NRS of 10 indicates worst possible pain.

### 2.4. Measurements

We recorded baseline demographic data including age, sex, weight, American Society of Anesthesiologists (ASA) physical status as well as comorbidities, long-term medication, and type of surgery. We further recorded routine intraoperative data including duration of anesthesia and surgery, amount of fluid administration, medications, vasopressors, hemodynamic and respiratory data, and continuous BIS values. Volatile anesthetic concentrations were recorded continuously and converted to minimum alveolar concentration (MAC) equivalents and expressed as an age-adjusted fraction. We also recorded the overall amount of postoperative piritramide and non-opioid analgesics at PACU.

### 2.5. Primary outcome

For our primary outcome, we evaluated the time to anesthesia recovery, which was defined as the time between arrival at PACU and reaching criteria for discharge from PACU, based on modified Aldrete score ≥ 12 points [20]. The modified Aldrete score consists of seven modalities (activity, respiration, circulation, consciousness, oxygenation, pain, emetic symptoms) with a score of 0–2 points in each criterion [20]. The modified Aldrete score was first assessed at arrival at PACU and thereafter repeated every five minutes until ≥12 points were reached for a maximum of 90 min. However, we observed an unexpected large number of patients with Aldrete score ≥ 12 points already at arrival to PACU. To evaluate the primary outcome in more detail, we additionally investigated the categorized binary outcome modified Aldrete score < 12 points at PACU arrival "Yes" versus "No".

### 2.6. Secondary outcomes

We recorded postoperative BIS values at PACU and further recorded the number of patients experiencing postoperative nausea or vomiting during PACU stay and for the first three postoperative days. Specifically, we asked patients for any subjective symptom of nausea or the occurrence of vomiting (defined as a PONV episode) throughout PACU stay and on the ward twice daily within the first three postoperative days.

### 2.7. Exploratory outcomes

We measured serum S100—B concentrations before surgery for baseline assessment, within one hour after surgery, and on the second postoperative day. We recorded the incidences of postoperative delirium using the 3D-Cognitive Assessment Method (3D-CAM) on the evening of the day of surgery and in the morning and evening for the first three postoperative days if the patient was not discharged. Postoperative cognitive dysfunction (POCD) was evaluated using the adapted Montreal Cognitive Assessment (telephone MoCA) before surgery for baseline assessment and 30 days after surgery via phone call [21,22].

### 2.8. Data management

Blinded research staff obtained all outcome data. Electronic data were recorded in the data management system "Clincase", version 2.7.0.12 hosted by IT Systems and Communications, Medical University of Vienna, Vienna, Austria.

### 2.9. Statistical analysis

All analyses were performed using the intention-to-treat sample, the primary outcome parameter was additionally analyzed using a per-protocol sample. Continuous variables were summarized using mean, standard deviation, median, and interquartile range. Categorical variables were summarized using absolute numbers and percentages.

For our primary outcome, which was the time between arrival at PACU and reaching an Aldrete score ≥ 12 points in PACU, we first performed a Wilcoxon test. Due to the large number of patients with Aldrete score ≥ 12 points at arrival at PACU, the outcome was additionally categorized into a binary variable modified Aldrete score < 12 points upon PACU arrival "Yes" or "No", "Yes" indicating that no sufficient postoperative recovery was reached already at PACU arrival. This binary outcome was first analyzed using a Chi-square test. Furthermore, to exploratory evaluate potential associations of factors as age, BMI, sex, ASA physical status, hypertension, cerebrovascular disease, TIA, and/or stroke, type of surgery, duration of anesthesia, amount of postoperative piritramide, intraoperative mean arterial pressure with the binary outcome, univariable logistic regression models with Firth correction (due to the small number of events) were performed. All variables being significant in the univariable models were additionally re-analyzed using a multivariable logistic regression model.

For our secondary outcomes we compared postoperative BIS values between the groups using Wilcoxon tests. Furthermore, univariable median regression models were performed for the group variable as well as same factors as for the primary outcome. All variables being significant in the univariable models, were analyzed using a multivariable regression model. The incidences of early PONV and late PONV were analyzed similar to the primary binary endpoint using logistic regression models.

For our exploratory outcomes, we compared maximum postoperative S100—B concentrations between the groups using Wilcoxon tests. The incidences of postoperative delirium and POCD, were analyzed similar to the primary binary endpoint. The analyses for postoperative delirium additionally included the postoperative S100—B concentrations as potential confounding factor. The analyses for POCD additionally accounted for baseline and postoperative S100—B concentrations and baseline MOCA scores as potential confounders.

All $p$-values <0.05 were considered as statistically significant. All analyses were performed using R, release 4.2.2.

### 2.10. Sample size

We estimated the number of patients required for this trial based on a previous trial, which evaluated the effect of desflurane-based versus sevoflurane-based anesthesia on postoperative recovery [12]. The median time to meet PACU discharge criteria was 71 ± 10 min in patients, who received sevoflurane, as compared to approximately 56 ± 20 min in the desflurane group [12]. Based on that, a reduction in time at PACU of 10 min (±20 min) was defined as clinically meaningful, therefore assuming a probability of 0.362 that an observation X in one group will be less than an observation Y in the other group. Using a Mann-Whitney-*U* test with a two-sided significance level of 0.05, a sample size of 92 patients per group was calculated to achieve a power of 0.9. We assumed a drop-out rate of 3%, resulting in 190 patients (95 patients per group).

## 3. Results

### 3.1. Patient characteristics

We enrolled 190 patients between May 2022 and April 2023 at the Medical University of Vienna. 95 patients were randomized to receive desflurane and 95 patients to receive sevoflurane. The enrolment of patients stopped after we reached our target sample size of 190 patients. Two patients in the desflurane group received sevoflurane due to

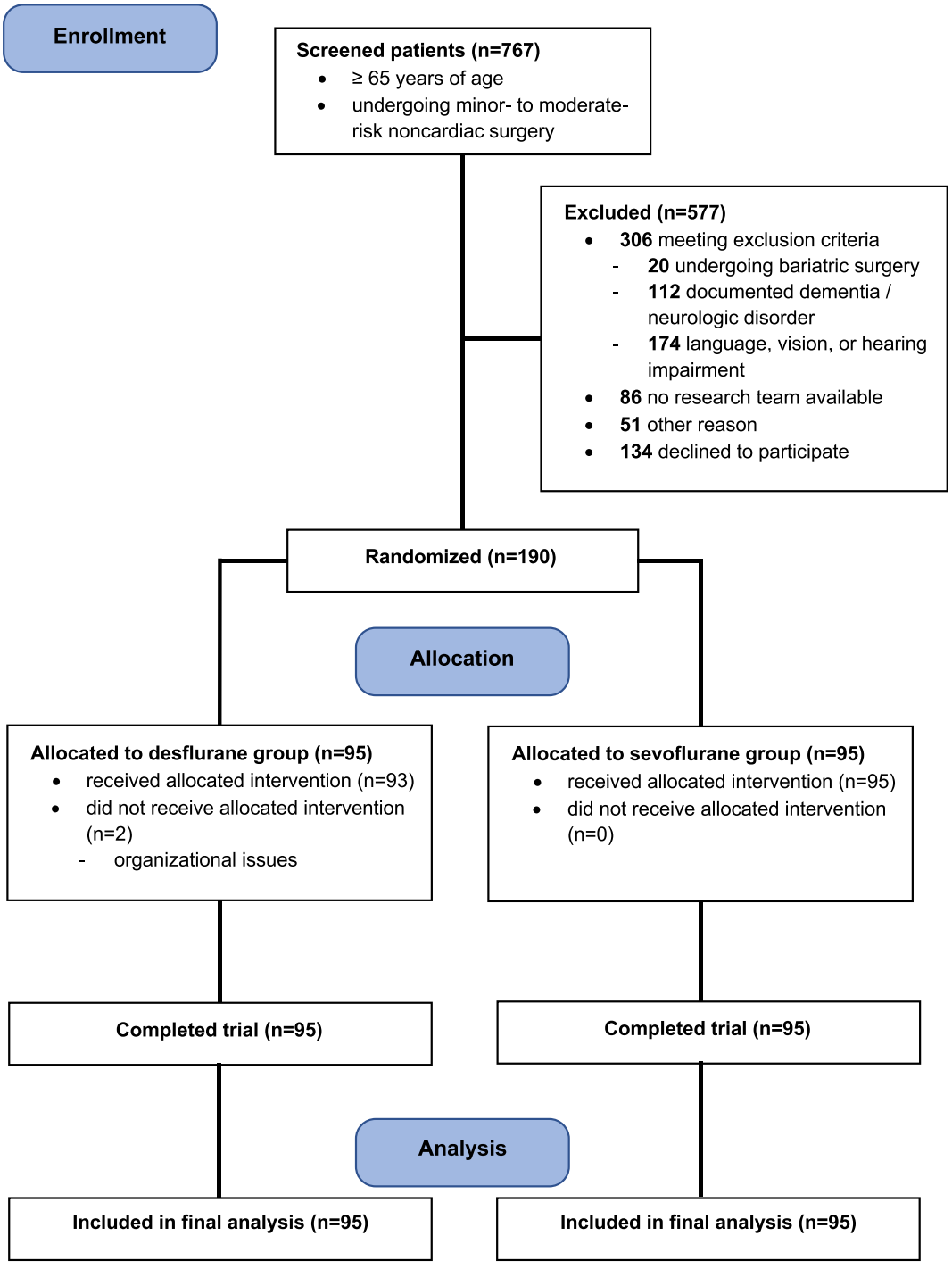


**Fig. 1.** Patient Flow Diagram; Design and form in accordance with the 2010 CONSORT guidelines [42].

organizational issues. (Fig. 1).

Baseline characteristics of patients including age, sex, BMI, ASA physical status, comorbidities, and long-term medications were balanced between the groups. (Table 1) Perioperative characteristics including type of surgery, duration of surgery and anesthesia, transfer time between operating room and PACU, fluid and vasopressor management were similar between the groups. (Table 2) Intraoperative mean arterial pressure and heart rate were significantly lower in the sevoflurane group. Intraoperative minimum alveolar concentration (MAC) fractions were significantly lower in the desflurane group (0.48) as compared to the sevoflurane group (0.58; $p < 0.001$). Mean intraoperative BIS values were 50 ± 7 in the desflurane group and 52 ± 6 in the sevoflurane group ($p = 0.071$). Detailed courses of intraoperative BIS values are presented in eFigure 1a and eFigure 1b of the Online Supplement. Number of patients in hospital at each postoperative timepoint are presented in eFigure 2 of the Online Supplement.

**Table 1**
Patient baseline characteristics. Summary characteristics are presented as counts (percentages) of patients or median [25th quartile; 75th quartile].

| | | Desflurane ($n$ = 95) | | Sevoflurane (n = 95) | |
|---|---|---|---|---|---|
| Age, *yrs.* | | 73 | [70; 80] | 73 | [70; 78] |
| Height, *cm* | | 170 | [164; 176] | 170 | [161; 178] |
| Weight, *kg* | | 75 | [66; 86] | 77 | [66; 87] |
| BMI, $kg*m^{-2}$ | | 26.0 | [23.5; 30.2] | 26.3 | [23.8; 28.7] |
| *Sex, n (%)* | Female | 44 | (46.3) | 46 | (48.4) |
| | Male | 51 | (53.7) | 49 | (51.6) |
| *ASA, n (%)* | I-II | 52 | (54.7) | 49 | (51.6) |
| | III | 43 | (45.3) | 46 | (48.4) |
| *Comorbidities, n (%)* | Hypertension | 55 | (57.9) | 57 | (60.0) |
| | Coronary artery disease | 7 | (7.3) | 9 | (9.5) |
| | Peripheral artery disease | 2 | (2.1) | 4 | (4.2) |
| | Carotid artery stenosis | 6 | (6.3) | 10 | (10.5) |
| | TIA/Stroke | 6 | (6.3) | 3 | (3.2) |
| | Atrial fibrillation | 21 | (22.1) | 12 | (12.6) |
| | COPD | 16 | (16.8) | 11 | (11.6) |
| | Diabetes | 18 | (18.9) | 20 | (21.1) |
| | Hyperlipidemia | 33 | (34.7) | 31 | (32.6) |
| | Smoking <2 years | 17 | (17.9) | 6 | (6.3) |
| *Long-term medication, n (%)* | Beta blockers | 30 | (31.6) | 30 | (31.6) |
| | ACE-I / ARB | 45 | (47.4) | 47 | (49.5) |
| | $Ca^{2+}$ channel blockers | 21 | (22.1) | 22 | (23.2) |
| | Diuretics | 16 | (16.8) | 24 | (25.3) |
| | Statin | 37 | (38.9) | 31 | (32.6) |
| | Acetylsalicylic acid | 20 | (21.1) | 22 | (23.2) |
| | Oral anticoagulant | 19 | (20.0) | 15 | (15.8) |
| | Metformin | 9 | (9.5) | 15 | (15.8) |
| *Type of Surgery, (%)* | Minor general | 12 | (12.6) | 7 | (7.4) |
| | Thyroidectomy | 3 | (25.0) | 2 | (28.6) |
| | Parathyroidectomy | 2 | (16.7) | 1 | (14.3) |
| | Lap. cholecystectomy | 2 | (16.7) | 1 | (14.3) |
| | Inguinal hernia surgery | 2 | (16.7) | 0 | (0) |
| | Lap. fundoplication surgery | 0 | (0) | 1 | (14.3) |
| | Ileostomy surgery | 2 | (16.7) | 0 | (0) |
| | Other | 1 | (8.3) | 2 | (28.6) |
| | Minor urologic | 53 | (55.8) | 49 | (51.6) |
| | TUR-B | 35 | (66.0) | 37 | (75.5) |
| | TUR-P | 11 | (20.8) | 7 | (14.3) |
| | Other | 7 | (13.2) | 5 | (10.2) |
| | Minor gynecologic | 30 | (31.6) | 39 | (41.1) |
| | Lap. ovariectomy | 1 | (3.3) | 1 | (2.6) |
| | Lap. salpingectomy | 4 | (13.3) | 5 | (12.8) |
| | Lap. hysterectomy | 6 | (20.0) | 4 | (10.3) |
| | Mamma resection | 19 | (63.3) | 29 | (74.4) |

BMI, body mass index; ASA, American Society of Anesthesiologists physical status; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE—I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; Lap., laparoscopic; TUR-B, transurethral resection of the bladder; TUR-P, transurethral resection of the prostate.

### 3.2. Primary outcome

There was no significant difference in the median duration to reach postoperative Aldrete scores ≥12 points in PACU between the desflurane group and the sevoflurane group (0 min [0;0] vs. 0 min [0;0]) in the intention-to-treat analysis ($p = 0.245$). In more detail, 77 patients (81.1%) in the desflurane group and 84 patients (88.4%) in the sevoflurane group already had Aldrete scores ≥12 points upon arrival at PACU (Chi-Square test: $p = 0.277$, Logistic regression with Firth Correction: OR 0.584; 95% CI: 0.247–1.327; $p = 0.200$).

In the univariable logistic regression models to evaluate potential further factors associated the binary categorization of the outcome (patients, who did or did not have ≥12 points upon PACU arrival), history of stroke and/or TIA, and the amount of postoperative piritramide were statistically significant in the univariable regression models and remained significant in the multivariable logistic regression model (TIA/Stroke OR 6.022; 95%CI: 1.416–26.405; $p = 0.016$; Piritramide OR 1.168; 95%CI: 1.065–1.228; $p = 0.001$) (Table 3).

We also performed a per-protocol analysis. There was also no significant difference between mean durations to reach postoperative Aldrete scores ≥12 points in PACU in the desflurane group and the sevoflurane group (0 [0;0] vs. 0 [0;0]; $p = 0.393$). The number of patients with Aldrete scores ≥12 points upon arrival at PACU were also not significantly different between the groups ($p = 0.435$).

### 3.3. Secondary outcomes

#### 3.3.1. Postoperative BIS values

Postoperative BIS values during PACU stay did not differ significantly between the desflurane group (94 [91;96]) and the sevoflurane group (93 [89;96]; $p = 0.197$). (eFigure 1c in the Online Supplement) In the median univariable regression model randomized group had no significant effect on postoperative BIS values (OR -0.726; 95%CI: −2.443–0.992; $p = 0.409$) (eTable 1 in the Online Supplement).

#### 3.3.2. Postoperative nausea and vomiting (PONV)

The incidence of early PONV (defined as PONV during PACU stay) did not differ significantly between the groups (three patients in the desflurane group, one patient in the sevoflurane group; $p = 0.606$). None of the evaluated factors were significantly associated with early PONV. (eTable 2 in Online Supplement).

The incidence of late PONV (defined as PONV after PACU stay in the first three postoperative days) did not differ significantly between the groups (26 (28%) patients in the desflurane group, 17 (18.5%) patients in the sevoflurane group; $p = 0.176$) (Fig. 2). The univariable logistic regression model showed no significant effect of desflurane versus sevoflurane on the incidence of late PONV (OR 0.590; 95%CI: 0.293–1.166; $p = 0.130$) (eTable 3 in the Online Supplement).

### 3.4. Exploratory outcomes

There was no significant difference in postoperative maximum S100—B concentrations between the desflurane and sevoflurane groups (0.11 $\mu g.L^{-1}$ [0.07;0.16] versus 0.10 $\mu g.L^{-1}$ [0.07;0.15]; $p = 0.821$) (Fig. 3). In the univariable logistic regression model randomized group was also not significant (OR 0.593; 95%CI: −0.071–1.258; $p = 0.082$) (eTable 4 in the Online Supplement).

There was no significant difference in the incidence of postoperative delirium between the desflurane group (7.4%) and the sevoflurane group (7.4%; $p = 1.000$). In the univariable logistic regression model for postoperative delirium randomized group was not statistically

**Table 2**
Perioperative characteristics. Summary characteristics of perioperative variables are presented as median [25th quartile; 75th quartile] or counts (percentages) of patients. All *p*-values are for Wilcoxon signed-rank tests.

| | Desflurane (n = 95) | | Sevoflurane (n = 95) | | | *p*-value |
|---|---|---|---|---|---|---|
| Duration of anesthesia, *min* | | 83 | [54; 109] | 80 | [58; 106] | 0.868 |
| Duration of surgery, *min* | | 55 | [28; 82] | 53 | [33; 75] | 0.746 |
| Duration transfer to PACU, *min* | | 8 | [7; 9] | 8 | [6; 9] | 0.888 |
| | Crystalloids, *ml* | 500 | [500; 1000] | 500 | [500; 1000] | 0.215 |
| | Propofol, *mg* | 90 | [70; 112] | 80 | [70; 105] | 0.505 |
| | Remifentanil, *mg* | 0.67 | [0.41; 1.02] | 0.61 | [0.43; 0.86] | 0.498 |
| | Rocuronium, *mg* | 50 | [40; 60] | 40 | [40;50] | 0.127 |
| | Phenylephrine, *mg* | 0.14 | [0.08; 0.24] | 0.22 | [0.1; 0.4] | 0.188 |
| | Etilefrine, *mg* | 4.0 | [2; 5.5] | 2.0 | [2.0; 3.5] | 0.247 |
| | Piritramide, *mg* | 3.0 | [2.0; 3.8] | 3.0 | [2.2; 3.5] | 0.436 |
| | HR, $beats.min^{-1}$ | 61 | [56; 67] | 58 | [54; 64] | **0.026** |
| | MAP, *mmHg* | 80 | [75; 87] | 77 | [72; 82] | **0.010** |
| | $etCO_2$, *mmHg* | 35 | [33; 37] | 35 | [33; 37] | 0.62 |
| | $FiO_2$, *%* | 50 | [43; 57] | 50 | [45; 57] | 0.332 |
| | insp. Agent, *%* | 3.4 | [2.9; 3.8] | 1.3 | [1.1; 1.4] | **<0.001** |
| | expir. Agent, *%* | 2.9 | [2.4; 3.3] | 1.0 | [0.9; 1.1] | **<0.001** |
| | Ta, *C°* | 36.4 | [36.1; 36.7] | 36.3 | [36.0; 36.5] | 0.304 |
| | BIS | 51 | [45; 55] | 52 | [48; 56] | 0.071 |
| *Intraoperative management* | MAC fraction | 0.48 | [0.37; 0.55] | 0.58 | [0.49; 0.70] | **<0.001** |
| | Piritramide, *mg* | 3.7 | [0.0; 7.5] | 3.0 | [0.0; 6.0] | 0.395 |
| | Diclofenac, *no. (%)* | 18 | (19.0) | 11 | (11.6) | 0.158 |
| | Metamizole, *no. (%)* | 41 | (43.2) | 33 | (34.7) | 0.234 |
| | Droperidol, *no. (%)* | 14 | (14.7) | 9 | (9.5) | 0.266 |
| | Ondansetron, *no. (%)* | 9 | (9.5) | 10 | (10.5) | 0.809 |
| | HR, $beats.min^{-1}$ | 72 | [64; 82] | 70 | [63; 80] | 0.363 |
| | MAP, *mmHg* | 111 | [101; 120] | 108 | [99; 116] | 0.098 |
| *At PACU* | NRS | 3 | [2; 5] | 2 | [0; 4] | 0.098 |

PACU, post-anesthesia care unit; HR, heart rate; MAP, mean arterial pressure; $etCO_2$, end-tidal carbon dioxide concentration; $FiO_2$, fraction of inspired oxygen; Ta, temperature; BIS, bispectral index; MAC, minimum alveolar concentration; NRS, numeric pain rating scale.

**Table 3**
Univariable logistic regression model (with Firth correction) and multivariable logistic regression model for the primary outcome parameter modified Aldrete score < 12 points at PACU arrival.

| Variable | | Comparison | Odds Ratio | Lower 95% CL | Upper 95% CL | *p*-Value |
|---|---|---|---|---|---|---|
| | Randomization group | Sevoflurane vs. Desflurane | 0.584 | 0.247 | 1.327 | 0.200 |
| | Age | | 1.037 | 0.974 | 1.102 | 0.250 |
| | BMI | | 1.001 | 0.946 | 1.017 | 0.911 |
| | Sex | Male vs. Female | 1.299 | 0.573 | 3.017 | 0.532 |
| | ASA | III vs. I-II | 1.384 | 0.593 | 3.279 | 0.450 |
| | Hypertension | Yes vs. No | 0.787 | 0.347 | 1.809 | 0.568 |
| | Carotid artery stenosis | Yes vs. No | 1.038 | 0.196 | 3.683 | 0.959 |
| Univariable logistic regression analysis | TIA/Stroke | Yes vs. No | 8.953 | 2.362 | 35.801 | **0.002** |
| | *Type of surgery* | | | | | |
| | | Urologic vs. General | 1.187 | 0.322 | 6.412 | 0.812 |
| | | Gynecologic vs. General | 1.235 | 0.317 | 6.859 | 0.776 |
| | | Gynecologic vs. Urologic | 1.041 | 0.430 | 2.446 | 0.928 |
| | Duration of anesthesia | | 1.007 | 0.997 | 1.016 | 0.155 |
| | Piritramide at PACU | | 1.191 | 1.088 | 1.311 | **<0.001** |
| | Intraoperative MAP | | 1.018 | 0.974 | 1.060 | 0.410 |
| Multivariable logistic regression analysis | TIA/Stroke | Yes vs. No | 6.002 | 1.416 | 26.405 | **0.016** |
| | Piritramide at PACU | | 1.168 | 1.065 | 1.288 | **0.001** |

CL, confidence limit; BMI, body mass index; ASA, American Society of Anesthesiologists physical status; TIA, transient ischemic attack; PACU, post-anesthesia care unit; MAP, mean arterial pressure.

significant (OR 1.000; 95%CI: 0.341–2.930; $p = 1.000$) (eTable 5 and eFigure 3 in the Online Supplement).

There was no significant difference in the incidence of POCD within 30 days after surgery between the desflurane group (4.2%) and the sevoflurane group (10.5%; $p = 0.159$). The univariable logistic regression models also showed no significant difference between the desflurane and sevoflurane groups (OR 1.084; 95%CI: 0.892–1.339; $p = 0.424$) (eTable 6 in the Online Supplement).

## 4. Discussion

In this prospective, randomized clinical trial we did not observe a significant difference in recovery from anesthesia between desflurane versus sevoflurane in older adults undergoing minor- to moderate-risk noncardiac surgery. Furthermore, we did not observe a significant difference in postoperative BIS values, the incidences of early and late PONV, postoperative maximum S100—B concentrations, and incidences of postoperative delirium or cognitive dysfunction between the groups.

In contrast to our results, previous studies indicated that recovery from anesthesia is significantly faster when using desflurane as compared to sevoflurane [9,10,12,13,15]. In fact, Heavner et al. observed a significantly faster early recovery (based on Aldrete score assessments) and an approximately 15 min faster intermediate recovery (based on Digit-Symbol-Substitution Tests) in the desflurane group [12].

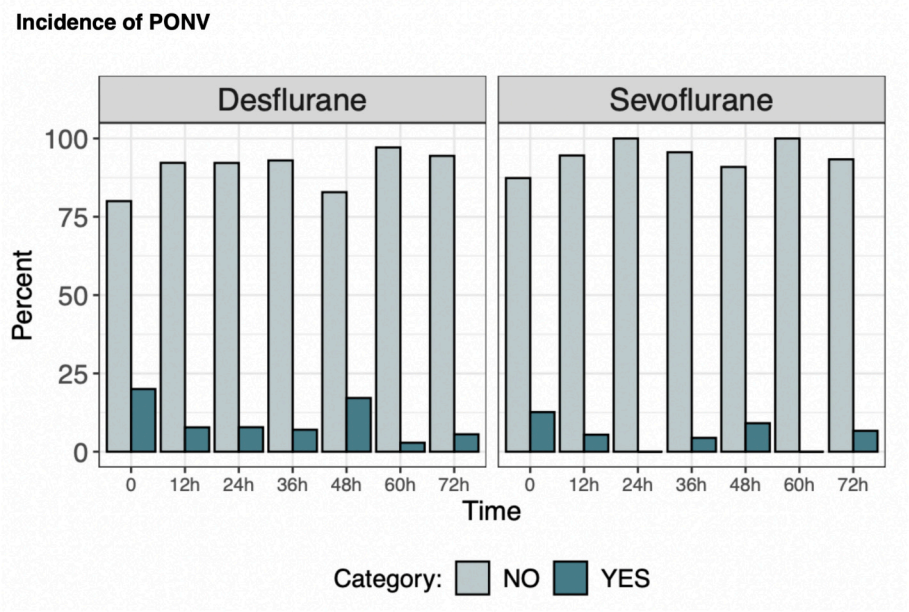


**Fig. 2.** Incidence of late PONV. Bar chart representing the incidence of late PONV on each assessment timepoint separately for the desflurane and sevoflurane groups.

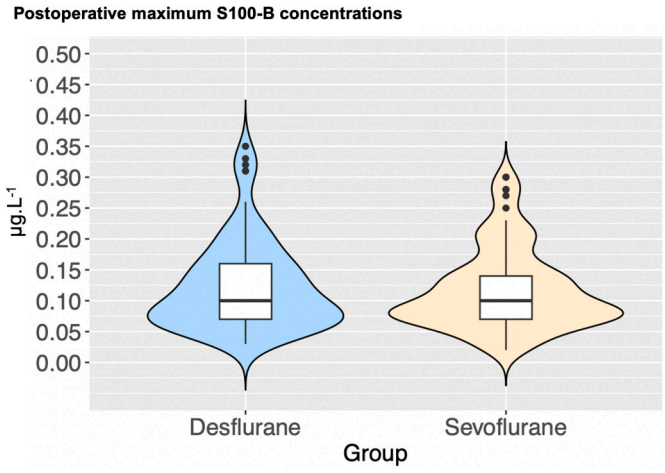


**Fig. 3.** Violin plots showing the distribution of postoperative maximum S100—B concentrations separately for the desflurane group (blue) and the sevoflurane group (yellow). Boxplots demonstrate medians and interquartile ranges, dots represent outliers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

However, duration of anesthesia was nearly twice as long as compared to our study [12]. It is known that context-sensitive decrement times of volatile anesthetics are mainly dependent on the blood/gas solubility coefficients and further on duration of anesthesia [23,24]. The significance of duration of anesthesia was demonstrated in a previous study, which showed that an administration of more than two hours leads to a steep increase in the 90% decrement time of sevoflurane but remains almost unaffected when using desflurane [23].

Another explanation for our results might be that in contrast to most previous studies, we performed BIS-guided anesthesia according to our study protocol. Specifically, we guided anesthesia to BIS values of 50 ± 5, which resulted in lower concentrations as previously described. In fact, the median intraoperative minimum alveolar concentration (MAC) was 0.48 in the desflurane group and 0.58 in the sevoflurane group. Interestingly, patients in the sevoflurane group required significantly higher minimum alveolar concentration (MAC) fractions to achieve our pre-specified BIS goal as compared to patients in the desflurane group. Although we included older adults, who are known to undergo age-related physiologic changes, for example an increase in the body fat compartment, decrease of alveolar surface area and a decrease in cardiac output [25], we did not observe a difference in recovery times. Thus, the combination of the short administration time and the relatively low concentrations of administered anesthetics might be the most reasonable cause for our observations. This might be further underlined by our observed postoperative BIS values during PACU stay, which differed only slightly between the groups. In fact, we observed very short postoperative recovery times in both groups. Thus, our results highlight that pharmacokinetics of desflurane and sevoflurane play a negligible role on neurocognitive recovery after short procedures. A strength of our study is that although we only included surgeries eligible for same-day discharge [2], patients stayed longer in the hospital according to our clinical standard and the discretion of the attending surgeon, respectively. Therefore, we were also able to test for possible long-term effects of desflurane versus sevoflurane on neurocognitive function after minor surgery. Interestingly, we observed an overall incidence of postoperative delirium of 7.4% and an incidence of POCD of 7.4% but they did not significantly differ between the groups.

The evidence regarding a possible higher risk after desflurane as compared to sevoflurane on the occurrence of PONV is still not entirely cleared. On the one hand, one meta-analysis, which included over 500 patients, showed a significantly increased risk for PONV within the first postoperative day after using desflurane [26]. On the other hand, another meta-analysis, which included 1498 patients, did not observe a significant difference in the incidence of PONV [16]. This is consistent with our findings. We did also not observe a significant difference in the incidences of early and late PONV between the groups. An explanation might be that all patients received 4 mg of dexamethasone for PONV prophylaxis according to our study protocol. The administration of antiemetic rescue therapy at PACU was not part of our study protocol but did not differ between the groups.

We further evaluated the effect of desflurane versus sevoflurane on postoperative maximum S100—B concentrations as surrogate parameter for a potential neuronal injury and an impaired blood-brain barrier function [27,28]. While it has been shown in former studies that S100—B is significantly increased after surgery and is associated with the development of postoperative cognitive dysfunction [18,29,30], the

effects of different volatile anesthetics on S100—B concentrations are still lacking. Specifically, a previous study showed that postoperative S100—B concentrations were significantly increased in patients with postoperative delirium as compared to patients without delirium [18]. We did not observe a significant difference in postoperative maximum S100—B concentrations between the groups. However, to clearly answer the question, if different types of volatile anesthetics significantly affect neurocognitive associated biomarkers indicating postoperative cognitive dysfunction or delirium, larger trials are needed.

The use of volatile anesthetics has come under significant criticism due to the environmental impact they pose [31,32]. Specifically, because of its longer atmospheric lifetime and higher global warming potential as compared to sevoflurane, a discontinuation of desflurane has been advocated [33]. However, recent articles highlighted that $CO_2$ emissions and water pollution caused by increased use of total intravenous anesthesia would also have significant deleterious effects on global warming, which are often underestimated [34–36].

The global potential effects of desflurane are mainly based on the calculation for global warming potential horizon of 100 years ($GWP_{100}$). However, the calculation should only be used for greenhouse gases with an atmospheric lifetime of at least 100 years (e.g., $CO_2$) [37]. Since the atmospheric lifetime of desflurane is only approximately 14 years, the $GWP_{100}$ formula is inadequate, which often leads to misinterpretation [37]. In fact, a recent review article concluded that the anesthetic technique should therefore be patient-focused [34].

Our trial showed that in older adult patients undergoing minor- to moderate-risk surgery the choice of volatile anesthetic does not significantly affect postoperative recovery and therefore sevoflurane rather than desflurane should be used in the interest of environmental sustainability. However, our results should not be extrapolated for major surgery, in which the effects of desflurane versus sevoflurane on postoperative cognitive complications are largely unknown. The discontinuation of an anesthetic should not be based solely on environmental reasons but also should be supported by clinical investigations in an evidence-based approach. In this context, we have started a large, randomized clinical trial in which we compare the effects of desflurane versus sevoflurane versus propofol on the incidence of postoperative delirium in older adult patients undergoing major noncardiac surgery. (ClinicalTrials.gov ID NCT05990790).

Our study has some limitations, which must be discussed. First, we did not measure postoperative expiratory anesthetic concentrations to assess context-sensitive decrement times between the groups. Thus, we are not able to provide a detailed pharmacokinetic model of desflurane and sevoflurane, respectively. However, possible differences are unlikely to be clinically meaningful since we did not observe a significant difference in postoperative recovery times and postoperative BIS values. Second, the anesthetists in the operating rooms were not blinded towards the allocated groups, which could have influenced intraoperative anesthetic management. However, our study protocol was standardized including depth of anesthesia, intra- and postoperative pain management, reversal of muscle relaxation. Furthermore, postoperative outcomes were only assessed by blinded investigators. Thus, an effect on our outcomes is unlikely. Third, some patients were discharged from hospital before the third postoperative day, which limited our delirium and late PONV assessments to patients, who were still hospitalized. It is therefore possible that patients developed postoperative delirium at home after hospital discharge, which would have been missed in our results. Furthermore, postoperative assessments of POCD were performed via phone. Although, we only used the adapted telephone MoCA, which yields similar results compared to the in-person assessments [21,22], there is still some risk that we might have missed POCD. Fourth, in our cohort we observed a large number of >80% of the patients reaching an Aldrete score $\geq 12$ points already at PACU arrival, which we did not expect in the planning phase of the trial based on previous studies [12,38–41]. To evaluate the primary outcome in more detail we therefore additionally investigated a corresponding binary endpoint to evaluate differences in patients' recovery between the two randomized groups. Because these analyses were not planned from the beginning this may lead to a reduction in power. Lastly, since our sample size calculation was performed to evaluate possible differences in postoperative recovery, the results of our secondary and exploratory outcomes need to be viewed as preliminary and need to be confirmed in future studies.

In summary, postoperative recovery times did not differ significantly between desflurane or sevoflurane for maintenance of anesthesia in older adults undergoing minor- to moderate-risk noncardiac surgery. In fact, we observed very short postoperative recovery times in both groups, which could be explained by the low anesthetic concentrations in both groups due to BIS-guided anesthesia. Based on that both volatile anesthetics are appropriate for same-day surgical procedures.

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## CRediT authorship contribution statement

**Edith Fleischmann:** Writing – review & editing, Writing – original draft, Conceptualization. **Katharina Horvath:** Writing – review & editing, Data curation. **Nikolas Adamowitsch:** Writing – review & editing, Data curation. **David Emler:** Writing – review & editing, Data curation. **Thomas Christian:** Writing – review & editing, Data curation. **Nicole Hantakova:** Writing – review & editing, Data curation. **Beatrix Hochreiter:** Writing – review & editing, Data curation. **Laura Höfer:** Writing – review & editing, Data curation. **Magdalena List:** Writing – review & editing, Data curation. **Barbara Rossi:** Writing – review & editing, Data curation. **Florian W. Zenz:** Writing – review & editing, Data curation. **Giulia Zanvettor:** Writing – review & editing, Data curation. **Oliver Zotti:** Writing – review & editing, Data curation. **Alexandra Graf:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Melanie Fraunschiel:** Writing – review & editing, Software, Formal analysis. **Christian Reiterer:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2024.111576.

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