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Effect of desflurane, sevoflurane or propofol on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major non-cardiac surgery: study protocol for a prospective, randomised, observer-blinded, clinical trial (RAPID-II trial)

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ABSTRACT

Introduction The effect of different anaesthetics on the incidence of postoperative delirium is still not entirely clear. Therefore, we will evaluate the effect of desflurane versus sevoflurane versus propofol for the maintenance of anaesthesia on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major non-cardiac surgery. We will further compare the incidences of delayed neurocognitive recovery, long-term postoperative neurocognitive disorder, postoperative nausea and vomiting between the groups.

Methods and analysis In this multicentre, prospective, observer-blinded, randomised controlled clinical trial, we will include 1332 patients ≥65 years of age undergoing moderate- to high-risk major non-cardiac surgery lasting at least 2 hours. Patients will be randomly 1:1:1 assigned to receive desflurane, sevoflurane or propofol for anaesthesia. Maintenance of anaesthesia will be performed in a goal-directed manner using processed electroencephalography with an intraoperative goal of bispectral index 40–60. Our primary outcome will be the incidence of postoperative delirium within the first five postoperative days. Postoperative delirium will be assessed using the three-dimensional-confusion assessment method (3D-CAM) or CAM-intensive care unit (ICU) in the morning and evening of the first five postoperative days by blinded study personnel. The primary outcome, the incidence of postoperative delirium, will be compared between the three study groups using a χ^2 test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed, accounting for randomised groups as well as other predefined confounding factors.

Ethics and dissemination This clinical trial has been approved by the ethics committee and the Federal Office for Safety in Healthcare as the competent authority for clinical trials in Austria. The results of this trial will be published in a peer-reviewed journal.

Trial registration number ClinicalTrials.gov NCT05990790.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be a multicentre prospective trial powered to detect a 10% absolute risk reduction in postoperative delirium between desflurane, sevoflurane and propofol.
⇒ This trial will achieve good internal validity due to randomisation and blinding of outcome assessors, as well as high external validity due to the large sample size and the inclusion of many types of non-cardiac surgery.
⇒ Postoperative delirium will be assessed in the morning and evening for the initial five postoperative days according to the current recommendations.
⇒ Due to the different methods of administration of the three anaesthetics, blinding of the attending anaesthetists will not be performed.

INTRODUCTION

Postoperative delirium is a major complication after cardiac and non-cardiac surgery and occurs more often in older adults.[1–3] Based on previous observational studies, the incidence of postoperative delirium in older

adults is between 20% and 45%.[4–6] Delirium is associated with prolonged stays in intensive care units (ICU) and hospitalisation, leading to higher hospitalisation costs, which are as high as costs caused by cardiovascular complications.[4 5 7 8] More importantly, postoperative delirium is associated with accelerated long-term neurocognitive decline and dementia and further increases morbidity and mortality.[4 5 9–12] In this context, the American College of Surgeons and the American Society of Anaesthesiologists have identified the prevention of postoperative delirium as a public health priority.[8 10] Nevertheless, a clear consensus on perioperative anaesthesiologic management of older adults undergoing major non-cardiac surgery with the specific goal of preventing postoperative delirium has not been established yet.[10]

Some previous studies evaluated the effects of volatile versus intravenous anaesthesia on the incidence of postoperative delirium.[13–16] However, these studies mostly compared sevoflurane versus propofol anaesthesia and showed conflicting results.[13–16] The most recent and largest randomised trial showed a significantly lower incidence of postoperative delirium after propofol-anaesthesia as compared with sevoflurane-anaesthesia.[16] However, so far, data regarding the effects of desflurane as compared with sevoflurane and propofol on the incidence of postoperative delirium is scarce. While it has been shown previously that desflurane anaesthesia leads to significantly faster immediate postoperative recovery as compared with sevoflurane,[17–21] we could not observe in one of our previous studies a significant difference in immediate postoperative recovery in older adults undergoing minor- to moderate-risk non-cardiac surgery.[22] Nevertheless, the effect of desflurane versus sevoflurane versus propofol on the incidence of postoperative delirium in older adults undergoing major non-cardiac surgery is still unclear.

Therefore, we will test our primary hypothesis that anaesthesia with desflurane will be associated with a significantly lower incidence of postoperative delirium within the first five postoperative days as compared with anaesthesia with sevoflurane or anaesthesia with propofol in older adults undergoing moderate- to high-risk major non-cardiac surgery lasting at least 2 hours. We will further test the secondary hypotheses that anaesthesia with desflurane will be associated with significantly lower incidences of delayed neurocognitive recovery and long-term neurocognitive disorder as compared with anaesthesia with sevoflurane or anaesthesia with propofol.

METHODS AND ANALYSIS

Trial design

We will conduct the RAPID-II trial, a multicentre, observer-blinded, prospective, randomised, three-arm parallel-arm clinical trial at the Medical University of Vienna and the Medical University of Innsbruck. All members of the RAPID-II investigator group are listed in online supplemental file 1). We will include 1332 patients ≥65 years of age undergoing moderate- to high-risk major non-cardiac surgery. The trial was approved by the ethics committee and the Federal Office for Safety in Healthcare as the competent authority for clinical trials in Austria on the 19th of June 2023 (CTIS Reference number: 2023-503717-30-00). We started patient enrolment on 3 September 2023, and currently the estimated date of primary completion is 31 December 2027, and the estimated study completion date is 31 December 2028.

Table 1 Inclusion and exclusion criteria

Inclusion criteria (1–-3)	
1.	Provided written informed consent
2.	≥65 years of age
3.	Scheduled for elective major non-cardiac surgery with estimated time of surgery≥2 hours
Exclusion criteria (1–9)	
1.	Patients undergoing emergency surgery
2.	Bdy mass index >45 kg/m^2
3.	History of diagnosed dementia
4.	Language, vision or hearing impairments that may compromise cognitive assessments
5.	History of malignant hyperthermia
6.	History of structural muscle disease
7.	History of organ transplantation (kidney, liver, lung and heart)
8.	Patients undergoing hyperthermic intraperitoneal chemotherapy surgery
9.	Intensive care unit patients undergoing surgery

Study population

The inclusion and exclusion criteria are presented in table 1. Study personnel will screen the surgical schedule the day before surgery and check for eligibility. Definitions of surgeries, which will be included, are listed in online supplemental eAppendix 2 of the Online Supplement. They will further approach eligible patients to obtain informed consent before surgery. A sample informed consent form is provided in the online supplemental file 2. Previous experience showed that 6–8 patients will be eligible per week. Therefore, we assume a period of 3–4.5 years to complete patient recruitment for this study.

Data management

Electronic data will be recorded in the data management system 'Clincase', V.2.7.0.12 hosted by IT services and strategic information management of the Medical University of Vienna, Vienna, Austria.

Randomisation and blinding

We will randomise patients within 1 hour before surgery. We will use the online randomisation programme 'Randomizer' (Randomizer, Medical University of Graz, Graz, Austria: https://www.meduniwien.ac.at/randomizer/web/login.php) provided by the IT services and

strategic information management Department of the Medical University of Vienna, Vienna, Austria. Randomisation will be performed with permutated blocks stratified by study centre, sex and age (65–79 years, ≥80 years). Randomisation will only be performed by registered personnel, who are not involved in postoperative outcome assessments. The attending anaesthetists will be informed about the randomly assigned group and will not be involved in postoperative outcome assessments. Only study personnel responsible for postoperative outcome assessments will be blinded regarding the randomly assigned group. Patients will be randomised 1:1:1 to the following three groups.

Desflurane group

After induction of anaesthesia, anaesthesia will be maintained with goal-directed administration of desflurane with an intraoperative goal of bispectral index (BIS) 40–60.

Sevoflurane group

After induction of anaesthesia, anaesthesia will be maintained with goal-directed administration of sevoflurane with an intraoperative goal of BIS 40–60.

Propofol group

After induction of anaesthesia, anaesthesia will be maintained with a goal-directed continuous infusion of propofol with an intraoperative goal of BIS 40–60.

Anaesthesia protocol

All patients will receive an ECG, blood pressure and peripheral oxygen saturation monitoring. An arterial line and/or central venous line will be placed and monitored at the discretion of the attending anaesthetist according to local clinical standard of care.

After endotracheal intubation, anaesthesia will be maintained using desflurane or sevoflurane in a mixed oxygen carrier gas or continuous propofol infusion according to the allocated randomised group. We will use the first 10 min after intubation to set anaesthesia to the target BIS value. Desflurane, sevoflurane and propofol, respectively, will be titrated and adjusted using processed electroencephalography (EEG) for a target BIS of 40–60 throughout surgery.

Fentanyl and remifentanil, respectively, will be administered at the discretion of the attending anaesthetist. We will give additional muscle relaxation to maintain 1–2 mechanical twitches in response to supramaximal stimulation (train-of-four stimulation, target <75%). For mechanical ventilation, we will maintain an inspiratory fractional inspired oxygen between 0.3 and 0.5 to achieve a oxygen saturation (SpO_2) of at least 93% or partial pressure of oxygen of >80 mm Hg. Tidal volumes will be set between 6 and 8 mL lean body weight to maintain end-tidal carbon dioxide (CO_2) within 35–40 mm Hg. Positive end-expiratory pressure will be set at 5 mm Hg or higher according to the patients' requirements. Intraoperative postoperative nausea and vomiting (PONV) prophylaxis will be administered at the discretion of the attending anaesthetist. We will actively warm patients with convective warming to maintain perioperative normothermia. Intraoperative mean arterial pressure will be held at a minimum of 65 mm Hg. Intraoperative fluid and vasopressor management will be performed at the discretion of the attending anaesthetist according to local clinical standard of care. We will maintain a haemoglobin of at least 8 g/dL. Anaesthesiologic adjuvants, for example, esketamine, clonidine, atropine, dexmedetomidine, midazolam and scopolamine should be avoided. The postoperative management of medication will be done according to the attending physicians.

At the end of surgery, we will stop the administration of desflurane, sevoflurane and propofol, respectively. In the case of planned intubated transfer to ICU after surgery, desflurane or sevoflurane will be stopped and propofol administration will be started (figure 1).

Outcomes

Our primary outcome will be the incidence of postoperative delirium within the first five postoperative days between the desflurane, sevoflurane and propofol groups.

Our secondary outcomes will include the incidence of delayed neurocognitive recovery, postoperative need of supplemental oxygen, length of stay in the ICU, incidence of PONV in the early and late postoperative periods, intraoperative hypotension and death within the first five postoperative days.

Our exploratory outcomes will include the number of days at home up to 30 days after surgery, long-term postoperative neurocognitive disorder 1 year after surgery and postoperative area under the curve of plasma concentrations of inflammatory biomarkers (C reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT)), cardiac biomarkers (troponin T, N-terminal probrain natriuretic peptide (NT-proBNP), copeptin) and neuronal injury biomarkers (S100-B, neuron-specific enolase (NSE)). Study-specific blood samples will be drawn shortly before induction of anaesthesia, within 2 hours after surgery and on the second postoperative day. Furthermore, we will assess 1 year all-cause mortality 1 year after surgery in all patients.

In a substudy, we will compare differences between preoperative and postoperative concentrations of advanced neurobiomarkers, including neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), between the groups.

A detailed description of primary, secondary, exploratory and substudy specific outcomes and their assessments is shown in table 2.

Measurements

Demographic and morphometric data

Basic data, including age, sex, body mass index and American Society of Anaesthesiologists (ASA) physical status, will be recorded. We will record medical history,

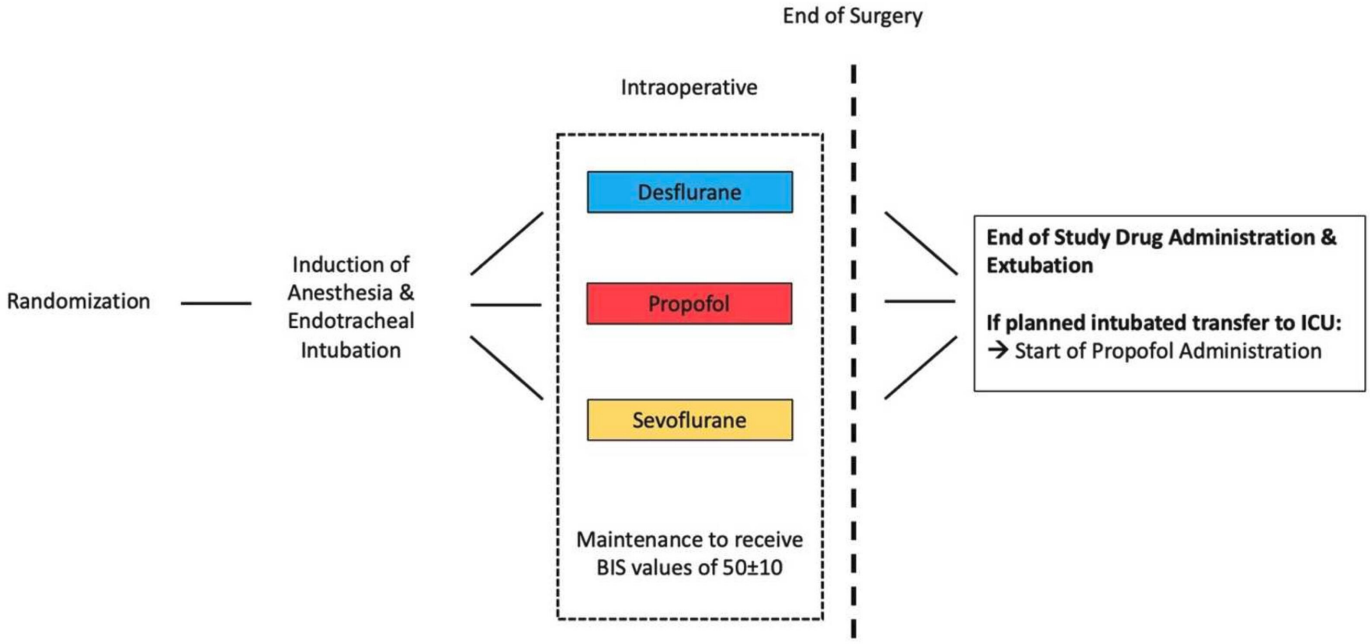

Figure 1 Study procedure. BIS, bispectral index; ICU, intensive care unit.

including comorbidities, long-term medication and history of tobacco or alcohol use and type of surgery.

Perioperative data

Routine intraoperative and postoperative anaesthesia-specific data will be extracted from our electronic anaesthesia records. Intraoperative data will include arterial blood gas analysis, durations of anaesthesia and surgery, intraoperative fluid management, intraoperative medication, vasopressors and haemodynamic data.

We will further record inspiratory and expiratory concentrations of the administered volatile anaesthetic and intraoperative amount of propofol. Intraoperative BIS data (BIS, Medtronic, Meerbusch, Germany), including BIS values and density spectral array (DSA), will be recorded and extracted directly from the BIS monitor.

Postoperative pain will be recorded based on the numeric pain rating scale in the postanaesthesia care unit (PACU), ICU and on the ward two times per day within the first five postoperative days. We will record the overall amount of piritramide, non-steroidal analgesics, duration of epidural anaesthesia and the amount of co-analgesics administered at the PACU, ICU or on the ward within the first five postoperative days.

Outcome measurements

All postoperative outcome assessments will be performed by trained study personnel, who are blinded to the assigned randomised group.

For our primary outcome, we will perform the three-dimensional-confusion assessment method (3D-CAM) evaluations starting on the evening of the day of surgery (18:00–22:00). Following 3D-CAM evaluations will be performed two times per day—in the mornings (05:00–11:00) and evenings (18:00–22:00) for the following five postoperative days if patients are still hospitalised.[23 24] In patients in the ICU, we will perform CAM-ICU evaluations.[23 24] Postoperative delirium will be defined as the occurrence of at least one positive 3D-CAM or CAM-ICU assessment in the first five postoperative days.

For the assessment of delayed neurocognitive recovery, we will perform digit symbol substitution tests (DSSTs) and trail-making tests (TMTs) part A and part B before surgery and on the fifth postoperative day if the patients are still hospitalised.[25 26] For the TMT, the time until test completion and the number of mistakes will be recorded. If the patients are intubated on the fifth postoperative day, the assessments will be postponed for 2 days. Delayed neurocognitive recovery will be defined in accordance with the ISPOCD-1 study (Long-term postoperative cognitive dysfunction in the elderly) when a patient has a Z-score on two or all tests or the combined Z-score is below—1.96 SD.[26]

For the assessment of neurocognitive disorder, we will further perform an adapted Montreal Cognitive Assessment (MoCA) test (telephone MoCA) before surgery and 1 year after surgery.[27–30] Postoperative neurocognitive disorder will be defined as a decrease of two points or more from baseline values.[27–30]

DSST, TMT, 3D-CAM, CAM-ICU and MoCA tests will be performed only by trained and blinded study personnel. PONV will be assessed on the evening of the day of surgery and in the morning and evening of the following 5 days. PONV will be defined as subjective symptoms of nausea and/or occurrence of vomiting at each time point. Oxygen supplementation will be recorded by the amount of L/min oxygen administered for SpO_2 ≥93% at PACU or ICU, respectively. Furthermore, we will record the intraoperative use of vasopressors. We will record

Table 2 Outcome assessments

Outcome	Measurements	Timepoint
Primary outcome		
Postoperative delirium	3D-CAM/CAM-ICU	Evening on the day of surgery and morning and evening of the first five postoperative days
Secondary outcomes		
Delayed neurocognitive recovery	Digit symbol substitution test, TMT Part A, TMT Part B	Preoperative, postoperative day 5
Need of supplemental oxygen	L/min	During postanaesthesia care unit/ICU stay
Length of stay in ICU	Number of days at ICU	During ICU stay
Early PONV	Patient assessment of PONV episode	First 2 hours after surgery
Late PONV	Patient assessment of PONV episode	Evening on the day of surgery and morning and evening of the first five postoperative days
Intraoperative hypotension	Intraoperative mean arterial pressure+cumulative catecholamine administration	Intraoperative
Death within 5 days		First five postoperative days
Exploratory outcomes		
Days at home up to 30 days after surgery (number of days at home in the first month after surgery)	Phone follow-Up, patient records	30 days after surgery
Long-term neurocognitive disorder	Montreal Cognitive Assessment test via phone follow-up	Preoperative, 1 year after surgery
AUC of inflammatory biomarkers	C reactive protein, interleukin-6, procalcitonin	Preoperative, within 2 hours after surgery, postoperative day 2
AUC of cardiac biomarkers	Troponin T, N-terminal probrain-natriuretic peptide, copeptin	Preoperative, within 2 hours after surgery, postoperative day 2
AUC of neuronal injury biomarkers	S100-B, neuron-specific enolase	Preoperative, within 2 hours after surgery, postoperative day 2
One-year all-cause mortality		One year after surgery
Substudy outcomes		
Advanced neurobiomarkers	Neurofilament light chain, glial fibrillary acidic protein	Preoperative, postoperative day 3

AUC, area under the curve; CAM, confusion assessment method; ICU, intensive care unit; PONV, postoperative nausea and vomiting; TMT, trail making test.

the duration of stay in the ICU for all patients. Phone follow-ups will be performed in all patients 30 days after surgery to determine the number of days at home up to 30 days after surgery and 1 year after surgery to perform the MoCA tests.

Study-specific blood samples will include CRP, IL-6, PCT, troponin T, NT-proBNP, copeptin, NSE, S100-B, NfL and GFAP. All laboratory parameters will be measured at the Department of Laboratory Medicine at the Medical University of Vienna and at the Department of Laboratory Medicine at the Medical University of Innsbruck, respectively. Blood samples will be treated with a standard of care to provide the best accuracy of measurement. Study-specific blood samples of CRP, IL-6, PCT, troponin T, NT-proBNP, copeptin, NSE and S100-B will be drawn shortly before induction of anaesthesia, within 2 hours after surgery and on the second postoperative day. Substudy-specific blood samples of NfL and GFAP will be collected shortly before induction of anaesthesia and on the third postoperative day. Substudy-specific blood samples will then be centrifuged and stored.

Statistical analysis

Data analysis

Baseline characteristics such as age, sex, ASA physical status, history of tobacco use, comorbidities, long-term medication and type of surgery will first be analysed descriptively. Descriptive statistics will be calculated overall and separately for the three groups. Continuous variables will be summarised using means, SD, median and IQRs. Categorical data will be summarised using absolute numbers and percentages.

Our primary outcome, the incidence of postoperative delirium, will be described in a descriptive way using absolute numbers and percentages per study group. First, we will compare the incidence of postoperative delirium between the three groups using a χ^2 test. Furthermore, a logistic regression model for the incidence of

postoperative delirium will be performed, accounting for the randomised group as well as other confounding factors (eg, age, BMI, ASA physical status, duration of anaesthesia, additional epidural/regional anaesthesia and history of cerebrovascular disease). All three groups will be analysed together in the logistic regression model and the pairwise comparison will be conducted within the model. Patients who die within the first five postoperative days will be excluded from the primary analysis of our trial unless a positive delirium assessment were performed before the patient's death. As a sensitivity analysis, to additionally account for death within 5 days after surgery, a logistic regression model for the probability of the combined endpoint (postoperative delirium or death) will be performed accounting, for a randomised group and other possible confounding factors. Significance levels for the primary outcome will be used as described in the sample size calculation section to account for the two interim analyses and the pairwise group comparisons to retain an overall level for the type I error of 0.05.

All analyses will be conducted on the intention to treat (ITT) population, defined as all randomised patients who received one of the study drugs, even if the patient does not receive the correct treatment or otherwise does not follow the protocol. In addition to the ITT analyses, also per-protocol analyses will be performed for the primary and secondary parameters. This analysis set comprises all subjects who received one of the study drugs and did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary objective, that is, without major protocol violations.

The secondary outcome, the incidence of delayed neurocognitive recovery, will be evaluated between the study groups using a χ^2 test. Furthermore, a logistic regression model for the probability of delayed neurocognitive recovery will be performed, accounting for the randomised group as well as other possible confounding factors.

The secondary outcome, the number of litres of administered supplemental oxygen in PACU or ICU to achieve a SpO_2 ≥93% will be compared between the study groups using Mann-Whitney U tests.

The secondary outcome, the length of stay in the ICU, will be compared between the groups using a competing risk model for time to discharge from the ICU and death as competing events accounting for the study group as well as other possible confounding factors.

The secondary outcomes, incidences of PONV in the early and late postoperative period, will be evaluated between the groups using χ^2 tests. Furthermore, logistic regression models for the incidences of PONV in the early and late postoperative periods will be performed.

The secondary outcome, intraoperative duration of MAP <65 mm Hg and the overall intraoperatively administered amount of catecholamines, will be compared between the groups using Mann-Whitney U tests.

The secondary outcome, death within 5 days after surgery, will be compared between the groups using a χ^2 test. Furthermore, a logistic regression model for the probability of death will be performed.

The exploratory outcome, the number of days at home up to 30 days after surgery, will be compared between the groups using Mann-Whitney U tests. The exploratory outcome, the incidence of neurocognitive disorder 1 year after surgery, will be compared using χ^2 tests. As exploratory outcomes, the area under the curves of perioperative inflammatory biomarkers, cardiac biomarkers and neuronal injury biomarkers will be calculated and compared between the groups using Mann-Whitney U tests. Lastly, the probability of all-cause death within 1 year after surgery will be presented between the groups using Kaplan-Meier curves. For secondary and exploratory outcomes, a significance level of 0.05 is used.

Sample size calculation

We estimated the number of patients required for this trial based on previous studies, which showed that the incidence of postoperative delirium in older adults undergoing major abdominal surgery lies between 5% and 50%,[5 31 32] whereas the largest study reported an incidence of 25%.[33] Using a conservative approach, we assumed the incidence of postoperative delirium at about 25%. A reduction of 10% points was assumed to be clinically relevant (25% vs 15%).

Two interim analyses, one after 1/3 and one after 2/3 of recruitment, are preplanned. To correct for the comparison of the three groups, Bonferroni-correction was applied, resulting in a two-sided overall significance level of 0.0167 (0.05/3 for three comparisons). To further correct for the two interim analyses (three total analyses including the final analysis), the Hwang-Shih-DeCani spending function for group sequential designs (with associated parameter—4) was used, resulting in a nominal alpha level of 0.001 for the first interim analysis, 0.004 for the second interim analysis and 0.015 for the final analysis to control the overall significance level of 0.0167 for each of the three group comparisons.

Using a group sequential z-test and assuming an OR of 0.529 (for proportions of 0.25 as compared with 0.15), we calculated a needed sample size of 431 patients per group to achieve a power of 0.9.

We assumed a dropout rate of 3% (including patients who die within the first five postoperative days), resulting in a needed sample size of 1332 patients (444 patients per group).

The sample size calculation was performed using NQuery 8.

Data safety monitoring board (DSMB)

The following experienced researchers will compromise the DSMB: Professor Dr Eva Base (Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Division of Cardiothoracic and Vascular Anaesthesia, Medical University of Vienna, Austria), Professor Dr Michael Wolzt (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Professor Dr Markus

Zeitlinger (Department of Clinical Pharmacology, Medical University of Vienna, Austria) and Professor Dr Gerd Silberhumer (Department of General Surgery, Medical University of Vienna, Austria).

Patients' safety will be monitored through the DSMB. The DSMB will evaluate adverse events (AEs) (serious AEs (SAEs), stands for suspected unexpected serious adverse reaction and adverse drug reaction) for the two preplanned interim analyses. In detail, the DSMB will evaluate AEs from 444 patients and 888 patients after all data are available. It will be the responsibility of this committee to alert the local ethics committee via a letter of any harmful effects in one of the study groups. This committee, along with the local ethics committee, will have the exclusive authority to stop the study either for futility, harm or clear benefit. Any morbidity potentially related to the study protocol will be reported to the ethics committee.

Emergency unblinding and termination of the study drug

Attending anaesthesiologists will not be blinded by respective anaesthetic agents. In the case of discontinuation or change of the randomly assigned group, assessments of postoperative outcomes will be continued according to the study protocol and patients will not be dropped out because of ITT. In the case an AE or a SAEs occurs, the blinded outcome assessor will inform the principal investigator or responsible study personnel immediately.

Termination of the study

In the case of a preterminal termination of the study because of a significant incidence of AEs evaluated by the DSMB, the sponsor (Medical University of Vienna) will notify the competent authorities of the end of the study, including an appropriate justification. If the study is terminated because of safety reasons, the European Medicines Agency will be notified as well.

Data monitoring

Data monitoring will be performed by the Clinical Trials Coordination Centre of the Medical University of Vienna, which is independent of the investigators and the sponsor, has no competing interests. Data monitoring will be performed at regular intervals after the inclusion of 50 patients per study site. The designated monitor will contact and visit the investigator on a regular basis and will be allowed to have direct access to all source documents, which are needed to verify all case report form (CRF) and electronic CRF (eCRF) entries and other protocol-related documents, provided that subject confidentiality is maintained in agreement with legal regulations. It will be the monitors' responsibility to inspect the CRFs and eCRFs at regular intervals according to the monitoring plan throughout the study to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

Data safety

All hard-copy forms, such as CRFs, source data and informed consents, will be stored in locked rooms within a secured area and are only accessible by investigators involved in the trial.

Access to data is strictly controlled and will only be provided to the sponsor (Medical University of Vienna), the study investigators, the ethics committee (ethics committee of the Medical University of Vienna) and, if requested, the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen).

Data will be stored after publishing of the trial and all of the substudies by Iron Mountain Austrian Archivierungs GmbH (Gewerbeparkstraße 3, 2282 Markgrafneusiedl, Austria) for a period of not less than 25 years in accordance with the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by the national laws.

Patient and public involvement

No patient or public involvement.

DISCUSSION

The RAPID-II trial will provide clinical evidence regarding the effects of desflurane, sevoflurane and propofol on postoperative delirium in older adults undergoing moderate- to high-risk major non-cardiac surgery.

The most recent and largest trial in over 1200 patients demonstrated that propofol-based anaesthesia was associated with a lower incidence of postoperative delirium within the first 5 days as compared with sevoflurane-based anaesthesia.[16] However, they further showed that the long-term cognitive function—assessed via telephone interviews—was significantly better in the sevoflurane group as compared with the propofol group 3 years after surgery.[16] Cao *et al* suggested that the choice of isoflurane or desflurane instead of sevoflurane would have led to similar results.[16] Nevertheless, it has to be emphasised that this is not based on any scientific evidence.

In fact, the pharmacokinetic characteristics of desflurane lead to significantly faster elimination as compared with sevoflurane.[34–36] Desflurane has a blood/gas coefficient of 0.45, which is the lowest of all available volatile anaesthetics.[34] Thus, the context-sensitive decrement time of desflurane is significantly faster as compared with sevoflurane.[35 36] Specifically, the time until 90% of sevoflurane is eliminated increases significantly after 2 hours of administration, while the time of elimination of 90% of desflurane remains relatively constant.[35 36] Some studies have shown that desflurane led to significantly faster extubation times, faster eye opening to verbal commands, faster reciting of full names and faster orientation as compared with sevoflurane.[17–21] Furthermore, a recent pilot study showed that in patients who received desflurane for major surgery, postoperative cognitive function assessed via the Mini Mental State Examination was significantly higher after desflurane anaesthesia as compared with sevoflurane.[37] Interestingly, studies investigating

different anaesthetics with clinically meaningful neurological outcomes are still lacking, specifically in regard to desflurane. Thus, the strength of our trial is that it will be the first adequately powered randomised study comparing the effects of desflurane on the incidence of postoperative delirium as compared with sevoflurane or propofol.

In addition, measuring anaesthetic depth by simply using the BIS value is not sufficient. In the study by Cao *et al* only 70% of patients were monitored with BIS and the BIS values and not raw EEG or colour DSA were used for the determination of anaesthetic depth.[16] It has been shown that during emergence, volatile anaesthetics induce higher power in frequencies above 15 Hz compared with propofol, resulting in higher BIS indices for this drug group.[38] Specific index values do not always correlate with the same clinical state of consciousness. We therefore plan to further compare colour DSAs between the groups.

The use of volatile anaesthetics has been criticised in recent years due to their environmental effects.[39 40] We are aware that a discontinuation of desflurane has been proposed recently.[41] These recommendations are often based on calculations of the global warming potential of 100 years (GWP_{100}), which should be used for gases with atmospheric lifetimes of at least 100 years.[42] However, since the atmospheric lifetime of desflurane is approximately 14 years, the GWP_{100} formula is inadequate, which often leads to overestimation of its global warming potential.[42–44] Furthermore, propofol leads to CO_2 emissions and water pollution, which have significant deleterious effects on global warming, which are often underestimated.[42 43 45] Therefore, it is of utmost importance to provide evidence on patient outcomes before decisions with wide clinical implications are made. The discontinuation of desflurane and the choice of general anaesthetic in routine care should not be based solely on environmental reasons but also should be supported by their clinical impact and evidence-based results.

This trial will have some limitations. First, due to the different methods of administration and because this is a large, multicentre, pragmatic trial, blinding of the attending anaesthetists will not be suitable. However, to provide equal depth of anaesthesia, the dosage of anaesthetics will be standardised for all patients with an aim of BIS values 40–60. Furthermore, DSA will be further analysed and compared between the groups. Nevertheless, it cannot be ruled out that BIS values might be different between the groups, which could pose as a significant confounder for postoperative delirium. Therefore, regular analyses of BIS values between the groups are planned for surveillance of protocol adherence regarding intraoperative BIS values at least after every 150 patients enrolled. To further limit possible bias, all postoperative outcomes will only be assessed by study personnel blinded towards the randomly assigned group. Second, we will only include patients planned for major non-cardiac surgery. Furthermore, we will only include patients ≥65 years of age, since the incidence of postoperative delirium is highest in this patient population.[2] Thus, the generalisability for emergency surgery, cardiac surgery and younger patients will be limited. Lastly, some patients might be discharged from the hospital before the fifth postoperative day, limiting the delirium assessments. However, based on the current clinical standard of care, patients with delirium are unlikely to be discharged from the hospital. Thus, the number of patients with delirium missed in our outcome assessment should be minimal.

In summary, the RAPID-II trial will be a multicentre, observer-blinded, prospective, randomised clinical trial that is adequately powered to evaluate the effects of desflurane versus sevoflurane versus propofol for maintenance of anaesthesia on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major non-cardiac surgery. The results of this trial might therefore provide evidence regarding the effects of anaesthetics on neurologic outcomes and, more importantly, will give clinicians guidance for the choice of general anaesthetics in highly vulnerable patients.

Trial status

Actual protocol: V.5.0, 5 March 2024. Patient recruitment started in September 2023.

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