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The effect of desflurane, sevoflurane, or propofol on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 maintenance of anaesthesia on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 multi-centre, prospective, observer-blinded, randomised controlled clinical trial we will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac surgery lasting at least two 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 50±10. Our primary outcome will be the incidence of postoperative delirium within the first five postoperative days. Postoperative delirium will be assessed using the 3D-Confusion Assessment Method (3D-CAM) or CAM-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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other pre-defined 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:

ClinicalTrials.gov NCT05990790;

https://clinicaltrials.gov/study/NCT05990790?term=NCT05990790&rank=1

Strengths and limitations of this study:

- This will be a properly powered multi-centre prospective trial to compare the effects of three commonly used anaesthetics on the incidence of postoperative delirium.
- 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 noncardiac 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 noncardiac 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 stay 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 Anesthesiologists 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 noncardiac 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 to sevoflurane-anaesthesia.[16] However, so far data regarding the effects of desflurane as compared to 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 to sevoflurane, [17–21] we could not observe in one of our previous studies a significant difference immediate postoperative recovery in older adults undergoing minor- to moderate-risk noncardiac surgery.[22] Nevertheless, the effect of desflurane versus sevoflurane versus propofol on the incidence of postoperative delirium in older adults undergoing major noncardiac 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 to anaesthesia with sevoflurane or anaesthesia with propofol in older adults undergoing

moderate- to high-risk major noncardiac surgery lasting at least two 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 to anaesthesia with sevoflurane or anaesthesia with propofol.

Methods and Analysis

Trial Design

We will conduct the RAPID-II trial, a multi-centre, observer-blinded, prospective, randomised, three-arm parallel arm clinical trial at the Medical University of Vienna and the Medical University Innsbruck. All members of the RAPID-II investigator group are listed in Online Supplement 1. We will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac 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. We started patient enrolment on the 3rd of September 2023.

The RAPID-II trial will test the primary hypothesis that general anaesthesia with desflurane will result in a significant reduction in the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac surgery as compared to general anaesthesia with sevoflurane. We further test that general anaesthesia with desflurane will result in a significant reduction in the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac surgery as compared to general anaesthesia with propofol.

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 eAppendix 2 of the Online Supplement. They will further approach eligible patients to obtain informed consent before surgery. 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", Version 2.7.0.12 hosted by IT Services & strategic information management of the Medical University of Vienna, Vienna, Austria.

Randomisation and blinding

We will randomise patients within one 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 & strategic information management Department of the Medical University of Vienna, 1090 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) 50±10.

Sevoflurane group: after induction of anaesthesia, anaesthesia will be maintained with goal-directed administration of sevoflurane with an intraoperative goal of bispectral index (BIS) 50±10.

Propofol group: after induction of anaesthesia, anaesthesia will be maintained with a goal-directed continuous infusion of propofol with an intraoperative goal of bispectral index (BIS) 50±10.

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 minutes after intubation to set anaesthesia to the target BIS value. Desflurane, sevoflurane and propofol respectively will be titrated and adjusted using processed electroencephalography for a target BIS of 50±10 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 supra-maximal stimulation (Train-of-four stimulation, target <75%). For mechanical ventilation, we will maintain an inspiratory FiO_2 between 0.3 and 0.5 to achieve a SpO_2 of at least 93% or pO_2 of >80mmHg. Tidal volumes will be set between 6 and 8mL lean body weight to maintain end-tidal CO_2 within 35-40mmHg. Positive end-expiratory pressure will be set at 5mmHg or higher according to the patients' requirements. Intraoperative 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 65mmHg. 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 $8 g.dL^{-1}$. Anaesthesiologic adjuvants, e.g. 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 intensive care units (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 postoperative nausea and vomiting (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 one 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 pro-brain natriuretic peptide

(NT-proBNP), Copeptin), and neuronal injury biomarkers (S100-B, Neuron-specific enolase (NSE)). Furthermore, we will assess one-year all-cause mortality one year after surgery in all patients.

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

A detailed description of primary, secondary, exploratory, and sub-study specific outcomes and their assessments is shown in Table 2.

Measurements

Demographic and morphometric data

Basic data including age, sex, body mass index, and ASA physical status, will be recorded. We will record medical history including comorbidities, long-term medication, and history of tobacco or alcohol use and type of surgery.

Perioperative data

Routine intra- 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 (NRS) in the PACU, ICU, and on the ward twice daily 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 3D-confusion assessment method (3D-CAM) evaluations starting on the evening of the day of surgery (6 p.m. – 10 p.m.). Following 3D-CAM evaluations will be performed twice daily – in the mornings (5 a.m. – 11 a.m.) and evenings (6 p.m. – 10 p.m.) 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]

For the assessment of delayed neurocognitive recovery, we will perform digit symbol substitution tests (DSST), trail making test (TMT) 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 two days. For the assessment of neurocognitive disorder, we will further perform an adapted Montreal Cognitive Assessment (MoCA) test (telephone MoCA) before surgery and one year after surgery.[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 five days. PONV will be defined as subjective symptoms of nausea and/or occurrence of vomiting at each timepoint. Oxygen supplementation will be recorded by number of litres.minute^{-1} oxygen administered for SpO2 ≥93% at PACU or ICU respectively. Furthermore, we will record the intraoperative use of vasopressors. We will record the duration of stay in the ICU in 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 one 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 Innsbruck respectively. Blood samples will be treated with standard of care to provide 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 two hours after surgery and on the second postoperative day. Sub-study specific blood samples of NfL and GFAP will be collected shortly before induction of anaesthesia and on the third postoperative day. Sub-study 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, standard deviations, median, and interquartile ranges. 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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other confounding factors (e.g. age, BMI, ASA physical status, duration of anaesthesia, additional epidural/regional anaesthesia, 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. As 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 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

The secondary outcome, the incidence of delayed neurocognitive recovery, will be evaluated between the study groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of

delayed neurocognitive recovery will be performed accounting for 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 ICU and death as competing event accounting for 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 Chi-Square-tests. Furthermore, logistic regression models for the incidences of PONV in the early and late postoperative period will be performed.

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

The secondary outcome, death within five days after surgery, will be compared between the groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of death will be performed.

The exploratory outcome, 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, incidence of neurocognitive disorder, will be compared using Chi-Square-tests. As exploratory outcomes, 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, probability of all-cause death within one 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 5-50%,[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% versus 15%).

Two interim analyses, one after 1/3 and one after 2/3 of recruitment are pre-planned. 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 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 odds ratio of 0.529 (for proportions of 0.25 as compared to 0.15), we calculated a needed sample size of 431 patients per group to achieve a power of 0.9.

We assumed a drop-out 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

The following experienced researchers will compromise the Data Safety Monitoring Board (DSMB): Prof. Dr. Eva Base (Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Division of Cardiothoracic and Vascular Anaesthesia, Medical University of Vienna, Austria), Prof. Dr. Michael Wolzt (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Markus Zeitlinger (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Gerd Silberhumer (Department of General Surgery, Medical University of Vienna, Austria).

Patients' safety will be monitored through the data and safety monitoring board. The DSMB will evaluate adverse events (AEs, SAEs, SUSARs, ADR) for the two pre-planned interim analyses. In detail, the DSMB will evaluate adverse events 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 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 for 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 intention to treat. In the case an adverse event or a serious adverse event 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 significant incidence of adverse events evaluated by the DSMB, the sponsor (Medical University of Vienna) will notify the competent authorities the end of the study including an appropriate justification. If the study will be terminated because of safety reasons the European Medicines Agency (EMA) will be notified as well.

Data monitoring

Data monitoring will be performed by the Clinical Trials Coordination Centre of the Medical University of Vienna. 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 CRF and 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, ethics committee (Ethic committee of the Medical University of Vienna), and if requested the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG)).

Data will be stored after publishing of the trial and all of the sub-studies by Iron Mountain Austrian Archivierungs GmbH (Gewerbeparkstraße 3, 2282 Markgrafneusiedl, Austria) for a period of not less than twenty-five 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 noncardiac 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 five days as compared to 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 to the propofol group three 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 emphasized that this is not based on any scientific evidence.

In fact, pharmacokinetic characteristics of desflurane lead to significantly faster elimination as compared to 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 to sevoflurane.[35,36] Specifically, the time until 90% of sevoflurane is eliminated increases significantly after two 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 command, faster reciting of full name, and faster orientation as compared to sevoflurane.[17–21] Furthermore, a recent pilot study showed that in patients, who received desflurane for major surgery, postoperative cognitive function assessed via Mini Mental State Examination (MMSE) was significantly higher after desflurane anaesthesia as compared to sevoflurane.[37] Interestingly, studies investigating different anaesthetics with a clinical meaningful neurological outcome are still lacking, specifically in regards 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 to 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

spectral density array 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 to 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 spectral density arrays between the groups.

The use of volatile anaesthetics has been criticized 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 has 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 will be 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. Firstly, due to the different methods of administration and because this is a large, multi-centre, pragmatic trial, blinding of the attending anaesthetists will not be suitable. However, to provide equal depth of anaesthesia, dosage of anaesthetics will be standardized for all patients with an aim of BIS values 50±10. Furthermore, DSA will be further analysed and compared between the groups. To further limit possible bias, all postoperative outcomes will only be assessed by study personnel blinded toward the randomly assigned group. Secondly, we will only include patients planned for major noncardiac 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 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 multi-centre, 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 noncardiac 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: Version 5.0, March 5, 2024. Patient recruitment started in September 2023.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests

The authors have no conflicts of interest.

Authors' contributions

AT, CR, EF, BK, BS: conceptualisation and study design; AT, CR, EF, AG: first draft of the manuscript; CE, KH, NA, NH, BH, OZ: data collection; MF, AG: data management; AG: statistical analysis; AT, EF, BK, BS, CE, KH, NA, NH, BH, OZ, MF, AG, CR: editing and critical review of the manuscript; All authors read and approved the final manuscript.

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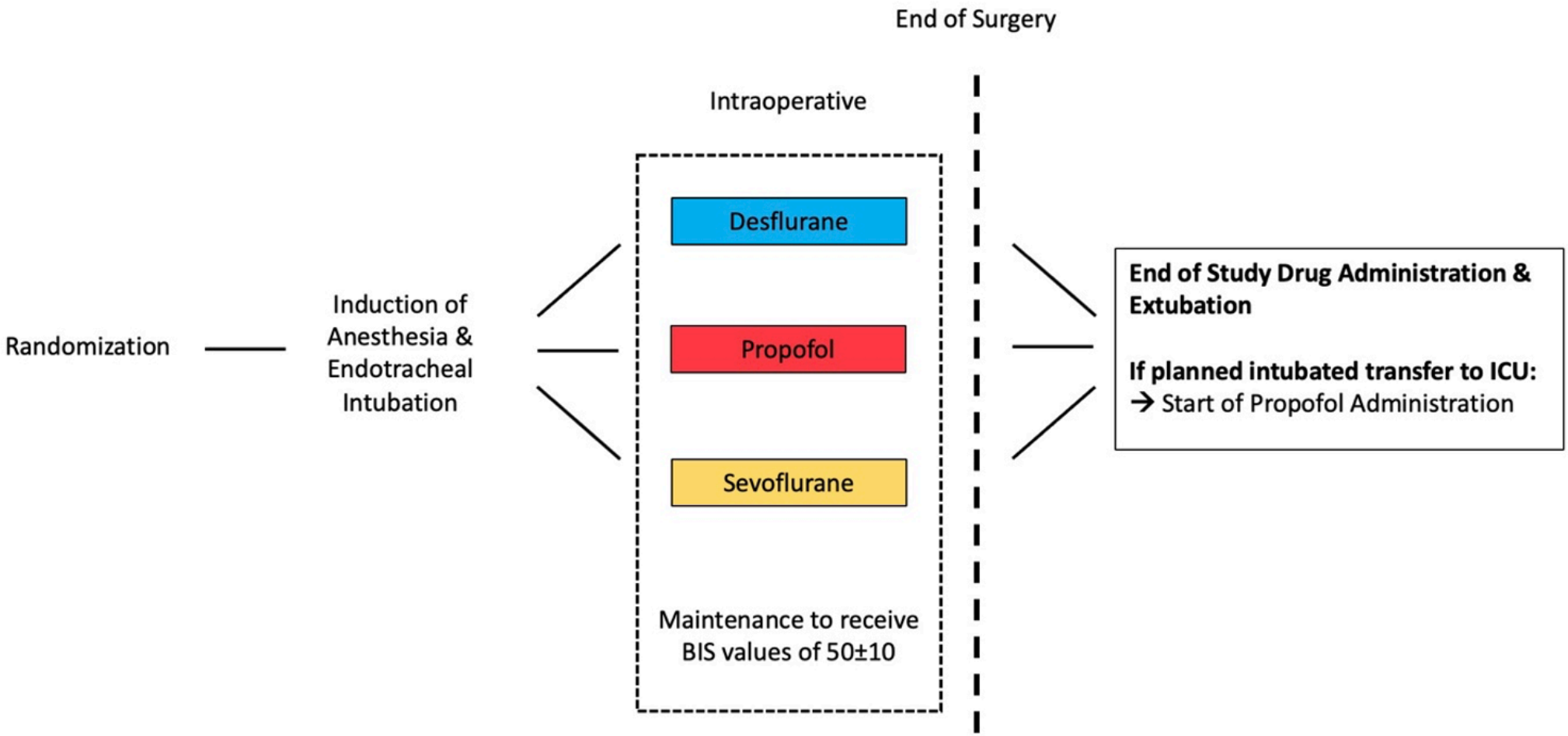
Figure 1. Study procedure



BIS, bispectral index; ICU, intensive care unit.

Supplementary Online Content

eAppendix 1. List of investigators RAPID II Trial

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. List of investigators RAPID II Trial

1. Medical University of Vienna: Nikolas Adamowitsch; David Emler; Edith Fleischmann; Melanie Fraunschiel; Alexandra Graf; Nicole Hantakova; Beatrix Hochreiter; Kira Margarete Hörl; Katharina Horvath; Barbara Kabon; Helena Langthaler; Magdalena List; Christian Reiterer; Barbara Rossi; Simon Schallmeiner; Mathias Stiefsohn; Alexander Taschner; Giulia Zanvettor; Florian Wolfgang Zenz; Oliver Zotti;
2. Medical University of Innsbruck: Christine Eckhardt; Iris Emshoff; Christoph Geiger; Nicole Innerhofer; Mario Kofler; Sasa Rajsic; Beatrix Reyer; Barbara Sinner; Susanne Trübsbach; Melanie Widmann;

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

We defined the following surgeries to meet the criteria for moderate- to high-risk major noncardiac surgery:

- Major general surgery: complex visceral resection, partial or total colectomy, gastrectomy, partial liver resection, pancreas resection, oesophageal resection, anterior rectal resection, retroperitoneal tumour resection, small bowel resection
- Major urologic surgery: prostatectomy, cystectomy, nephrectomy, retroperitoneal tumour resection, major open lymphadenectomy
- Major gynaecologic surgery: retroperitoneal tumour resection, exenteration, cytoreduction surgery, open hysterectomy
- Major orthopaedic surgery: total hip replacement, partial hip replacement, total knee replacement

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. BMI > 45kg.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, heart)
8. Patients undergoing hyperthermic intraperitoneal chemotherapy surgery
9. ICU patients undergoing surgery

BMI, body mass index; ICU, intensive care unit.

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	DSST, TMT Part A, TMT Part B	Preoperative, postoperative day 5
	Need of supplemental oxygen	Litres.minute^{-1}	During PACU/ICU stay
	Length of stay in ICU	Number of days at ICU	During ICU stay
	Early PONV	Patient assessment of PONV episode	First two 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 (DAH_{30})	Phone Follow-Up, patient records	30 days after surgery
	Long-term neurocognitive disorder	MoCA test via phone Follow-Up	Preoperative, 1 year after surgery
	AUC of inflammatory biomarkers	CRP, IL-6, PCT	Preoperative, within two hours after surgery, postoperative day 2
	AUC of cardiac biomarkers	Troponin T, NT-proBNP, Copeptin	Preoperative, within two hours after surgery, postoperative day 2
	AUC of neuronal injury biomarkers	S100-B, NSE	Preoperative, within two hours after surgery, postoperative day 2
	One-year all-cause mortality		One year after surgery
Sub-Study Outcomes			
	Advanced Neuro-Biomarkers	NfL, GFAP	Preoperative, postoperative day 3

CAM, confusion assessment method; ICU, intensive care unit; dNR, delayed neurocognitive recovery; DSST, digit symbol substitution test; TMT, trail making test; PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; DAH_{30}, number of days at home in the first month after surgery; NCD, neurocognitive disorder; MoCA, Montreal Cognitive Assessment; AUC, area under the curve; CRP, C-reactive protein; IL-6, Interleukin-6; PCT, Procalcitonin; NT-proBNP, N-terminal pro-brain-natriuretic peptide; NSE, neuron-specific enolase; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein.

BMJ Open

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

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Primary Subject Heading:	Anaesthesia
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The effect of desflurane, sevoflurane, or propofol on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 maintenance of anaesthesia on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 multi-centre, prospective, observer-blinded, randomised controlled clinical trial we will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac surgery lasting at least two 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 to 60. Our primary outcome will be the incidence of postoperative delirium within the first five postoperative days. Postoperative delirium will be assessed using the 3D-Confusion Assessment Method (3D-CAM) or CAM-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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other pre-defined 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:

ClinicalTrials.gov NCT05990790;

https://clinicaltrials.gov/study/NCT05990790?term=NCT05990790&rank=1

Strengths and limitations of this study:

- This will be a multi-centre 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 noncardiac 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 noncardiac 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 stay 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 Anesthesiologists 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 noncardiac 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 to sevoflurane-anaesthesia.[16] However, so far data regarding the effects of desflurane as compared to 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 to sevoflurane, [17–21] we could not observe in one of our previous studies a significant difference immediate postoperative recovery in older adults undergoing minor- to moderate-risk noncardiac surgery.[22] Nevertheless, the effect of desflurane versus sevoflurane versus propofol on the incidence of postoperative delirium in older adults undergoing major noncardiac 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 to anaesthesia with sevoflurane or anaesthesia with propofol in older adults undergoing

moderate- to high-risk major noncardiac surgery lasting at least two 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 to anaesthesia with sevoflurane or anaesthesia with propofol.

Methods and Analysis

Trial Design

We will conduct the RAPID-II trial, a multi-centre, observer-blinded, prospective, randomised, three-arm parallel arm clinical trial at the Medical University of Vienna and the Medical University Innsbruck. All members of the RAPID-II investigator group are listed in Online Supplement 1. We will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac 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 the 3rd of September 2023.

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 eAppendix 2 of the Online Supplement. They will further approach eligible patients to obtain informed consent before surgery. 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.

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. BMI > 45kg.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, heart)
8. Patients undergoing hyperthermic intraperitoneal chemotherapy surgery
9. ICU patients undergoing surgery

BMI, body mass index; ICU, intensive care unit.

Data management

Electronic data will be recorded in the data management system "Clincase", Version 2.7.0.12 hosted by IT Services & strategic information management of the Medical University of Vienna, Vienna, Austria.

Randomisation and blinding

We will randomise patients within one 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 & strategic information management Department of the Medical University of Vienna, 1090 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 to 60.

Sevoflurane group: after induction of anaesthesia, anaesthesia will be maintained with goal-directed administration of sevoflurane with an intraoperative goal of bispectral index (BIS) 40 to 60.

Propofol group: after induction of anaesthesia, anaesthesia will be maintained with a goal-directed continuous infusion of propofol with an intraoperative goal of bispectral index (BIS) 40 to 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 minutes after intubation to set anaesthesia to the target BIS value. Desflurane, sevoflurane and propofol respectively will be titrated and adjusted using processed electroencephalography for a target BIS of 40 to 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 supra-maximal stimulation (Train-of-four stimulation, target <75%). For mechanical ventilation, we will maintain an inspiratory FiO_2 between 0.3 and 0.5 to achieve a SpO_2 of at least 93% or pO_2 of >80mmHg. Tidal volumes will be set between 6 and 8mL lean body weight to maintain end-tidal CO_2 within 35-40mmHg. Positive end-expiratory pressure will be set at 5mmHg or higher according to the patients' requirements. Intraoperative 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 65mmHg. 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 $8 g.dL^{-1}$. Anaesthesiologic adjuvants, e.g. 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 intensive care units (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 postoperative nausea and vomiting

(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 one 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 pro-brain 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 two hours after surgery and on the second postoperative day. Furthermore, we will assess one-year all-cause mortality one year after surgery in all patients.

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

A detailed description of primary, secondary, exploratory, and sub-study specific outcomes and their assessments is shown in Table 2.

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	DSST, TMT Part A, TMT Part B	Preoperative, postoperative day 5
	Need of supplemental oxygen	Litres.minute^{-1}	During PACU/ICU stay
	Length of stay in ICU	Number of days at ICU	During ICU stay
	Early PONV	Patient assessment of PONV episode	First two 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 (DAH_{30})	Phone Follow-Up, patient records	30 days after surgery
	Long-term neurocognitive disorder	MoCA test via phone Follow-Up	Preoperative, 1 year after surgery
	AUC of inflammatory biomarkers	CRP, IL-6, PCT	Preoperative, within two hours after surgery, postoperative day 2
	AUC of cardiac biomarkers	Troponin T, NT-proBNP, Copeptin	Preoperative, within two hours after surgery, postoperative day 2
	AUC of neuronal injury biomarkers	S100-B, NSE	Preoperative, within two hours after surgery, postoperative day 2
	One-year all-cause mortality		One year after surgery
Sub-Study Outcomes			
	Advanced Neuro-Biomarkers	NfL, GFAP	Preoperative, postoperative day 3

CAM, confusion assessment method; ICU, intensive care unit; dNR, delayed neurocognitive recovery; DSST, digit symbol substitution test; TMT, trail making test; PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; DAH_{30}, number of days at home in the first month after surgery; NCD, neurocognitive disorder; MoCA, Montreal Cognitive Assessment; AUC, area under the curve; CRP, C-reactive protein; IL-6, Interleukin-6; PCT, Procalcitonin; NT-proBNP, N-terminal pro-brain-natriuretic peptide; NSE, neuron-specific enolase; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein.

Measurements

Demographic and morphometric data

Basic data including age, sex, body mass index, and ASA physical status, will be recorded. We will record medical history including comorbidities, long-term medication, and history of tobacco or alcohol use and type of surgery.

Perioperative data

Routine intra- 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 (NRS) in the PACU, ICU, and on the ward twice daily 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 3D-confusion assessment method (3D-CAM) evaluations starting on the evening of the day of surgery (6 p.m. – 10 p.m.). Following 3D-CAM evaluations will be performed twice daily – in the mornings (5 a.m. – 11 a.m.) and evenings (6 p.m. – 10 p.m.) 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 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 (DSST), trail making test (TMT) 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 two days. Delayed neurocognitive recovery will be defined in accordance with the

ISOPOCD-1 study when a patient has a Z-score on two or all tests or the combined Z-score is below -1.96 standard deviation.[26]

For the assessment of neurocognitive disorder, we will further perform an adapted Montreal Cognitive Assessment (MoCA) test (telephone MoCA) before surgery and one 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 five days. PONV will be defined as subjective symptoms of nausea and/or occurrence of vomiting at each timepoint. Oxygen supplementation will be recorded by number of litres.minute^{-1} oxygen administered for SpO2 ≥93% at PACU or ICU respectively. Furthermore, we will record the intraoperative use of vasopressors. We will record the duration of stay in the ICU in 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 one 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 Innsbruck respectively. Blood samples will be treated with standard of care to provide 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 two hours after surgery and on the second postoperative day. Sub-study specific blood samples of NfL and GFAP will be collected shortly before induction of anaesthesia and on the third postoperative day. Sub-study 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, standard deviations, median, and interquartile ranges. 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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other confounding factors (e.g. age, BMI, ASA physical status, duration of anaesthesia, additional epidural/regional anaesthesia, 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 positive delirium assessment were performed before patients' death. As 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 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 ITT population, defined as all randomized 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 intention to treat 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, i.e., without major protocol violations.

The secondary outcome, the incidence of delayed neurocognitive recovery, will be evaluated between the study groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of

delayed neurocognitive recovery will be performed accounting for 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 ICU and death as competing event accounting for 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 Chi-Square-tests. Furthermore, logistic regression models for the incidences of PONV in the early and late postoperative period will be performed.

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

The secondary outcome, death within five days after surgery, will be compared between the groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of death will be performed.

The exploratory outcome, 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, incidence of neurocognitive disorder one year after surgery, will be compared using Chi-Square-tests. As exploratory outcomes, 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, probability of all-cause death within one 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 5-50%,[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% versus 15%).

Two interim analyses, one after 1/3 and one after 2/3 of recruitment are pre-planned. 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 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 odds ratio of 0.529 (for proportions of 0.25 as compared to 0.15), we calculated a needed sample size of 431 patients per group to achieve a power of 0.9.

We assumed a drop-out 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

The following experienced researchers will compromise the Data Safety Monitoring Board (DSMB): Prof. Dr. Eva Base (Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Division of Cardiothoracic and Vascular Anaesthesia, Medical University of Vienna, Austria), Prof. Dr. Michael Wolzt (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Markus Zeitlinger (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Gerd Silberhumer (Department of General Surgery, Medical University of Vienna, Austria).

Patients' safety will be monitored through the data and safety monitoring board. The DSMB will evaluate adverse events (AEs, SAEs, SUSARs, ADR) for the two pre-planned interim analyses. In detail, the DSMB will evaluate adverse events 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 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 for 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 intention to treat. In the case an adverse event or a serious adverse event 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 significant incidence of adverse events evaluated by the DSMB, the sponsor (Medical University of Vienna) will notify the competent authorities the end of the study including an appropriate justification. If the study will be terminated because of safety reasons the European Medicines Agency (EMA) will be notified as well.

Data monitoring

Data monitoring will be performed by the Clinical Trials Coordination Centre of the Medical University of Vienna, who are independent from the investigators and the sponsor and who have no competing interests. Data monitoring will be performed in regular intervals after 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 CRF and 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, ethics committee (Ethic committee of the Medical University of Vienna), and if requested the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG)).

Data will be stored after publishing of the trial and all of the sub-studies by Iron Mountain Austrian Archivierungs GmbH (Gewerbeparkstraße 3, 2282 Markgrafneusiedl, Austria) for a period of not less than twenty-five 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 noncardiac 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 five days as compared to 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 to the propofol group three 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 emphasized that this is not based on any scientific evidence.

In fact, pharmacokinetic characteristics of desflurane lead to significantly faster elimination as compared to 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 to sevoflurane.[35,36] Specifically, the time until 90% of sevoflurane is eliminated increases significantly after two 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 command, faster reciting of full name, and faster orientation as compared to sevoflurane.[17–21] Furthermore, a recent pilot study showed that in patients, who received desflurane for major surgery, postoperative cognitive function assessed via Mini Mental State Examination (MMSE) was significantly higher after desflurane anaesthesia as compared to sevoflurane.[37] Interestingly, studies investigating different anaesthetics with a clinical meaningful neurological outcome are still lacking, specifically in regards 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 to 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

spectral density array 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 to 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 spectral density arrays between the groups.

The use of volatile anaesthetics has been criticized 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 has 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 will be 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. Firstly, due to the different methods of administration and because this is a large, multi-centre, pragmatic trial, blinding of the attending anaesthetists will not be suitable. However, to provide equal depth of anaesthesia, dosage of anaesthetics will be standardized for all patients with an aim of BIS values 40 to 60. Furthermore, DSA will be further analysed and compared between the groups. To further limit possible bias, all postoperative outcomes will only be assessed by study personnel blinded toward the randomly assigned group. Secondly, we will only include patients planned for major noncardiac 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 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 multi-centre, 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 noncardiac 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: Version 5.0, March 5, 2024. Patient recruitment started in September 2023.

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Competing Interests

The authors have no conflicts of interest.

Authors' contributions

AT, CR, EF, BK, BS: conceptualisation and study design; AT, CR, EF, AG: first draft of the manuscript; CE, KH, NA, NH, BH, OZ, DE, KMH, HL, ML, BR, SS, MS, GZ, FWZ, IE, CG, NI, MK, SR, BR, ST, MW: data collection; MF, AG: data management; AG: statistical analysis; AT, EF, BK, BS, CE, KH, NA, NH, BH, OZ, MF, AG, CR: editing and critical review of the manuscript; All authors read and approved the final manuscript. AT is the guarantor.

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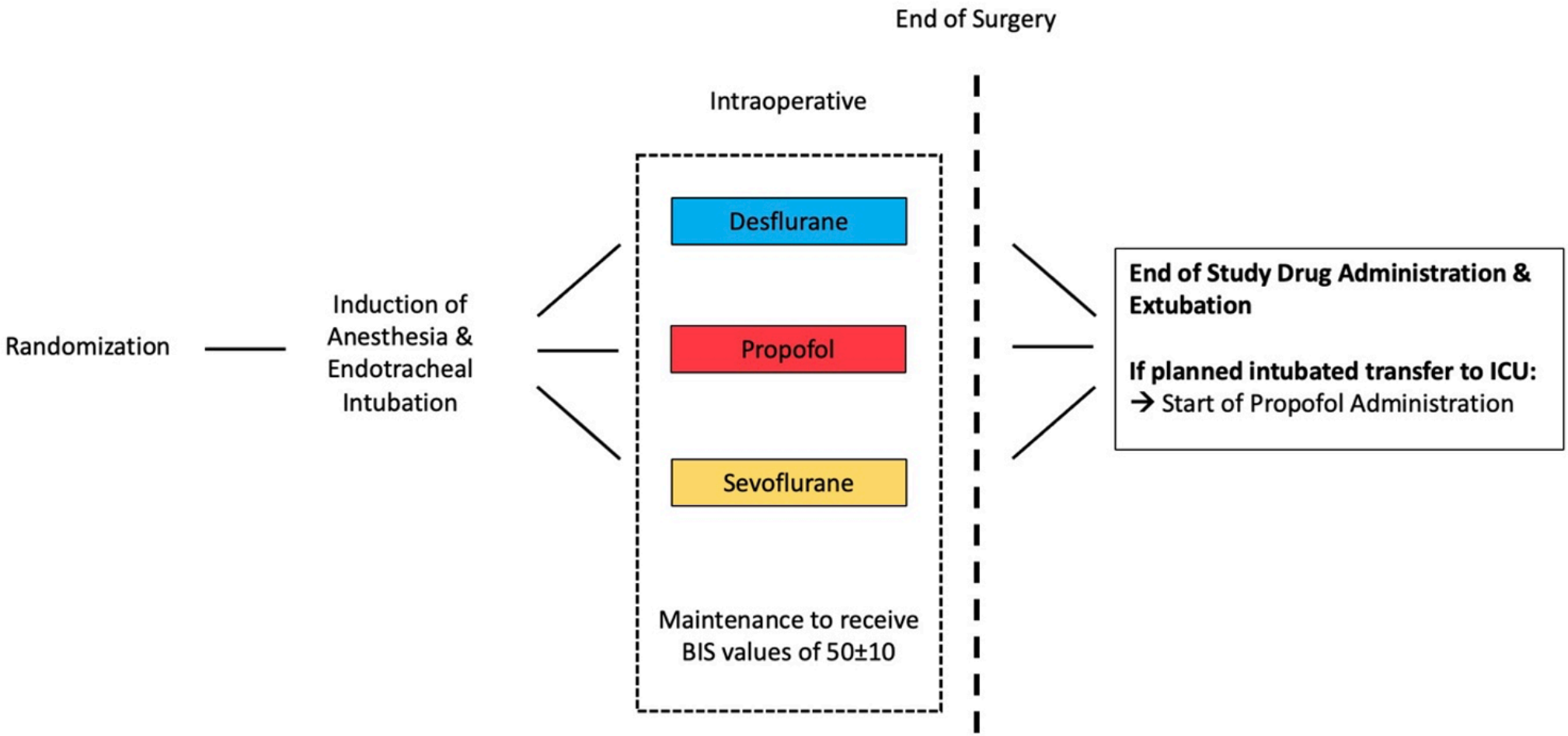
Captions for Figures

Figure 1. Study procedure

Figure 1. Study procedure



BIS, bispectral index; ICU, intensive care unit.

Supplementary Online Content

eAppendix 1. List of investigators RAPID II Trial

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. List of investigators RAPID II Trial

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2. Medical University of Innsbruck: Christine Eckhardt; Iris Emshoff; Christoph Geiger; Nicole Innerhofer; Mario Kofler; Sasa Rajsic; Beatrix Reyer; Barbara Sinner; Susanne Trübsbach; Melanie Widmann;

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

We defined the following surgeries to meet the criteria for moderate- to high-risk major noncardiac surgery:

- Major general surgery: complex visceral resection, partial or total colectomy, gastrectomy, partial liver resection, pancreas resection, oesophageal resection, anterior rectal resection, retroperitoneal tumour resection, small bowel resection
- Major urologic surgery: prostatectomy, cystectomy, nephrectomy, retroperitoneal tumour resection, major open lymphadenectomy
- Major gynaecologic surgery: retroperitoneal tumour resection, exenteration, cytoreduction surgery, open hysterectomy
- Major orthopaedic surgery: total hip replacement, partial hip replacement, total knee replacement

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

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The effect of desflurane, sevoflurane, or propofol on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 maintenance of anaesthesia on the incidence of postoperative delirium in older adults undergoing moderate- to high-risk major noncardiac 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 multi-centre, prospective, observer-blinded, randomised controlled clinical trial we will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac surgery lasting at least two 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 to 60. Our primary outcome will be the incidence of postoperative delirium within the first five postoperative days. Postoperative delirium will be assessed using the 3D-Confusion Assessment Method (3D-CAM) or CAM-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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other pre-defined 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:

ClinicalTrials.gov NCT05990790;

https://clinicaltrials.gov/study/NCT05990790?term=NCT05990790&rank=1

Strengths and limitations of this study:

- This will be a multi-centre 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 noncardiac 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 noncardiac 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 stay 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 Anesthesiologists 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 noncardiac 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 to sevoflurane-anaesthesia.[16] However, so far data regarding the effects of desflurane as compared to 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 to sevoflurane, [17–21] we could not observe in one of our previous studies a significant difference immediate postoperative recovery in older adults undergoing minor- to moderate-risk noncardiac surgery.[22] Nevertheless, the effect of desflurane versus sevoflurane versus propofol on the incidence of postoperative delirium in older adults undergoing major noncardiac 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 to anaesthesia with sevoflurane or anaesthesia with propofol in older adults undergoing

moderate- to high-risk major noncardiac surgery lasting at least two 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 to anaesthesia with sevoflurane or anaesthesia with propofol.

Methods and Analysis

Trial Design

We will conduct the RAPID-II trial, a multi-centre, observer-blinded, prospective, randomised, three-arm parallel arm clinical trial at the Medical University of Vienna and the Medical University Innsbruck. All members of the RAPID-II investigator group are listed in Online Supplement 1. We will include 1332 patients ≥ 65 years of age undergoing moderate- to high-risk major noncardiac 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 the 3rd of September 2023 and currently the estimated date of primary completion is 31st of December 2027 and the estimated study completion date is 31st of December 2028.

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 eAppendix 2 of the Online Supplement. They will further approach eligible patients to obtain informed consent before surgery. 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.

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. BMI > 45kg.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, heart)
8. Patients undergoing hyperthermic intraperitoneal chemotherapy surgery

9. ICU patients undergoing surgery

BMI, body mass index; ICU, intensive care unit.

Data management

Electronic data will be recorded in the data management system "Clincase", Version 2.7.0.12 hosted by IT Services & strategic information management of the Medical University of Vienna, Vienna, Austria.

Randomisation and blinding

We will randomise patients within one 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 & strategic information management Department of the Medical University of Vienna, 1090 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 to 60.

Sevoflurane group: after induction of anaesthesia, anaesthesia will be maintained with goal-directed administration of sevoflurane with an intraoperative goal of bispectral index (BIS) 40 to 60.

Propofol group: after induction of anaesthesia, anaesthesia will be maintained with a goal-directed continuous infusion of propofol with an intraoperative goal of bispectral index (BIS) 40 to 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 minutes after intubation to set anaesthesia to the target BIS value. Desflurane, sevoflurane and propofol respectively will be titrated and adjusted using processed electroencephalography for a target BIS of 40 to 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 supra-maximal stimulation (Train-of-four stimulation, target <75%). For mechanical ventilation, we will maintain an inspiratory FiO_2 between 0.3 and 0.5 to achieve a SpO_2 of at least 93% or pO_2 of >80mmHg. Tidal volumes will be set between 6 and 8mL lean body weight to maintain end-tidal CO_2 within 35-40mmHg. Positive end-expiratory pressure will be set at 5mmHg or higher according to the patients' requirements. Intraoperative 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 65mmHg. 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 $8 g.dL^{-1}$. Anaesthesiologic adjuvants, e.g. 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 intensive care units (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 postoperative nausea and vomiting (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 one 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 pro-brain 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 two hours after surgery and on the second postoperative day. Furthermore, we will assess one-year all-cause mortality one year after surgery in all patients.

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

A detailed description of primary, secondary, exploratory, and sub-study specific outcomes and their assessments is shown in Table 2.

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	DSST, TMT Part A, TMT Part B	Preoperative, postoperative day 5

	Need of supplemental oxygen	Litres.minute^{-1}	During PACU/ICU stay
	Length of stay in ICU	Number of days at ICU	During ICU stay
	Early PONV	Patient assessment of PONV episode	First two 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 (DAH_{30})	Phone Follow-Up, patient records	30 days after surgery
	Long-term neurocognitive disorder	MoCA test via phone Follow-Up	Preoperative, 1 year after surgery
	AUC of inflammatory biomarkers	CRP, IL-6, PCT	Preoperative, within two hours after surgery, postoperative day 2
	AUC of cardiac biomarkers	Troponin T, NT-proBNP, Copeptin	Preoperative, within two hours after surgery, postoperative day 2
	AUC of neuronal injury biomarkers	S100-B, NSE	Preoperative, within two hours after surgery, postoperative day 2
	One-year all-cause mortality		One year after surgery
Sub-Study Outcomes			
	Advanced Neuro-Biomarkers	NfL, GFAP	Preoperative, postoperative day 3

CAM, confusion assessment method; ICU, intensive care unit; dNR, delayed neurocognitive recovery; DSST, digit symbol substitution test; TMT, trail making test; PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; DAH_{30}, number of days at home in the first month after surgery; NCD, neurocognitive disorder; MoCA, Montreal Cognitive Assessment; AUC, area under the curve; CRP, C-reactive protein; IL-6, Interleukin-6; PCT, Procalcitonin; NT-proBNP, N-terminal pro-brain-natriuretic peptide; NSE, neuron-specific enolase; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein.

Measurements

Demographic and morphometric data

Basic data including age, sex, body mass index, and ASA physical status, will be recorded. We will record medical history including comorbidities, long-term medication, and history of tobacco or alcohol use and type of surgery.

Perioperative data

Routine intra- 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 (NRS) in the PACU, ICU, and on the ward twice daily 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 3D-confusion assessment method (3D-CAM) evaluations starting on the evening of the day of surgery (6 p.m. – 10 p.m.). Following 3D-CAM evaluations will be performed twice daily – in the mornings (5 a.m. – 11 a.m.) and evenings (6 p.m. – 10 p.m.) 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 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 (DSST), trail making test (TMT) 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 two days. Delayed neurocognitive recovery will be defined in accordance with the ISOPOCD-1 study when a patient has a Z-score on two or all tests or the combined Z-score is below -1.96 standard deviation.[26]

For the assessment of neurocognitive disorder, we will further perform an adapted Montreal Cognitive Assessment (MoCA) test (telephone MoCA) before surgery and one 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 five days. PONV will be defined as subjective symptoms of nausea and/or occurrence of vomiting at each timepoint. Oxygen supplementation will be recorded by number of litres.minute^{-1} oxygen administered for SpO2 ≥93% at PACU or ICU respectively. Furthermore, we will record the intraoperative use of vasopressors. We will record the duration of stay in the ICU in 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 one 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 Innsbruck respectively. Blood samples will be treated with standard of care to provide 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 two hours after surgery and on the second postoperative day. Sub-study specific blood samples of NfL

and GFAP will be collected shortly before induction of anaesthesia and on the third postoperative day. Sub-study 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, standard deviations, median, and interquartile ranges. 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 Chi-Square-test. Furthermore, a logistic regression model for the incidence of postoperative delirium will be performed accounting for randomised group as well as other confounding factors (e.g. age, BMI, ASA physical status, duration of anaesthesia, additional epidural/regional anaesthesia, 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 positive delirium assessment were performed before patients' death. As 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 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 ITT population, defined as all randomized 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 intention to treat 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, i.e., without major protocol violations.

The secondary outcome, the incidence of delayed neurocognitive recovery, will be evaluated between the study groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of delayed neurocognitive recovery will be performed accounting for 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 ICU and death as competing event accounting for 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 Chi-Square-tests. Furthermore, logistic regression models for the incidences of PONV in the early and late postoperative period will be performed.

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

The secondary outcome, death within five days after surgery, will be compared between the groups using a Chi-Square-test. Furthermore, a logistic regression model for the probability of death will be performed.

The exploratory outcome, 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, incidence of neurocognitive disorder one year after surgery, will be compared using Chi-Square-tests. As exploratory outcomes, 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, probability of all-cause death within one 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 5-50%,[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% versus 15%).

Two interim analyses, one after 1/3 and one after 2/3 of recruitment are pre-planned. 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 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 odds ratio of 0.529 (for proportions of 0.25 as compared to 0.15), we calculated a needed sample size of 431 patients per group to achieve a power of 0.9.

We assumed a drop-out 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

The following experienced researchers will compromise the Data Safety Monitoring Board (DSMB): Prof. Dr. Eva Base (Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Division of Cardiothoracic and Vascular Anaesthesia, Medical University of Vienna, Austria), Prof. Dr. Michael Wolzt (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Markus Zeitlinger (Department of Clinical Pharmacology, Medical University of Vienna, Austria), Prof. Dr. Gerd Silberhumer (Department of General Surgery, Medical University of Vienna, Austria).

Patients' safety will be monitored through the data and safety monitoring board. The DSMB will evaluate adverse events (AEs, SAEs, SUSARs, ADR) for the two pre-planned interim analyses. In detail, the DSMB will evaluate adverse events 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 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 for 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 intention to treat. In the case an adverse event or a serious adverse event 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 significant incidence of adverse events evaluated by the DSMB, the sponsor (Medical University of Vienna) will notify the competent authorities the end of the study including an appropriate justification. If the study will be terminated because of safety reasons the European Medicines Agency (EMA) will be notified as well.

Data monitoring

Data monitoring will be performed by the Clinical Trials Coordination Centre of the Medical University of Vienna, who are independent from the investigators and the sponsor and who have no competing interests. Data monitoring will be performed in regular intervals after 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 CRF and 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, ethics committee (Ethic committee of the Medical University of Vienna), and if requested the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG)).

Data will be stored after publishing of the trial and all of the sub-studies by Iron Mountain Austrian Archivierungs GmbH (Gewerbeparkstraße 3, 2282 Markgrafneusiedl, Austria) for a period of not less than twenty-five 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 noncardiac 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 five days as compared to 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 to the propofol group three 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 emphasized that this is not based on any scientific evidence.

In fact, pharmacokinetic characteristics of desflurane lead to significantly faster elimination as compared to 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 to sevoflurane.[35,36] Specifically, the time until 90% of sevoflurane is eliminated increases significantly after two 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 command, faster reciting of full name, and faster orientation as compared to sevoflurane.[17–21] Furthermore, a recent pilot study showed that in patients, who received desflurane for major surgery, postoperative cognitive function assessed via Mini Mental State Examination (MMSE) was significantly higher after desflurane anaesthesia as compared to sevoflurane.[37] Interestingly, studies investigating different anaesthetics with a clinical meaningful neurological outcome are still lacking, specifically in regards 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 to 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

spectral density array 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 to 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 spectral density arrays between the groups.

The use of volatile anaesthetics has been criticized 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 has 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 will be 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. Firstly, due to the different methods of administration and because this is a large, multi-centre, pragmatic trial, blinding of the attending anaesthetists will not be suitable. However, to provide equal depth of anaesthesia, dosage of anaesthetics will be standardized for all patients with an aim of BIS values 40 to 60. Furthermore, DSA will be further analysed and compared between the groups. Nevertheless, it can't be ruled out that BIS values might be different between the groups, which could pose as 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 toward the randomly assigned group. Secondly, we will only include patients planned for major noncardiac 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 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 multi-centre, 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 noncardiac 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: Version 5.0, March 5, 2024. Patient recruitment started in September 2023.

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Competing Interests

The authors have no conflicts of interest.

Authors' contributions

AT, CR, EF, BK, BS: conceptualisation and study design; AT, CR, EF, AG: first draft of the manuscript; CE, KH, NA, NH, BH, OZ, DE, KMH, HL, ML, BR, SS, MS, GZ, FWZ, IE, CG, NI, MK, SR, BR, ST, MW: data collection; MF, AG: data management; AG: statistical analysis; AT, EF, BK, BS, CE, KH, NA, NH, BH, OZ, MF, AG, CR: editing and critical review of the manuscript; All authors read and approved the final manuscript. AT is the guarantor.

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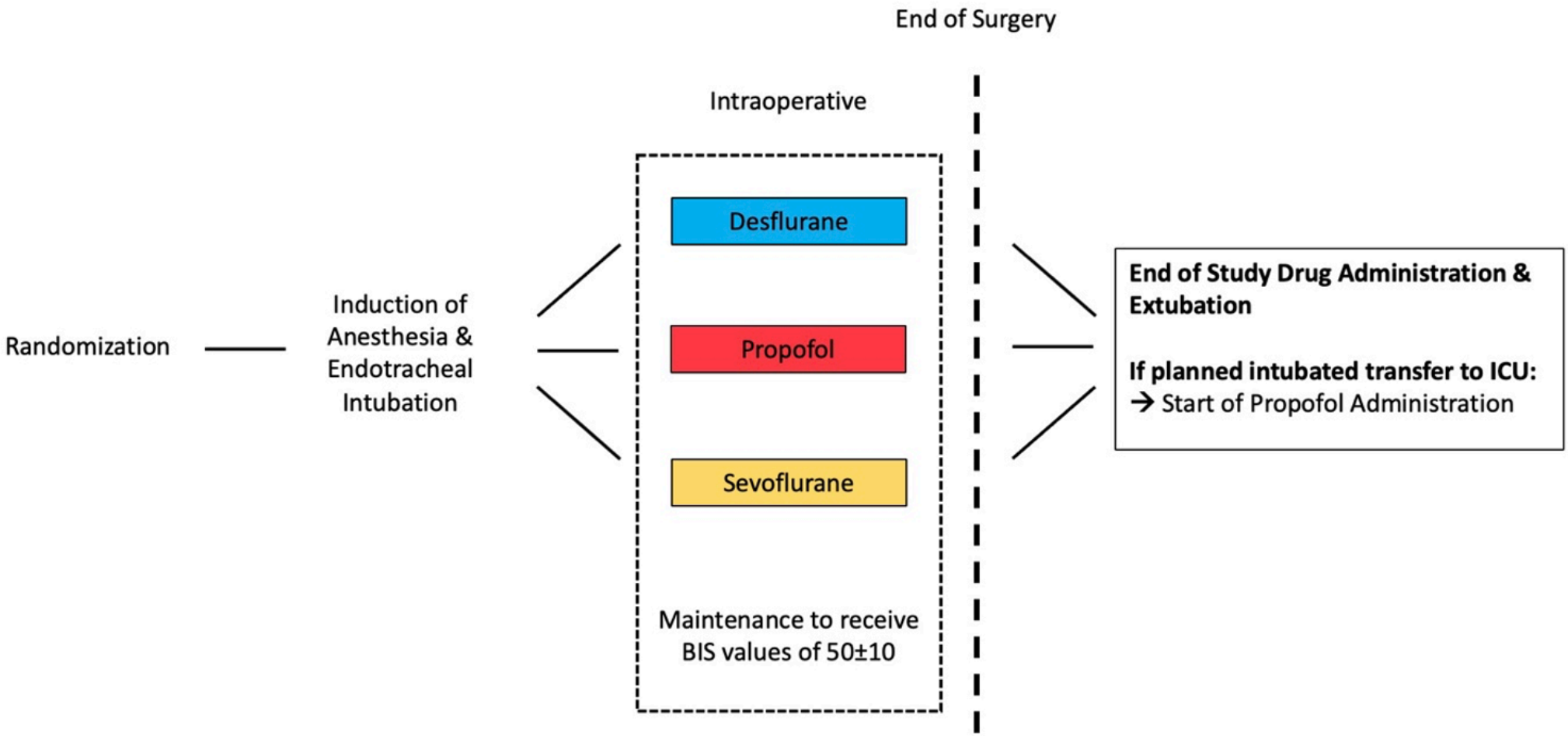
Captions for Figures

Figure 1. Study procedure

Figure 1. Study procedure



BIS, bispectral index; ICU, intensive care unit.

Supplementary Online Content

eAppendix 1. List of investigators RAPID II Trial

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. List of investigators RAPID II Trial

1. Medical University of Vienna: Nikolas Adamowitsch; David Emler; Edith Fleischmann; Melanie Fraunschiel; Alexandra Graf; Nicole Hantakova; Beatrix Hochreiter; Kira Margarete Hörl; Katharina Horvath; Barbara Kabon; Helena Langthaler; Magdalena List; Christian Reiterer; Barbara Rossi; Simon Schallmeiner; Mathias Stiefsohn; Alexander Taschner; Giulia Zanvettor; Florian Wolfgang Zenz; Oliver Zotti;
2. Medical University of Innsbruck: Christine Eckhardt; Iris Emshoff; Christoph Geiger; Nicole Innerhofer; Mario Kofler; Sasa Rajsic; Beatrix Reyer; Barbara Sinner; Susanne Trübsbach; Melanie Widmann;

eAppendix 2. Definition of moderate- to high-risk major noncardiac surgery

We defined the following surgeries to meet the criteria for moderate- to high-risk major noncardiac surgery:

- Major general surgery: complex visceral resection, partial or total colectomy, gastrectomy, partial liver resection, pancreas resection, oesophageal resection, anterior rectal resection, retroperitoneal tumour resection, small bowel resection
- Major urologic surgery: prostatectomy, cystectomy, nephrectomy, retroperitoneal tumour resection, major open lymphadenectomy
- Major gynaecologic surgery: retroperitoneal tumour resection, exenteration, cytoreduction surgery, open hysterectomy
- Major orthopaedic surgery: total hip replacement, partial hip replacement, total knee replacement

PatientInneninformation[1] und Einwilligungserklärung

zur Teilnahme an der klinischen Studie

Einfluss von Desfluran versus Sevofluran versus Propofol auf das Auftreten von Delir bei älteren PatientInnen, die sich einer nicht-herzchirurgischen Operation mit mittelgroßem oder großem Risiko unterziehen

Eine prospektive, verblindete, randomisierte, klinische Studie

The effect of Desflu**R**ane versus Sevoflur**A**ne versus **P**ropofol on postoperat**i**ve **D**elirium in elderly patients undergoing moderate- to high-risk abdominal surgery – a prospective observer-blinded, randomized, clinical trial

RAPID-II Trial

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,

[1] Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter.

- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck der klinischen Studie?

Der Sponsor dieser Studie ist: *Medizinische Universität Wien.* Der Sponsor ist für die Verfassung und für die ordnungsgemäße Durchführung der Studie verantwortlich.

Ältere Patienten haben nach größeren nicht-herzchirurgischen Operationen ein erhöhtes Risiko nach einer Operation ein Delir zu entwickeln. Unter Delir nach Operationen versteht man einen kurzfristigen Verwirrtheitszustand, der bis zu mehreren Tagen anhalten kann. Darüber hinaus haben Studien gezeigt, dass Delir nach Operationen auch langfristig die neurokognitive Funktion, das heißt die Denkleistung, beeinträchtigen kann. Zusätzlich ist ein Delir nach Operationen auch mit einem verzögerten Erholungsverlauf nach der Operation vergesellschaftet. Interessanterweise gibt es bis jetzt keine eindeutigen Studien, welche vorbeugende Gegenmaßnahmen zur Entstehung von Delir beweisen konnten. Aus diesem Grund untersuchen wir in der vorliegenden Studie, ob möglicherweise die Wahl des Narkosemittels einen Einfluss auf die Entstehung von Delir haben könnte.

Für die Aufrechterhaltung von Narkosen während einer Operation werden üblicherweise Narkosegase, wie zum Beispiel Desfluran oder Sevofluran, bzw. ein flüssiges Narkosemittel, wie zum Beispiel Propofol verwendet. Alle diese Narkosemittel werden routinemäßig im klinischen Betrieb eingesetzt. Daten bezüglich eines möglichen Vorteils eines dieser Narkosemittel bezugnehmend auf das Auftreten von Delir nach Operationen liegen bis dato noch nicht vor. Alle diese Narkosemittel haben einen ähnlichen Wirkmechanismus, unterscheiden sich jedoch an der Geschwindigkeit, welche das Narkosemittel braucht, um wieder aus dem Körper ausgeschieden zu werden. Das führt dazu, dass auch die Wirkdauer der Narkosemittel unterschiedlich ist. Daher nehmen wir an, dass das Narkosemittel mit der kürzesten Wirkdauer einen positiven Effekt, im Speziellen den größten vorbeugenden Effekt auf die Entstehung von Delir nach Operationen hat, verglichen mit den länger-wirkenden Narkosemitteln.

Ziel dieser Studie ist es, herauszufinden, ob durch die Gabe von den oben genannten drei unterschiedlichen Narkosemedikamenten (Desfluran, Sevofluran, Propofol) zur Narkoseaufrechterhaltung während Ihrer Operation ein verringertes Auftreten von Delir nach Operationen erzielt werden kann.

2.Welche anderen Behandlungsmöglichkeiten gibt es?

Zur Aufrechterhaltung Ihrer Narkose werden derzeit routinemäßig Desfluran, Sevofluran und Propofol im klinischen Alltag verwendet. An unserer Klinik werden keine anderen Narkosemittel für die Aufrechterhaltung

der Narkose während einer Operation routinemäßig verwendet. Derzeit gibt es keinen festgelegten klinischen Standard, welches Narkosemedikament zu verwenden ist. Die jeweilige Wahl des Narkosemedikaments für die Operation richtet sich demnach ausschließlich nach dem Ermessen des behandelnden Arztes.

3. Wie läuft die klinische Prüfung ab?

Diese klinische Prüfung wird an der Universitätsklinik für Anästhesie, Allgemeine Intensivmedizin und Schmerztherapie der Medizinischen Universität Wien, der Universitätsklinik für Anästhesiologie und Intensivmedizin der Medizinischen Universität Graz und der Universitätsklinik für Anästhesie und Intensivmedizin der Medizinischen Universität Innsbruck durchgeführt, und es werden insgesamt 1332 Patienten daran teilnehmen.

Ihre Teilnahme an dieser klinischen Prüfung wird am Tag vor Ihrer Operation beginnen. Bei Teilnahme an dieser klinischen Prüfung wird die Narkose wie üblich mit einem Narkosemittel und einem Schmerzmittel über die Vene eingeleitet. Für die Dauer der Operation werden Sie zur Beatmung einen Beatmungsschlauch erhalten. Erst nachdem Sie bereits in Vollnarkose sind, wird dieser von Ihrem Narkosearzt vorsichtig eingeführt. Danach wird das Narkosegas über die Atemluft zugeführt oder das Narkosemittel über die Vene durchgehend für die Aufrechterhaltung Ihrer Narkose verabreicht. Während der gesamten Operation wird die Tiefe Ihrer Narkose anhand eines Monitors genau überwacht und gesteuert. Sobald die Operation beendet ist, wird die Zufuhr des Narkosemedikamentes beendet. Nachdem Sie wieder selbstständig atmen und Sie kontaktierbar sind, wird – wie derzeitiger klinischer Standard – der Beatmungsschlauch wieder entfernt und Sie werden zur weiteren Überwachung in den Aufwachraum oder die Intensivstation transferiert. Im Aufwachraum und Intensivstation werden Ihr Blutdruck, Ihre Herzfrequenz und Ihre Sauerstoffsättigung durchgehend überwacht und aufgezeichnet. Ebenso werden Sie nach Übelkeit, Stärke der Schmerzen, mögliche Einschränkungen Ihrer Atmung gefragt. In den ersten fünf Tagen nach der Operation wird ein Studienmitarbeiter Sie zweimal täglich auf der Intensivstation oder Normalstation besuchen und einen Fragebogen zur Erhebung eines eventuellen Verwirrtheitszustandes mit Ihnen durchgehen, der circa 5 bis 10 Minuten in Anspruch nimmt.

Insgesamt umfasst die Teilnahme an dieser klinischen Prüfung den Zeitraum von dem Tag vor der Operation bis ein Jahr nach der Operation. 30 Tage und ein Jahr nach der Operation werden Sie von einem Studienmitarbeiter telefonisch kontaktiert und nach Ihrem Gesundheitszustand befragt. Bei der telefonischen Befragung wird außerdem ein Mitarbeiter von uns einen Fragebogen mit insgesamt 9 Fragen zur Feststellung Ihrer Denkleistung mit Ihnen durchführen. Das Telefongespräch wird ungefähr 5 bis 10 Minuten in Anspruch nehmen.

Diese Studie wird **randomisiert** und **verblindet** durchgeführt.

Randomisiert bedeutet, dass Sie am Tag Ihrer Operation per Zufallsprinzip einer der drei Gruppen zugeteilt werden.

Verblindet bedeutet, dass Sie nicht wissen, ob Sie Desfluran, Sevofluran oder Propofol erhalten. Ebenso weiß der Untersucher auf der Intensivstation und auf der Normalstation nicht, ob Sie Desfluran, Sevofluran oder Propofol erhalten haben.

Am Tag der Operation werden Sie mittels Zufallsgenerator einer der folgenden Gruppen zugeteilt:

Gruppe 1 (Desfluran): Nach Einleitung der Narkose wird Desfluran zur Aufrechterhaltung der Narkose während der gesamten Operation verwendet.

Gruppe 2 (Sevofluran): Nach Einleitung der Narkose wird Sevofluran zur Aufrechterhaltung der Narkose während der gesamten Operation verwendet.

Gruppe 3 (Propofol): Nach Einleitung der Narkose wird Propofol zur Aufrechterhaltung der Narkose während der gesamten Operation verwendet.

Bei Teilnahme an dieser Studie kommt es zu keiner Veränderung Ihrer klinischen Behandlung, es werden ausschließlich die unterschiedlichen Eigenschaften der oben genannten Narkosemedikamente auf das Auftreten von Delir untersucht.

Substudie I – Nierenfunktion: Im Rahmen dieser Substudie wird im Zuge der Studien-spezifischen Blutabnahmen eine zusätzliche Bestimmung der Nierenfunktion durchgeführt.

Substudie II – Neue Laborparameter zur Bestimmung der möglichen Schädigung von Nervenzellen: Im Rahmen dieser Substudie wird im Zuge der Studien-spezifischen Blutabnahmen weitere Laborwerte bestimmt, und zwar zur Messung einer möglichen Schädigung von Nervenzellen. Dafür werden vor der Operation und am zweiten Tag nach der Operation 4 Röhrchen mit insgesamt circa 50mL Blut entnommen. Folgende Biomarker geben Auskunft über Nervenschaden und werden im Rahmen dieser Substudie bestimmt: NFL, GFAP, HMGB1, MANF.

Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:

a) Montreal Cognitive Assessment (MoCA): Hierbei handelt es sich um einen Fragebogen, welcher zur Erfassung Ihrer Denkleistung dient. Dafür wird ein Studienmitarbeiter am Tag vor Ihrer Operation einen Fragebogen mit Ihnen durchführen. Dies wird ca. 5 bis 10 Minuten Ihrer Zeit in Anspruch nehmen. 30 Tage sowie ein Jahr nach Ihrer Operation werden Sie telefonisch von einem unserer Studienmitarbeiter kontaktiert. Im Rahmen dieses Telefonats wird nochmals der Fragebogen, welcher auch vor der Operation verwendet wurde, um Ihre Denkleistung zu ermitteln, durchgeführt. Dies wird erneut ca. 5 bis 10 Minuten Ihrer Zeit in Anspruch nehmen.

b) 3D-Cognitive Assessment Method (3D-CAM): Hierbei handelt es sich um ein Testinstrument, welches den Verwirrtheitszustand nach Operationen beurteilen soll. In der Früh und am Abend in den ersten fünf Tagen nach der Operation wird ein Studienmitarbeiter Sie auf der Intensivstation oder Bettenstation besuchen und einen Fragebogen mit Ihnen durchgehen. Ein Studienmitarbeiter wird Ihnen insgesamt 10 Fragen stellen. Außerdem wird erhoben, ob Ihnen seit der Operation übel war oder ob sie erbrechen mussten. Diese Fragen werden jeweils ca. 5-10 Minuten Ihrer Zeit in Anspruch nehmen.

c) Digit Symbol Substitution Test (DSST): Hierbei handelt es sich um ein Testinstrument, das Hinweise auf das Vorhandensein einer möglichen Hirnfunktionsstörung oder auch Demenz gibt. Im Rahmen dieses Tests müssen Sie Ziffern- und Symbolkombinationen so schnell wie möglich miteinander verbinden. Dieser Test wird am Tag vor Ihrer Operation und am fünften Tag nach Ihrer Operation durchgeführt und nimmt jeweils ungefähr 5 bis 10 Minuten Ihrer Zeit in Anspruch.

d) Trail Making Tests (Teil A, Teil B): Dieser Test kann einen Hinweis auf eine mögliche Hirnfunktionsstörung geben und besteht aus zwei Teilen. Bei Teil A müssen Sie Ziffern in aufsteigender Reihenfolge so schnell wie möglich miteinander verbinden. Bei Teil B müssen Sie Ziffern und Buchstaben in aufsteigender Reihenfolge so schnell wie möglich miteinander verbinden. Dieser Test wird am Tag vor Ihrer Operation und am fünften Tag nach Ihrer Operation durchgeführt und nimmt jeweils ungefähr 5 bis 10 Minuten Ihrer Zeit in Anspruch.

Während dieser klinischen Studie werden folgende Blutabnahmen durchgeführt: vor Beginn der Operation wird eine Blutabnahme zur Bestimmung der Herzenzyme, Nierenfunktion, Entzündungswerte und Laborparamater spezifisch für die Gehirnzellfunktion, um die Ausgangswerte zu bestimmen, durchgeführt (3 Röhrchen mit max. 15 ml Blut). Innerhalb der ersten zwei Stunden nach Operationsende sowie am zweiten Tag nach der Operation werden die Herzenzyme, Nierenfunktionswerte, Entzündungswerte und Laborparamater spezifisch für die Gehirnzellfunktion erneut bestimmt (3 Röhrchen mit max. 15 ml Blut). Die im Rahmen dieser Studie durchgeführten Blutabnahmen werden, wenn möglich über einen liegenden Katheter durchgeführt. Sollte kein liegender Katheter vorhanden sein, wird Ihnen Blut über eine Vene durch einen Stich abgenommen. Für diese Studie gilt, dass die gewonnenen Blutproben auch nach den Analysen aufbewahrt werden und gegebenenfalls zukünftige Analysen durchgeführt werden. Ihre Blutproben werden an dem jeweiligen Studienzentrum bei -80°C aufbewahrt: Medizinische Universität Wien, Univ. Klinik für Anästhesie, Allgemeine Intensivmedizin und Schmerztherapie, Spitalgasse 23, 1090 Wien (verantwortlicher Prüfarzt: PD Dr. Christian Reiterer, PhD; Medizinische Universität Graz, Univ. Klinik für Anästhesiologie und Intensivmedizin, Auenbruggerplatz 5/5, 8036 Graz (verantwortlicher Prüfarzt: Dr. Michael Eichlseder); Medizinische Universität Innsbruck, Univ. Klinik für Anästhesie und Intensivmedizin, Anichstrasse 35, 6020 Innsbruck (verantwortliche Prüfärztin: Dr. Christine Eckhardt, PhD). Etwaige Analysen werden erst nach Vorliegen einer neuerlichen projektbezogenen befürwortenden Stellungnahme der Ethikkommission durchgeführt. Eine Weitergabe an Dritte erfolgt dabei nicht.

Während dieser klinischen Studie werden im Rahmen ihres Aufenthalts im Krankenhaus Informationen zu ihrem Genesungsverlauf nach Ihrer Operation gesammelt. Zu diesem Zweck wird Einsicht in ihre medizinischen Befunde genommen und Informationen über ihre Behandlung eingeholt.

4. Was ist Desfluran bzw. Sevofluran bzw. Propofol?

Desfluran ist ein routinemäßig eingesetztes Narkosegas, das zur Aufrechterhaltung von Narkosen verwendet wird. Es handelt sich dabei um ein klares flüssiges Medikament, das mit Hilfe eines Verdampfers verdampft wird und das resultierende Gas wird über die Narkosemaschine kontrolliert in Ihre Atemluft abgegeben. Die Aufnahme erfolgt über die Lunge. Der Vorteil von Desfluran im Vergleich zu anderen Narkosegasen ist eine besonders geringe Löslichkeit im Blut, was dazu führt, dass es zu einer guten Steuerbarkeit während der Operation, und zu einem schnelleren Erwachen nach Beendigung der Narkosegas-Zufuhr kommt.

Sevofluran ist ein routinemäßig eingesetztes Narkosegas, das zur Aufrechterhaltung der Narkose verwendet wird. Es handelt sich dabei um ein klares flüssiges Medikament, das mit Hilfe eines Verdampfers verdampft wird und das resultierende Gas wird über die Narkosemaschine kontrolliert in Ihre Atemluft abgegeben. Die Aufnahme erfolgt über die Lunge. Im Vergleich zu Desfluran ist Sevofluran löslicher im Blut, was Ihre Aufwachzeit verlängern könnte.

Propofol ist ein routinemäßig eingesetztes Narkosemedikament, das zur Einleitung sowie zur Aufrechterhaltung der Narkose verwendet wird. Es handelt sich hierbei um ein flüssiges Medikament, welches für die Aufrechterhaltung der Narkose durchgehend während der Operation über ein Blutgefäß verabreich wird. Aufgrund des raschen Wirkungseintritts und der relativ geringen Anreicherung im Körper ist Propofol während der Operation gut steuerbar.

5. Worin liegt der Nutzen einer Teilnahme an der Klinischen Studie?

Mit der Anwendung eines der drei Narkosemittel kann möglicherweise das Auftreten von Delir nach der Operation verhindert werden und daher im Weiteren eine mögliche Einschränkung der Denkleistung verhindert werden. Es ist jedoch auch möglich, dass Sie durch Ihre Teilnahme an dieser klinischen Prüfung keinen direkten Nutzen für Ihre Gesundheit ziehen.

Die Ergebnisse dieser klinischen Prüfung sollen dazu beitragen, dass für andere Patienten, die dieselben geplanten Operation erhalten wie Sie, eine Verbesserung der Behandlungsmöglichkeiten während und nach Operationen gefunden wird.

6. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Die Verwendung von Desfluran kann zu Nebenwirkungen oder Beschwerden führen. Unerwünschte Ereignisse, die möglicherweise auf die Verabreichung von Desfluran zurückzuführen sind, sind mit der Häufigkeit angegeben und zwar sehr häufig (von bis zu 0-1 von 10), häufig (zwischen 1 von 100 und 0-1 von 10): Übelkeit oder Erbrechen (sehr häufig), Husten (sehr häufig), Rachenentzündung (häufig), Anhalten des Atems (häufig), Kopfschmerzen (häufig), Bindehautentzündung (häufig), Herzstolpern (häufig), verminderte Herzfrequenz (häufig), erhöhte Herzfrequenz (häufig), erhöhter Blutdruck (häufig), vermehrter Speichelfluss (häufig). Wie bei jeder Substanz können auch bei Anwendung von Desfluran neue, bisher unbekannte Nebenwirkungen auftreten.

Die Verwendung von Sevofluran kann zu Nebenwirkungen oder Beschwerden führen. Unerwünschte Ereignisse, die möglicherweise auf die Verabreichung von Sevofluran zurückzuführen sind, sind mit der Häufigkeit angegeben und zwar sehr häufig (von bis zu 0-1 von 10), häufig (zwischen 1 von 100 und 0-1 von 10): Aufgeregtheit (sehr häufig), verminderte Herzfrequenz (sehr häufig), verminderter Blutdruck (sehr häufig), Übelkeit oder Erbrechen (sehr häufig), Husten (sehr häufig), Benommenheit (häufig), erhöhte Herzfrequenz (häufig), erhöhter Blutdruck (häufig), verkrampfte Stimmbänder (häufig), vermehrter Speichelfluss (häufig), Temperaturabfall (häufig). Wie bei jeder Substanz können auch bei Anwendung von Sevofluran neue, bisher unbekannte Nebenwirkungen auftreten.

Die Verwendung von Propofol kann zu Nebenwirkungen oder Beschwerden führen. Unerwünschte Ereignisse, die möglicherweise auf die Verabreichung von Propofol zurückzuführen sind, sind mit der Häufigkeit angegeben und zwar sehr häufig (von bis zu 0-1 von 10), häufig (zwischen 1 von 100 und 0-1 von 10): Kopfschmerzen während der Aufwachphase (häufig), verminderte Herzfrequenz (sehr häufig), verminderter Blutdruck (sehr häufig), Husten während der Einleitung der Narkose (häufig), Übelkeit oder Erbrechen während der Aufwachphase (sehr häufig), lokalisierte Schmerzen während der Einleitung der Narkose (sehr häufig).

Die im Rahmen dieser Studie durchgeführten Blutabnahmen werden, wenn möglich über einen liegenden Katheter durchgeführt. Sollte kein liegender Katheter vorhanden sein, wird Ihnen Blut über eine Vene durch einen Stich abgenommen. Dies kann zu Schmerzen an der Einstichstelle, Schwindel, Ohnmacht, Blutergüssen, Infektionen an der Einstichstelle führen.

7. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Es ergeben sich keine zusätzlichen Verpflichtungen.

8. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrem Arzt mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

9. Versicherung

Als Teilnehmer an dieser klinischen Prüfung besteht für Sie der gesetzlich vorgeschriebene verschuldensunabhängige Versicherungsschutz (Personalschadenversicherung gemäß § 40 Arzneimittelgesetz, der alle Schäden abdeckt, die an Ihrem Leben oder Ihrer Gesundheit durch die an Ihnen durchgeführten Maßnahmen der klinischen Prüfung verursacht werden können, mit Ausnahme von Schäden auf Grund von Veränderungen des Erbmaterials in Zellen der Keimbahn.

Die Versicherung wurde für Sie bei der Zürich Versicherung-Aktiengesellschaft (Leopold-Ungar-Platz 2, 1190 Wien, Österreich; Tel.: 0800 080 80 80) unter der Polizzennummer 07229622-2 abgeschlossen. Auf Wunsch können Sie in der Versicherungsunterlagen Einsicht nehmen.
Im Schadensfall können Sie sich direkt an den Versicherer wenden und Ihre Ansprüche selbstständig geltend machen. Für den Versicherungsvertrag ist österreichisches Recht anwendbar, die Versicherungsansprüche sind in Österreich einklagbar.
Zur Unterstützung können Sie sich auch an die Patientenanwaltschaft, Patientenvertretung oder Patientenombudsschaft wenden.

Um den Versicherungsschutz nicht zu gefährden:

- dürfen Sie sich während der Dauer der klinischen Prüfung einer anderen medizinischen Behandlung nur im Einvernehmen mit Ihrem behandelnden Prüfarzt unterziehen **(ausgenommen davon sind Notfälle)**. Dies gilt auch für die zusätzliche Einnahme von Medikamenten oder die Teilnahme an einer anderen Studie.
- müssen Sie dem behandelnden Prüfarzt – oder der oben genannten Versicherungsgesellschaft – eine Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte, unverzüglich mitteilen.
- müssen Sie alles Zumutbare tun um Ursache, Hergang und Folgen des Versicherungsfalles aufzuklären und den entstandenen Schaden gering zu halten. Dazu gehört ggf. auch, dass Sie Ihre behandelnden Ärzte ermächtigen, vom Versicherer geforderte Auskünfte zu erteilen.

10. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden, ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Prüfarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Prüfarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der klinischen Prüfung nicht entsprechen;

b) Ihr Prüfarzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Prüfung nicht in Ihrem Interesse ist.

11. Datenschutz

Im Rahmen dieser klinischen Studie werden Daten über Sie erhoben und verarbeitet. Es ist grundsätzlich zu unterscheiden zwischen

1) jenen personenbezogenen Daten, anhand derer eine Person direkt identifizierbar ist (z.B. Name, Geburtsdatum, Adresse, Sozialversicherungsnummer, Bildaufnahmen...),
2) pseudonymisierten personenbezogenen Daten, das sind Daten, bei denen alle Informationen, die direkte Rückschlüsse auf die konkrete Person zulassen, entweder entfernt, durch einen Code (z. B. eine Zahl) ersetzt oder (z.B. im Fall von Bildaufnahmen) unkenntlich gemacht werden. Es kann jedoch trotz Einhaltung dieser Maßnahmen nicht vollkommen ausgeschlossen werden, dass es unzulässigerweise zu einer Re-Identifizierung kommt.
3) anonymisierten Daten, bei denen eine Rückführung auf die konkrete Person ausgeschlossen werden kann.

Zugang zu den Daten, anhand derer Sie direkt identifizierbar sind (siehe Punkt 1), haben der Prüfarzt und andere Mitarbeiter des Studienzentrums, die an der klinischen Studie oder Ihrer medizinischen Versorgung mitwirken. Zusätzlich können autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Sponsors Medizinische Universität Wien sowie Beauftragte von in- und/ oder ausländischen Gesundheitsbehörden und jeweils zuständige Ethikkommissionen in diese Daten Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der klinischen Studie notwendig bzw. vorgeschrieben ist. Sämtliche Personen, die Zugang zu diesen Daten erhalten, unterliegen im Umgang mit den Daten den jeweils geltenden nationalen Datenschutzbestimmungen und/oder der EU-Datenschutz-Grundverordnung (DSGVO).

Der Code, der eine Zuordnung der pseudonymisierten Daten zu Ihrer Person ermöglicht, wird nur an Ihrem Studienzentrum aufbewahrt. Eine Weitergabe der Daten erfolgt nur in pseudonymisierter oder anonymisierter Form. Für etwaige Veröffentlichungen werden nur die pseudonymisierten oder anonymisierten Daten verwendet. Im Rahmen dieser klinischen Prüfung ist keine Weitergabe von Daten in Länder außerhalb der EU (Drittland) vorgesehen.

Ihre Einwilligung bildet die Rechtsgrundlage für die Verarbeitung Ihrer personenbezogenen Daten. Sie können die Einwilligung zur Erhebung und Verarbeitung Ihrer Daten jederzeit ohne Begründung widerrufen. Nach Ihrem

Widerruf werden keine weiteren Daten mehr über Sie erhoben. Die bis zum Widerruf erhobenen Daten können allerdings weiter im Rahmen dieser klinischen Studie verarbeitet werden.

Nach der DSGVO stehen Ihnen grundsätzlich die Rechte auf Auskunft, Berichtigung, Löschung, Einschränkung der Verarbeitung, Datenübertragbarkeit und Widerspruch zu, soweit dies die Ziele der klinischen Studie nicht unmöglich macht oder ernsthaft beeinträchtigt und soweit dem nicht andere gesetzliche Vorschriften widersprechen.

Das gemäß DSGVO vorgesehene Recht auf Löschung Ihrer im Rahmen dieser klinischen Prüfung verarbeiteten Daten steht Ihnen aufgrund von Regelungen nach dem Arzneimittelgesetz und Medizinproduktegesetz nicht zu. Zusätzliche ist bei einer klinischen Prüfung nach dem Arzneimittelgesetz das Recht auf Datenübertragbarkeit außer Kraft gesetzt.

Die voraussichtliche Dauer der klinischen Studie ist zwei Jahre. Die Dauer der Speicherung Ihrer Daten über das Ende oder den Abbruch der klinischen Studie hinaus ist durch Rechtsvorschriften geregelt.

Falls Sie Fragen zum Umgang mit Ihren Daten in dieser klinischen Studie haben, wenden Sie sich zunächst an Ihren Prüfarzt. Dieser kann Ihr Anliegen ggf. an die Personen, die für den Datenschutz verantwortlich sind, weiterleiten.

Kontaktdaten der Datenschutzbeauftragten der an dieser klinischen Studie beteiligten Institutionen:

Datenschutzbeauftragter des Sponsors: datenschutz@meduniwien.ac.at

Kontaktdaten der Datenschutzbeauftragten der an dieser klinischen Studie beteiligten Institutionen:

Name der Datenschutzbeauftragten

Sie haben das Recht, bei der österreichischen Datenschutzbehörde eine Beschwerde über den Umgang mit Ihren Daten einzubringen (www.dsb.gv.at; E-Mail: dsb@dsb.gv.at).

12. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten. Es ist keine Vergütung vorgesehen.

13. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Studienarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: **Name**

Erreichbar unter: Telefonnummer

Name der Kontaktperson: **Name**

Erreichbar unter: Telefonnummer

14. Wo kann ich weitere Informationen einholen?

Name der Patientenanwaltschaft

15. Einwilligungserklärung

Name des Patienten:

Geb.Datum:

Ich erkläre mich bereit, an der klinischen Studie „**Einfluss von Desfluran versus Sevofluran versus Propofol auf das Auftreten von Delir bei älteren PatientInnen, die sich einer nicht-herzchirurgischen Operation mit mittelgroßem oder großem Risiko unterziehen**“ teilzunehmen. Ich bin darüber aufgeklärt worden, dass ich die Teilnahme ohne nachteilige Folgen, insbesondere für meine medizinische Betreuung, ablehnen kann.

Ich bin von Frau/Herrn (Dr.med.) ..... ausführlich und verständlich über die klinische Studie, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie und die sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt *12* Seiten umfasst, gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und zufriedenstellend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile, insbesondere für meine medizinische Betreuung, entstehen.

Ich stimme ausdrücklich zu, dass meine im Rahmen dieser klinischen Studie erhobenen Daten wie im Abschnitt „Datenschutz“ dieses Dokuments beschrieben verarbeitet werden.

Für den Fall, dass ich aus der klinischen Prüfung ausscheide, bin ich einverstanden, dass meine Proben weiterhin aufbewahrt und analysiert werden, wie in dieser Information und – wenn zutreffend – in den Informationen zu den Substudien beschrieben:

☐ ja ☐ nein

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

.....

(Datum und Unterschrift des Patienten)

.....

(Datum, Name und Unterschrift des verantwortlichen Prüfarztes)