



Sevoflurane multiple Wash In/Wash Out at the end of anesthesia to reduce agitation: A multicenter double-blind randomized controlled trial

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ABSTRACT

Background: Postoperative agitation is common after non-cardiac surgery. It is associated with postoperative delirium and cognitive dysfunction, leading to prolonged hospital stay and delayed social readjustment. Prevention and treatment strategies are lacking. We assessed the efficacy of a novel approach, the Wash In/Wash Out procedure, in reducing post-anesthetic agitation.

Methods: This multicenter, parallel-group, double-blind randomized controlled trial is enrolling 200 patients undergoing open abdominal surgery. Participants are randomly assigned to either a control group receiving standard recovery methods or an investigational group undergoing the Wash In/Wash Out procedure. In the Wash In/Wash Out procedure group, sevoflurane is stopped and then promptly restarted when the patient shows the first signs of awakening to achieve an end-tidal concentration of 1 minimum alveolar concentration (MAC) for 5 min. This stop-and-restart cycle is performed three times. The trial's primary outcome is the rate of postoperative agitation. Secondary outcomes include rate of postoperative delirium and cognitive dysfunction, postoperative nausea and vomiting, and length of intensive care and hospital stay.

Discussion: The OPERA trial investigates the effect of the Wash In/Wash Out procedure to reduce post-anesthetic agitation in non-cardiac surgery. This study could offer a significant contribution to improving patient outcomes and optimizing recovery protocols in surgical settings.

1. Introduction

Inhalation anesthesia is a frequently used technique and is performed in the majority of surgeries worldwide [1]. Sevoflurane, a halogenated inhalational anesthetic agent, constitutes the primary choice in a significant proportion of anesthetic procedures [1].

Early neurocognitive disorders are common after surgery [2] and volatile anesthesia might be a risk factor [3]. Currently, postoperative neurocognitive disorders, including agitation, appear to be clinical manifestations of a complex pathophysiological process commonly referred to as neuroinflammation [4,5]. Agitation not only lengthens post anesthetic awakening time and need for advanced patient

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monitoring, but may be a predisposing factor in the development of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) [6]. In turn, POD and POCD are independent predictors of mortality, prolonged intensive care unit (ICU) and hospital stay, and of extended time of social reintegration for surgical patients [7,8].

No ‘golden bullet’ exists to minimize postoperative neurological complications [9], and the rate of early postoperative agitation in adult patients remains as high as 20 % [10,11]. Continuity and adequacy of anesthesia [12], and avoidance of excessively deep or too superficial levels of anesthesia [13] failed to prevent agitation in the early postoperative period. Similarly, midazolam [14], propofol [15], opioids [16], and non-opioid analgesics [17] did not demonstrate beneficial effects when used in comparison to standard care for preventing agitation. No specific prophylaxis or treatment exists for postoperative agitation [18].

Initial personal observations suggested that re-deepening volatile anesthesia before extubation improved the quality of awakening and reduced postoperative agitation and delirium, especially when performed several times. In literature we found a reduction (from 24.7 % to 4.4 %) in agitation rates among pediatric patients following a modified anesthesia induction protocol using sevoflurane [19]: a Wash In/Wash Out protocol entailed a temporary cessation of anesthesia after the child lost consciousness, followed by a period of reawakening and subsequent re-induction. These beneficial effects were hypothesized to stem from a preconditioning effect induced by anesthetics. We are applying a Wash In/Wash Out technique by implementing it during the emergence phase of surgery (wave-like awaking).

In the hypothesis that implementing the Wash In/Wash Out technique before patient emergence from anesthesia may reduce the incidence of postoperative agitation, we are performing the multicenter OPERA Trial in patients undergoing open abdominal surgery.

2. Methods

2.1. Study design, approval, and registration

OPERA is a multicenter, parallel-group, randomized, double-blind, controlled trial of 200 patients undergoing open abdominal surgery. The trial was registered at clinicaltrials.gov on February 19, 2021 (NCT04765488). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist for our paper is provided [Supplementary Material File S1](#).

2.2. Study aim

The aim of our study is to test the hypothesis that the Wash In/Wash Out procedure reduces the incidence of postoperative agitation after anesthesia with sevoflurane.

2.3. Study participants

We include patients who meet the following criteria: (1) age ≥ 18 years; (2) open elective abdominal surgery; (3) general anesthesia; and (4) patients’ written informed consent. Exclusion criteria are: (1) pregnant and breastfeeding patients; (2) mental disorders; (3) epilepsy, Parkinson disease, Alzheimer, peripheral nerve and neuromuscular junction pathology (amyotrophic lateral sclerosis, Guillain-Barre syndrome, myasthenia gravis etc.); (4) use of antidepressants, antipsychotics, sedatives, psychoactive drugs within a month before surgery. The eligibility criteria are presented in [Table 1](#).

2.4. Patient recruitment

Study personnel systematically identify eligible candidates from the daily surgical list and approach them for participation. Detailed information about the study is provided to these patients, ensuring thorough

Table 1
OPERA eligibility criteria.

Inclusion criteria:	Exclusion criteria:
age ≥ 18 years open elective abdominal surgery general anesthesia	pregnant patients and breastfeeding patients mental disorders
written informed consent	epilepsy, Parkinson disease, Alzheimer, peripheral nerve and neuromuscular junction pathology (amyotrophic lateral sclerosis, Guillain-Barre syndrome, myasthenia gravis etc.) use of antidepressants, antipsychotics, sedatives, psychoactive drugs within a month before surgery.

understanding. Informed consent is then obtained from each willing participant the day before surgery, securing their voluntary enrollment in the study. [Fig. 1](#) shows the trial flow chart.

2.5. Randomization and blinding

All eligible patients are randomly assigned in a 1:1 ratio using method of opaque sealed and sequentially numbered envelopes at the time of making a decision about the possibility of extubation. The randomization is stratified based on the participating center to ensure balance. Patients, data collectors and outcome assessors are blinded to the study intervention. Due to the nature of the intervention, the attending anesthesiologist is not blinded.

The blinding process employed in this clinical study is rigorously

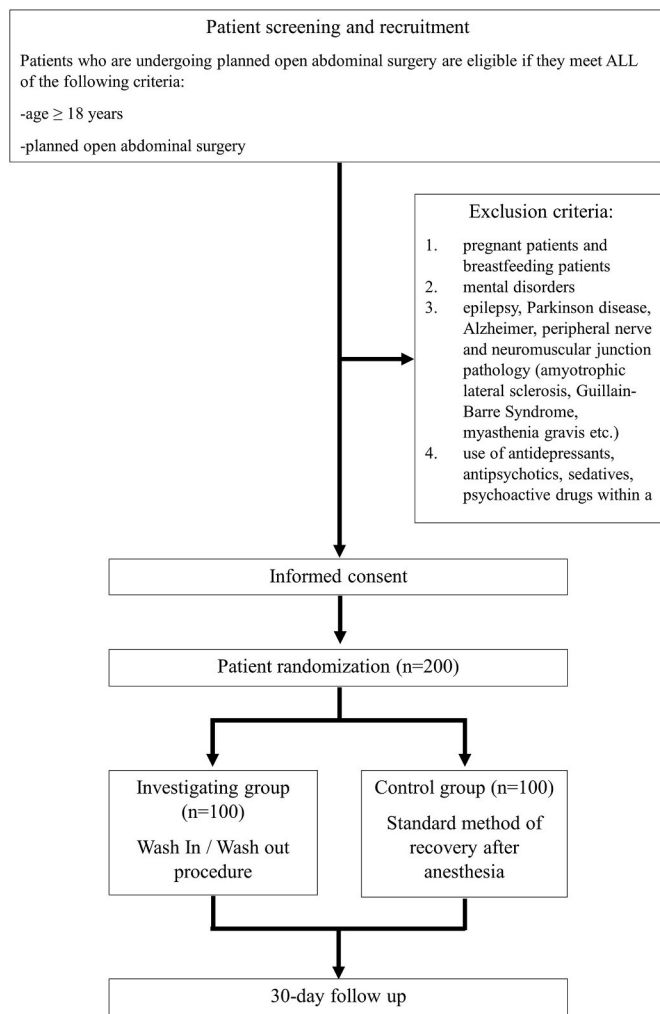


Fig. 1. The OPERA trial flow-chart.

structured to preserve methodological integrity (Table 2). The Case Report Form (CRF), a critical instrument in data capture, is separated into two distinct databases, this segregation being pivotal in upholding blindness.

The first part of the CRF contains detailed preoperative and intraoperative information, capturing the patient’s baseline health status and a thorough record of the intraoperative phase, encompassing surgical data. The second section of the CRF is dedicated to the postoperative phase, begins with the patient’s immediate status upon emergence from anesthesia and follows the patient’s progress post-surgery till the 30-day postoperative follow-up.

The study’s randomization procedure is executed once patient readiness for extubation is confirmed.

Upon completion of the surgical team’s work, the awakening procedure is carried out in accordance with the randomization group. After the first and only discontinuation of inhaled anesthetic in the control group or the third discontinuation in the study group, a dedicated outcome assessor is called to the operating room to evaluate the patient’s immediate post-anesthetic condition and oversee further postoperative monitoring.

This systematic approach, particularly the post-randomization involvement of a dedicated outcome assessor, is important for the study’s blinding mechanism. By engaging the outcome assessor only after randomization and devoid of prior group assignment knowledge, the study maintains objective postoperative assessments. This meticulous methodology is essential for an impartial evaluation of the patient’s awakening and recovery characteristics, thus bolstering the clinical trial’s reliability and validity.

2.6. Standard clinical practice

In the OPERA Trial, continuous intraoperative monitoring includes the following parameters: non-invasive arterial blood pressure (systolic, diastolic, mean), electrocardiographic monitoring with heart rate, pulse oximetry, and analysis of exhaled gases (carbon dioxide, sevoflurane). Arterial or mixed venous blood acid-base balance analysis is conducted for those patients in both groups whose saturation falls below 95 %. During premedication, induction, and maintenance of anesthesia the use of benzodiazepines, ketamine, and antipsychotics is not allowed.

In this clinical study, two different induction methods are allowed following anesthesiologists’ practice. In the propofol induction protocol patients <55 years receive 2 mg/kg of ideal body weight until loss of consciousness, while patients >55 years old and those in American Society of Anesthesiologists (ASA) classes III and IV receive 1 mg/kg. In addition, fentanyl is used at a dose of 2–3 µg/kg for this induction type. In the sevoflurane induction protocol, mask induction was performed with sevoflurane at 6 l/min at 3 MAC, complemented by fentanyl at a concentration of 1–2 µg/kg. In both induction methods, rocuronium 0.6 mg/kg is routinely used for muscle relaxation.

In all patients, anesthesia maintenance is performed with

sevoflurane 1 MAC while fentanyl (0.05–0.1 mg) is added as per anesthesiologist’s discretion. Choice of muscle relaxants, vasoactive drugs and infusion solutions is determined by the attending anesthesiologist.

After surgery, we systematically gather data on the duration between the cessation of sevoflurane administration and the occurrences of spontaneous breathing, eye opening, extubation, and orientation. Extubation readiness in patients is assessed based on the attainment of a minimum score of 9 on the Aldrete scale. The Richmond Agitation-Sedation Scale (RASS) scale is administered promptly upon awakening and subsequently at 15- and 30-min intervals post-awakening.

After awakening the patient is evaluated for the necessity of prolonged mechanical ventilation, vasopressor or inotropic support, and need for ICU monitoring. Patients are moved to a recovery room or to an ICU based on their condition assessed by the Aldrete Scale, with continued monitoring of hemodynamics (NIBP, ECG, SpO2), general state assessment, laboratory parameters, and postoperative therapy as per current practice.

Preoperative examination, anesthesia management, and pre- and postoperative therapy align with established practices. All laboratory and instrumental data, along with medical documentation (anesthesia protocol, anesthesia card, ICU patient management cards, prescriptions) are accessible to the treating physician as part of the clinical study.

2.7. Trial interventions

All eligible patients are randomly assigned to one of two groups.

In the control group patients are managed traditionally. In this group during the awakening period we stop supplying sevoflurane and extubate patients after they achieve at least 9 points on the Aldrete scale.

In the intervention group patients receive the Wash In/Wash Out procedure. In this group we stop the administration of sevoflurane till the first signs of awakening, record the sevoflurane MAC, and then resume the supply of sevoflurane with a target of 1 MAC awake. Anesthesia is then maintained for 5 min before stopping the supply of sevoflurane again till signs of awakening. After recording the sevoflurane MAC, we will resume the supply of sevoflurane with a target of 1 MAC awake for 5 min and then sevoflurane supplementation is finally interrupted and the patient extubated after achieving at least 9 points on the Aldrete scale.

During the awakening phase in both groups, the protocol involves the utilization of high flow fresh gas (8 l/min) following the cessation of volatile anesthetic administration. Specifically, within the intervention group, this practice of employing high flow fresh gas is consistently applied after each cycle of discontinuation during every awakening phase.

2.8. Trial outcomes

The primary outcome is the rate of postoperative agitation after anesthesia with sevoflurane. Agitation is defined as a RASS score of ≥

Table 2
Workflow diagram for research team members aimed at maintaining the essential level of blinding.

	Screening, consent	Preoperative data	Intraoperative data	Randomization	Study intervention	Emergence after anesthesia assessment	Postoperative data	30-day follow-up
Anesthesiologist								
Outcome assessor								

Abbreviations: White cell - the researcher does not participate in this stage of work; Gray cell - the researcher participates in this stage of work.

+2 during the awakening period after anesthesia, between the time of cessation of anesthetic administration and the time when the patient achieves a score of 9 on the Aldrete scale.

Key secondary outcomes will be postoperative delirium and cognitive dysfunction. Postoperative delirium is diagnosed when there is at least one positive result on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or ICDSC, confirming the presence of delirium, during the postoperative part of the day of surgery and also within the first three postoperative days. Postoperative cognitive dysfunction is diagnosed according to DSM-5 as a decline of one or more standard deviations from a normative group based on the results of the MoCA (Montreal Cognitive Assessment).

Other secondary outcomes will be postoperative nausea and vomiting, patient satisfaction with the anesthesia experience, ICU free days and hospital free days.

Outcomes definitions are available in the [Supplementary Material File S2](#).

2.9. Data collection

The participant timeline based on the SPIRIT diagram is provided as [Table 3](#).

Study personnel follows patients throughout their time in hospital evaluating the patients and reviewing their medical records and recording any outcomes. Study personnel contacts all patients by telephone at 30 days after randomization to assess the occurrence of clinically relevant events or rehospitalizations that might meet any study outcome or serious adverse event definitions. In case the administration of the study interventions deviates from the protocol, study personnel continue to collect data on study outcomes at 30 days after randomization and analyzes them according to the intention to treat principle, unless the participants explicitly state that they do not want to be followed. If this happens, study personnel requests data collection to be performed through their healthcare provider. If the patient also refuses this, no further data will be collected on the patient.

2.10. Data management

Study personnel at the participating centers records data on case report forms (CRFs) and submits the CRFs through a secure web-based computerized database. This system ensures the confidentiality and integrity of patient data, with access restricted to authorized study personnel.

2.11. Statistical considerations

2.11.1. Sample size

For the primary endpoint's (the rate of postoperative agitation), we anticipated a relative decrease from an estimated baseline of 20 % to a targeted rate of 6.5 %, linked to the wash-in/wash-out procedure.

Table 3
Summary of data collection.

Activity	Before randomization (Day -1)	Day 0	Day 1	Day 2	Day 3	Day 7	Day 30
Screening	X						
Consent	X						
Randomization		X					
Study interventions		X					
Baseline sociodemographic and clinical data collection	X						
Operative data collection		X					
Clinical outcome assessment and data collection			X	X	X	X	X
MoCA testing	X					X	
CAM-ICU testing		X	X	X	X		
ICDSC testing		X	X	X	X		

Abbreviations: MoCA, Montreal Cognitive Assessment; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICDSC, Intensive Care Delirium Screening Checklist.

Considering a type I error rate of 5 % and aiming for 80 % power (implying a type II error rate of 20 %), we determined that each group needs 98 patients. To compensate for potential dropouts, our goal is to recruit 100 patients for each arm of the surgery study, totaling 200 patients.

2.11.2. Data analysis

All data will be analyzed according to the intention-to-treat principle. We will not apply any imputation for missing data. Per-protocol and as-treated analyses will also be performed. Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Unadjusted univariate analyses, to compare the two treatment groups, will be based on Chi-square or Fisher's exact test. Relative risks and 95 % confidence intervals will be calculated by means of the two-by-two table method with the use of log-normal approximation. Continuous variables will be reported as mean \pm standard deviation (SD) or median and interquartile range (IQR). Between-group differences will be evaluated using the *t*-test or Wilcoxon signed rank test, in accordance with normality of the distribution.

A logistic regression model using a stepwise selection will be used to estimate the treatment effect and predictors of primary endpoint. The pre-randomization clinical data and center will be entered into the model if their univariate *p* value is < 0.1 and there is no correlation between them. Collinearity and overfitting will be assessed using a stepwise regression model and Pearson correlation test. The treatment group will be forced into the multivariate model. Additionally, a subgroup analysis is planned to investigate the effects of different anesthesia induction techniques (sevoflurane or propofol).

2.11.3. Interim analyses

An independent safety committee will perform three interim analyses after recruitment of 25 %, 50 % and 75 % of patients. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and De Mets', and will employ O'Brien-Fleming Z-test boundaries, which are very conservative early in the trial. For the first interim analysis the efficacy stopping rule would require an extremely low *p* value ($p < 0.000015$). For the second interim analysis $p < 0.003$ will be taken as efficacy stopping rule. For the third interim analysis $p < 0.02$ will be taken as efficacy stopping rule. Investigators will be kept blind to the interim analysis results.

2.12. Oversight and monitoring

First University Clinical Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation acts as both the sponsor and the coordinating hub for this trial. Within the institute, a team of scientists is responsible for overseeing the trial's central randomization and conducting data analyses. Concurrently, a

dedicated team of trial monitors manages the trial database, performs data consistency checks, and coordinates the efforts of all participating centers.

2.13. Ethics and dissemination

This study has received approval from the Local Ethics Committee of I.M. Sechenov First Moscow Medical University (Approval Number: 01–21).

The Steering Committee includes Prof. G. Landoni, Prof. V. Likhvantsev, Prof. A. Yavorovskiy, L. Berikashvili, MD, PhD.

2.13.1. Adverse event reporting

Reporting of adverse events is restricted to events that are considered to be related to study treatment (possibly, probably or definitely). Any adverse events thought to be study treatment related is reported to the coordinating center within 7 days of discovery. The site principal investigator is responsible for determining the causal relationship as either possible, probable or definitely study treatment related. The coordinating center is notified. All adverse events will be reviewed by the coordinating center staff and is periodically reported to the data safety monitoring board.

2.13.2. Serious adverse event (SAE) reporting

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is an important medical event that jeopardizes the study patient and requires intervention to prevent one of the other outcomes listed in the definition above.

The classification of 'serious adverse event' is not related to the assessment of the severity of the event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. Given that critically ill patients are likely to meet any of the above listed criteria in the course of their ICU admission, only serious events that are thought to be related to study treatment will be reported.

Sites are required to report serious adverse events to the coordinating center within 24 h of study staff becoming aware of their occurrence. A member of the coordinating center is available 24 h a day for out of 'business hours' reporting. The site principal investigator is responsible for determining the causal relationship as either possible, probable or definitely study treatment related. The coordinating center is notified. All serious adverse events are reviewed by the coordinating center staff and are periodically reported to the data safety monitoring board.

The coordinating center staff is responsible for following-up all serious adverse events to ensure all details are available. The coordinating center is also responsible for alerting other participating sites to the reported serious adverse events and reporting to the regulatory authorities within required time frames.

2.13.3. Dissemination plan

The study results will be published in peer-reviewed journals and a full report on the data will be prepared by the researchers. Results will be presented at national and international conferences. Personal data of participants will not be disclosed in publications or presentations.

2.13.4. Trial progress

The initial patient was enrolled in the study on January 17, 2022. As per December 2023 half of the participants have completed the 1-month follow up in one of four enrolling centers. At the current rate of enrollment, is expected to complete enrollment in December 2024.

3. Discussion

The OPERA trial, a comprehensive clinical investigation into the

post-anesthetic recovery processes in non-cardiac surgery, focuses on the innovative application of the wave-like awaking technique (Wash In/Wash Out). This study directly addresses critical clinical concerns in anesthesiology, namely optimizing post-anesthetic recovery protocols and assessing the effectiveness of conventional methods in reducing postoperative complications such as agitation, delirium, and cognitive dysfunction.

Inhalation anesthesia might be associated with early neurocognitive disorders. The rate of early postoperative agitation in adult patients can be as high as 20 % and this underscores the urgency for novel approaches in anesthesia management [11]. Current methods, including the adjustment of anesthesia continuity and depth, and the use of various pharmacological agents like midazolam, propofol, and opioids, did not prevent postoperative agitation [12–18]. This gap in effective management strategies highlights the need for innovative approaches, such as the one proposed in the OPERA trial.

The Wash In/Wash Out technique, was originally tested in pediatric populations at anesthesia induction with encouraging results [19]. A temporary cessation of anesthesia followed by a subsequent re-induction could induce a preconditioning response, potentially reducing the incidence of postoperative agitation [19]. The OPERA trial refines this technique by implementing the awakening phase after surgery, and mitigate risks associated with the original pediatric protocol. This adaptation focuses on enhancing patient safety and operational efficiency, while specifically targeting perioperative challenges such as the risk of aspiration, difficulties in mask ventilation, and hypoxia, which can arise from unprotected airways. This modification aims to leverage the preconditioning benefits while addressing concerns related to time efficiency and patient safety.

If successful, this adaptation of the Wash In/Wash Out technique could lead to significant advancements in anesthesia management, promoting more individualized and potentially safer recovery strategies. If the study technique will be effective and will be able to decrease postoperative neurocognitive disorders (agitation, delirium or POCD), it will also have the possibility to improve patient outcomes such as lengths of stay in ICU and hospitals, and to aid in a swift social reintegration of surgical patients. The results of our study will likely have to be replicated in patients receiving total intravenous anesthesia to understand if the effect is to be attributed to volatile agents or if the results of the Wash In/Wash Out technique applies to any anesthesia technique.

We acknowledge that for the secondary outcomes, including postoperative delirium, the study can be underpowered to detect differences.

4. Conclusion

The OPERA study will be the first randomized controlled trial to evaluate the impact of the Wash In/Wash Out procedure during the awakening phase after sevoflurane anesthesia on postoperative agitation.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Giovanni Landoni: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Valery V. Likhvantsev:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Levan B. Berikashvili:** Writing – original draft, Project administration, Investigation. **Andrey G. Yavorovskiy:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Pavel S. Bagdasarov:** Writing – original draft, Investigation. **Anastasia V. Smirnova:** Writing – original draft, Investigation. **Tatiana S. Serkova:** Writing – original draft, Investigation. **Valery V. Subbotin:** Writing – original draft,

Supervision, Investigation. **Kristina K. Kadantseva**: Writing – original draft, Investigation. **Alexey M. Ovezov**: Writing – original draft, Supervision, Investigation. **Mikhail Ya Yadgarov**: Writing – original draft. **Alexey A. Yakovlev**: Writing – original draft. **Andrea Lamacchia**: Writing – original draft, Investigation. **Lorenzo Gallo**: Writing – original draft, Investigation. **Nadezhda D. Gracheva**: Writing – original draft, Investigation. **Pavel V. Ryzhkov**: Writing – original draft, Investigation. **Rachele Zilocchi**: Writing – original draft, Investigation. **Jessica De Vecchi**: Writing – original draft, Investigation. **Maksim A. Aleinikov**: Writing – original draft, Investigation. **Pavel S. Mayuk**: Writing – original draft, Investigation. **Alina A. Pivovarova**: Writing – original draft, Investigation. **Maria M. Shemetova**: Writing – original draft, Supervision, Investigation.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2024.101316>.

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