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ORIGINAL RESEARCH ARTICLE

Effect of sevoflurane *versus* propofol on neutrophil-to-lymphocyte ratio in healthy individuals: a sub-study of a randomised crossover trial☆

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☆This paper will be appended to the PhD thesis 'Anaesthesia in colorectal cancer surgery: the impact on short and long term outcomes' by RPH at University of Copenhagen.

Abstract

Background: Sevoflurane and propofol are commonly used drugs in general anaesthesia. However, their effects on perioperative immune function are incompletely understood. We hypothesised that sevoflurane and propofol differentially affect immune function in healthy individuals. Therefore, we investigated the effect of sevoflurane and propofol on neutrophil-to-lymphocyte ratio before, during, and after general anaesthesia.

Methods: In this randomised crossover study, 19 healthy individuals underwent 2 h of general anaesthesia with either propofol or sevoflurane. After 4 weeks, anaesthesia was repeated using the other drug. Blood samples were obtained before, during, 1 h after, and 1 day after anaesthesia. The primary outcome was whole-blood neutrophil-to-lymphocyte ratio, and secondary outcomes were specific white blood cell differential counts. A linear mixed-effects model was used to estimate effect sizes.

Results: The neutrophil-to-lymphocyte ratio was higher in the propofol compared with the sevoflurane group during anaesthesia, 2.8 (confidence interval [CI]: 2.3–3.3) *vs* 1.6 (CI: 1.1–2.1), and 1 day after anaesthesia, 2.6 (CI: 2.1–3.1) *vs* 1.9 (CI: 1.4–2.4). In all patients, we observed transient lymphopaenia during propofol anaesthesia, 1.1 $\times$ 10^9 cells $\times$ L^{-1} (CI: 0.9–1.4), compared with sevoflurane anaesthesia, 1.9 $\times$ 10^9 cells $\times$ L^{-1} (CI: 1.7–2.1). In addition, neutrophil counts were higher 1 day after propofol anaesthesia, 4.4 $\times$ 10^9 cells $\times$ L^{-1} (CI: 4.0–4.9), compared with sevoflurane anaesthesia, 3.5 $\times$ 10^9 cells $\times$ L^{-1} (CI: 3.1–4.0). We observed no differences in the remaining white blood cell subgroups.

Conclusions: In healthy individuals undergoing general anaesthesia without surgery, the neutrophil-to-lymphocyte ratio was affected by the type of hypnotic used. Transient lymphopaenia was observed in all participants during propofol anaesthesia.

Keywords: lymphocytes; neutrophil-to-lymphocyte ratio; oncoanaesthesia; propofol; sevoflurane

The introduction of general anaesthesia in the mid-18th century revolutionised the field of surgery.[1] Surgery evolved from the last resort to advanced surgical techniques used to treat numerous diseases. In general anaesthesia, the two most commonly used hypnotic agents, sevoflurane and propofol, both provide adequate sleep or unconsciousness required to perform surgery. The choice of hypnotic agent varies between countries, and their potential benefits and harms are under investigation.[2,3]

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Sevoflurane is a halogenated anaesthetic vapour administered to the lungs through inhalation. Sevoflurane induces sleep through actions on ligand-gated ion channels and gamma-aminobutyric acid receptors of the CNS.[4–6] Propofol is administered intravenously and acts on gamma-aminobutyric acid receptors and excitatory acetylcholine receptors of the CNS.[7] Yet, the effects outside the CNS remain incompletely explored. It is hypothesised that the impact of anaesthetic agents on perioperative immune function may affect short- and long-term outcomes after surgery.[8] Although most evidence of perioperative immune modulation by anaesthesia is based on animal and laboratory studies, observational studies using clinical data have suggested that inhalational anaesthesia by volatile agents is related to increased recurrence of cancer after surgery.[9–12] In addition, the effects of anaesthetics on metastasis formation may be mediated by effects on perioperative immune function.[13]

Neutrophil-to-lymphocyte ratio in peripheral blood is a general marker of perioperative immune function. Surgery causes physiological stress that increases inflammation, reflected in increased neutrophil counts. Moreover, surgical stress suppresses cell-mediated immune function as indicated by decreased lymphocyte counts.[14] The result is an increased neutrophil-to-lymphocyte ratio in the perioperative period, reflecting the balance between activation of inflammatory pathways and impairment of adaptive immune function. In cancer surgery, lymphocytes are essential to preventing cancer recurrence by detecting and eliminating circulating cancer cells in the perioperative phase.[15–17] Accordingly, the extent of postoperative increase in the neutrophil-to-lymphocyte ratio is associated with increased mortality after cancer surgery.[18–22]

In this explorative study, we hypothesised that differences in the immune-modulating effects between sevoflurane and propofol lead to differences in the neutrophil-to-lymphocyte ratio. Differences in neutrophil-to-lymphocyte ratios could explain the association between inhalational anaesthesia and increased recurrence rates after cancer surgery. Therefore, we aimed to assess the isolated effect of propofol and sevoflurane in healthy volunteers in a highly standardised anaesthesia set-up.

Methods

This study was a sub-study of the randomised crossover study 'Neuroplasticity induced by general anaesthesia', which investigates the effects of sevoflurane and propofol on the CNS in healthy volunteers (ClinicalTrials.gov identifier: NCT04125121). The study was approved by the Research Ethics Committee in the Capital Region of Denmark (reference no. H-18028925; approved on 17 August 2019), European Union Drug Regulating Authorities Clinical Trials Database (EUDRA-CT), and Danish Medicines Agency (no. 2018-001252-35; approved on 10 September 2019). The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines,[23] and the CONSORT checklist and flow diagram are appended (Supplementary Fig. S4; Supplementary Table S2).

Participants

After informed consent, healthy volunteers aged 18–35 yr were recruited for the study. All participants had ASA physical status 1, BMI 18–30 kg m^{-2}, and no indication of expected difficult intubation. Because the main study was focused on MRI of the brain before and after anaesthesia, the exclusion criteria included several points addressing MRI and anaesthesia safety, brain health, and medications (Supplementary Table S1).

Trial design and intervention

After an overnight fast, each volunteer reported to the Department of Anaesthesiology, Rigshospitalet Glostrup, Copenhagen, Denmark, and underwent 2 h of general anaesthesia randomised to be maintained with either propofol or sevoflurane. After a washout period of a minimum of 4 weeks, the session was repeated using the other drug. For both sessions, general anaesthesia was induced by a bolus infusion of propofol in combination with remifentanil to permit tracheal intubation. Induction doses depended on target-controlled infusions based on age, sex, and weight corresponding to propofol doses between 1.5 and 2.5 mg kg^{-1} and remifentanil doses between 2.4 and 4 μg kg^{-1}. Tracheal intubation was performed by video laryngoscopy; after intubation, remifentanil was discontinued. Ventilation was maintained using a standard ventilator (Dräger Primus®; Drägerwerk AG & Co., Lubeck, Germany) with an inspiratory oxygen concentration between 30% and 45% and an end-tidal CO_2 of 4.0–5.7 kPa. According to the randomisation, anaesthesia was maintained for 2 h with either sevoflurane or propofol. Initial doses were minimum alveolar concentration 1.5 for sevoflurane and 4–12 mg kg^{-1} h^{-1} for propofol. Subsequently, doses were adjusted to a target bispectral index of 40–60 with no clinical response to pain stimuli applied every 15 min. After discontinuation of anaesthetic agents and subsequent emergence, the participants were extubated and transferred to the PACU for observation for a minimum of 2 h. For all study sessions, normal saline 500 ml was administered during anaesthesia. A detailed description of the interventions is available in the published protocol article for the main study.[24]

Table 1 Neutrophil-to-lymphocyte ratio and lymphocyte and neutrophil counts before, during, and after anaesthesia in healthy volunteers undergoing sevoflurane or propofol anaesthesia.

	Propofol (95% CI)	Sevoflurane (95% CI)	P-value
Neutrophil-to-lymphocyte ratio			
Pre-anaesthesia	1.9 (1.4–2.4)	2.1 (1.6–2.6)	Reference
Intra-anaesthesia	2.8 (2.3–3.3)	1.6 (1.1–2.1)	<0.001
Post-anaesthesia	1.6 (1.1–2.1)	1.4 (0.9–1.9)	0.422
Day 1	2.6 (2.1–3.1)	1.9 (1.4–2.4)	0.019
Lymphocytes (× 10^9 cells L^{-1})			
Pre-anaesthesia	1.8 (1.6–2.0)	1.7 (1.5–1.9)	Reference
Intra-anaesthesia	1.1 (0.9–1.4)	1.9 (1.7–2.1)	<0.001
Post-anaesthesia	2.0 (1.8–2.2)	2.0 (1.8–2.2)	0.264
Day 1	2.0 (1.8–2.2)	1.9 (1.7–2.1)	0.645
Neutrophils (× 10^9 cells L^{-1})			
Pre-anaesthesia	3.3 (2.8–3.7)	3.4 (2.9–3.8)	Reference
Intra-anaesthesia	2.9 (2.5–3.4)	2.8 (2.3–3.2)	0.513
Post-anaesthesia	2.9 (2.5–3.4)	2.7 (2.3–3.2)	0.502
Day 1	4.4 (4.0–4.9)	3.5 (3.1–4.0)	0.013

Mean values and 95% confidence intervals (CIs) were based on a linear mixed-effects regression model.

Outcomes

The primary outcomes were perioperative differences in the neutrophil-to-lymphocyte ratio between the two interventions. Secondary outcomes were differences in white blood cell subgroups measured by differential counts.

Blood sampling

After puncture of the cubital vein, 2 ml of whole blood was sampled in tubes with ethylenediaminetetraacetic acid as anticoagulant. Samples were collected before induction of anaesthesia, 1 h and 50 min after the start of anaesthesia, 1 h after tracheal extubation, and on post-anaesthesia Day 1. White blood cells were counted using the Sysmex (Kobe, Japan) XN-9000™ analyser, used in clinical practice at the Department of Clinical Biochemistry, Rigshospitalet Glostrup.

Randomisation and blinding

Randomisation of the order of propofol and sevoflurane for each participant was performed using a computer-generated random sequence by a third party. The allocation sequence was stored in sealed envelopes until the start of the first anaesthesia session for each participant. The participants were blinded to the treatment they received at each study session. Moreover, laboratory technicians performing the differential counts were blinded to the assigned intervention.

Statistical methods and sample size

The present study was a sub-study of a trial focusing on perioperative neuromodulation measured by MRI. Therefore, the study size was determined by sample size calculations for the main study. Thus, this sub-study was not considered when

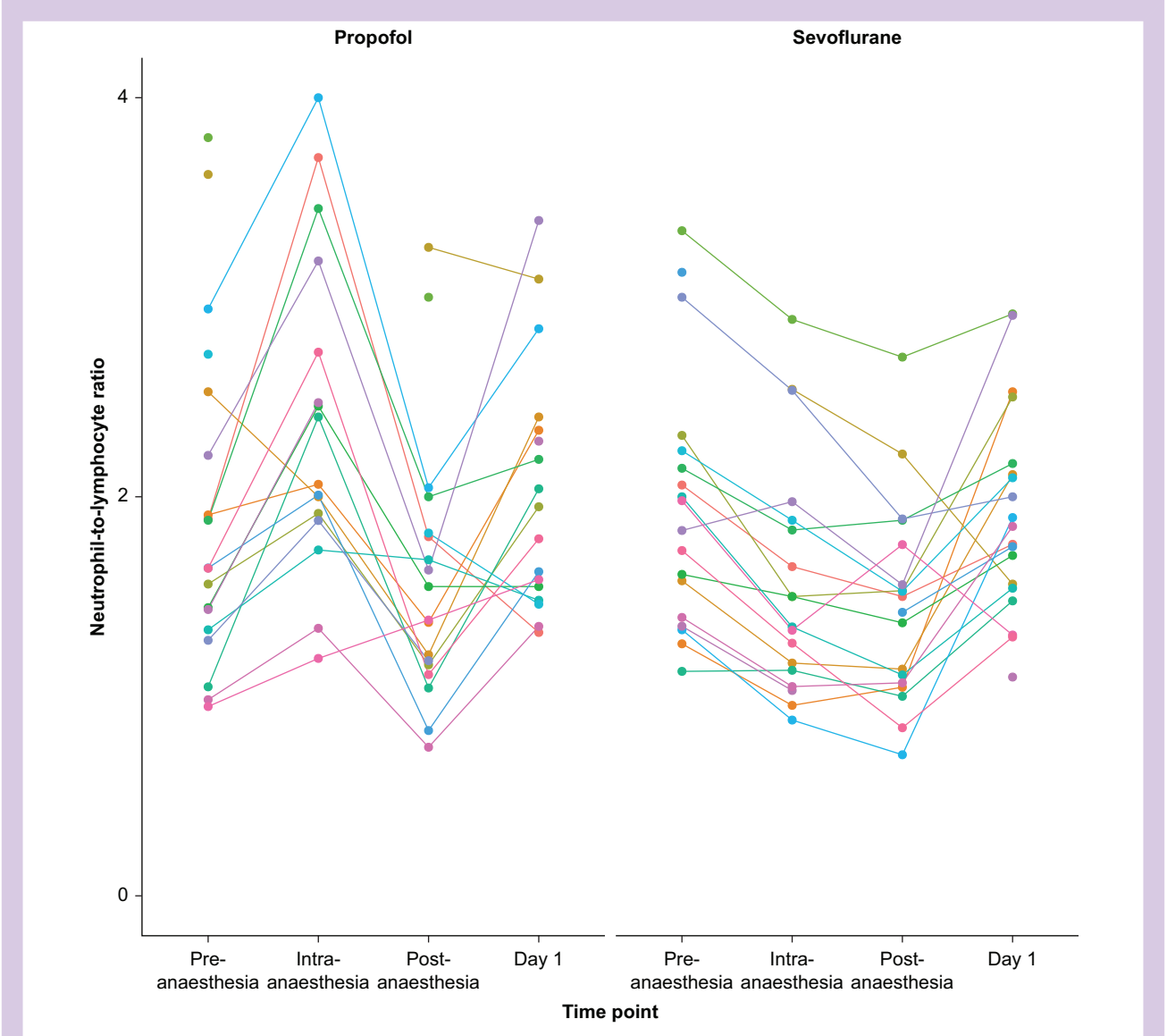

Fig 1. Neutrophil-to-lymphocyte ratios for healthy individuals undergoing sevoflurane and propofol anaesthesia.

the sample size calculation was performed. Initially, the sample size was set to 30 individuals undergoing both interventions. However, because of lockdowns related to the COVID-19 pandemic, the study was terminated after 20 patients had completed the study.

Changes in the neutrophil-to-lymphocyte ratio were analysed using a linear mixed-effects model with variables defined as either fixed or random effects. The participant indicator was defined as a random effect, and the intervention and time point of blood sampling were defined as fixed effects. This method generates effect estimates that take the correlation between samples from each patient into account. Results were presented as mean predicted values with 95% confidence intervals (CIs). The same approach was used to estimate mean white blood cell differential counts. All tests were two-sided, and *P*-values below 0.05 were considered statistically significant. Analyses were performed using the statistical software R version 3.6.1,[25] (R Foundation for Statistical Computing, Vienna, Austria) and the packages 'tidyverse', 'nlme', and 'emmeans' were used for the analyses.

Results

The first anaesthesia session was on 12 September 2019 and the last was on 5 August 2021. In total, 33 participants were recruited. Amongst the recruited participants, 10 withdrew from participation before the first study session. Three completed only one anaesthesia session, and one patient did not have blood samples taken because of logistical challenges. Thus, 19 patients were evaluated. The participants had a median age of 21 (inter-quartile range [IQR]: 20–25) yr, and 10 (52.6%) were male. The median time from sampling to final results of white blood cell counts was 19 (IQR: 8–46) min with no difference between the study groups.

Neutrophil-to-lymphocyte ratio

Baseline neutrophil-to-lymphocyte ratios were similar between the propofol and sevoflurane groups. During anaesthesia, we observed higher neutrophil-to-lymphocyte ratios for participants undergoing propofol anaesthesia compared with sevoflurane, 2.8 (95% CI: 2.3–3.3) *vs* 1.6 (95% CI: 1.1–2.1); *P*<0.001. One hour after tracheal extubation, neutrophil-to-lymphocyte ratios were similar between the groups (propofol 1.6 [95% CI: 1.1–2.1] *vs* sevoflurane 1.4 [95% CI: 0.9–1.9]; *P*=0.422). On post-anaesthesia Day 1, neutrophil-to-lymphocyte ratios again were higher for participants undergoing propofol compared with sevoflurane anaesthesia, 2.6 (95% CI: 2.1–3.1) *vs* 1.9 (95% CI: 1.9 [1.4–2.4]; *P*=0.019 (Table 1; Figs 1 and 2).

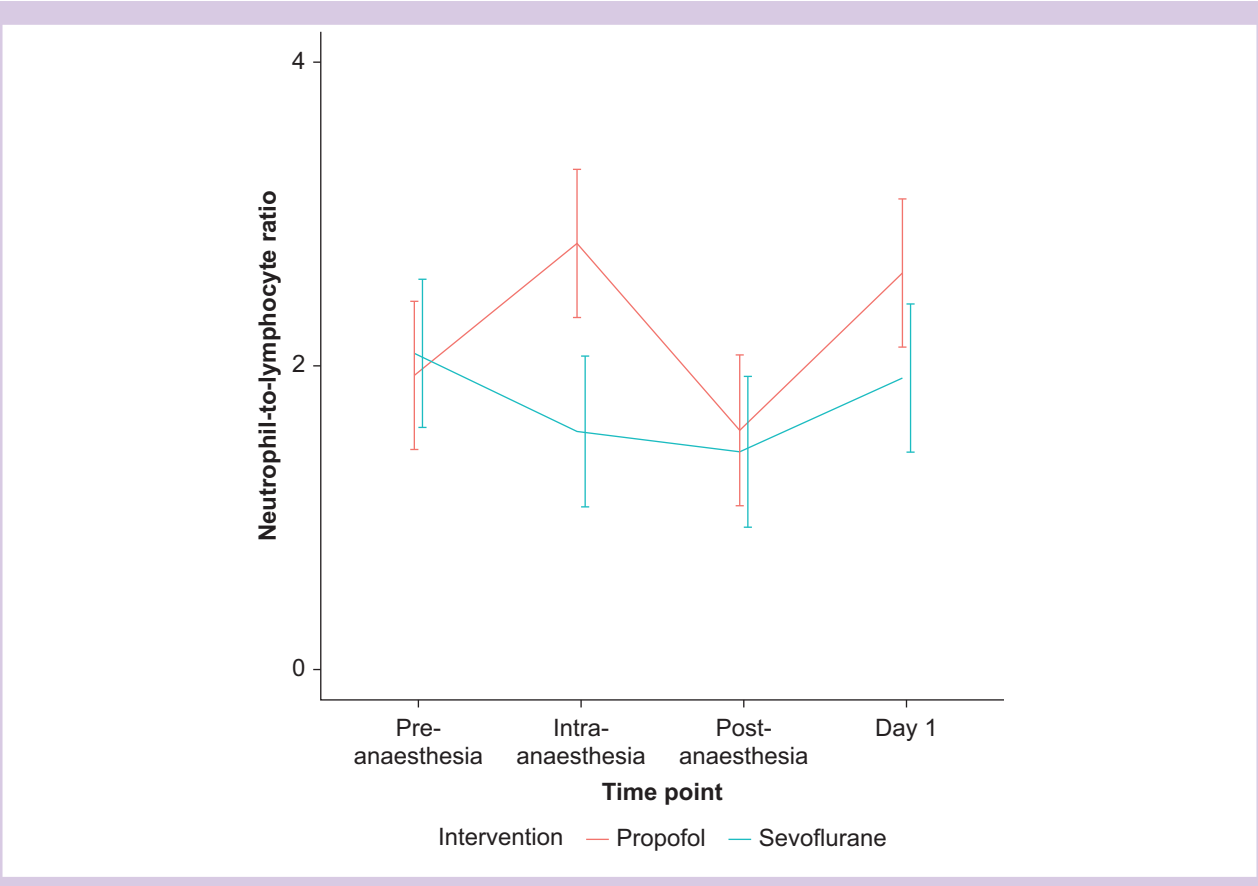

Fig 2. Mean predicted neutrophil-to-lymphocyte ratios with 95% confidence intervals for healthy individuals undergoing sevoflurane or propofol anaesthesia. Estimates based on a linear mixed-effects model with time point and intervention as fixed effects and participant as a random effect.

White blood cell differential counts

White blood cell counts were comparable between the study groups before anaesthesia. Although lymphocyte counts remained unchanged throughout the peri-anaesthetic period for participants undergoing sevoflurane anaesthesia, they decreased in all participants during propofol anaesthesia. The lymphocyte count returned to the baseline level 1 h after extubation in the propofol group (Fig. 3; Supplementary Fig. S1).

Neutrophil counts were comparable between the study groups before, during, and 1 h after anaesthesia. However, on Day 1, we observed slightly higher counts in some patients undergoing propofol anaesthesia compared with sevoflurane. This increase was not observed in all patients undergoing propofol anaesthesia (Fig. 4; Supplementary Fig. S2). We observed no difference between the study groups for basophils, eosinophils, monocytes, or promyelocytes. Counts of these white blood cells are presented in Supplementary Figure S3.

Discussion

In this randomised crossover trial in healthy volunteers undergoing propofol or sevoflurane anaesthesia, we found that neutrophil-to-lymphocyte ratios differed between the two treatments. We observed transient lymphopaenia restored 1 h after anaesthesia during propofol anaesthesia. Moreover, we found slightly higher neutrophil counts 1 day after propofol anaesthesia compared with sevoflurane.

The increased neutrophil-to-lymphocyte ratio during propofol anaesthesia was caused by lower lymphocyte counts in the propofol group compared with sevoflurane. Conversely, the increased neutrophil-to-lymphocyte ratio on Day 1 after propofol anaesthesia was driven by higher neutrophil counts

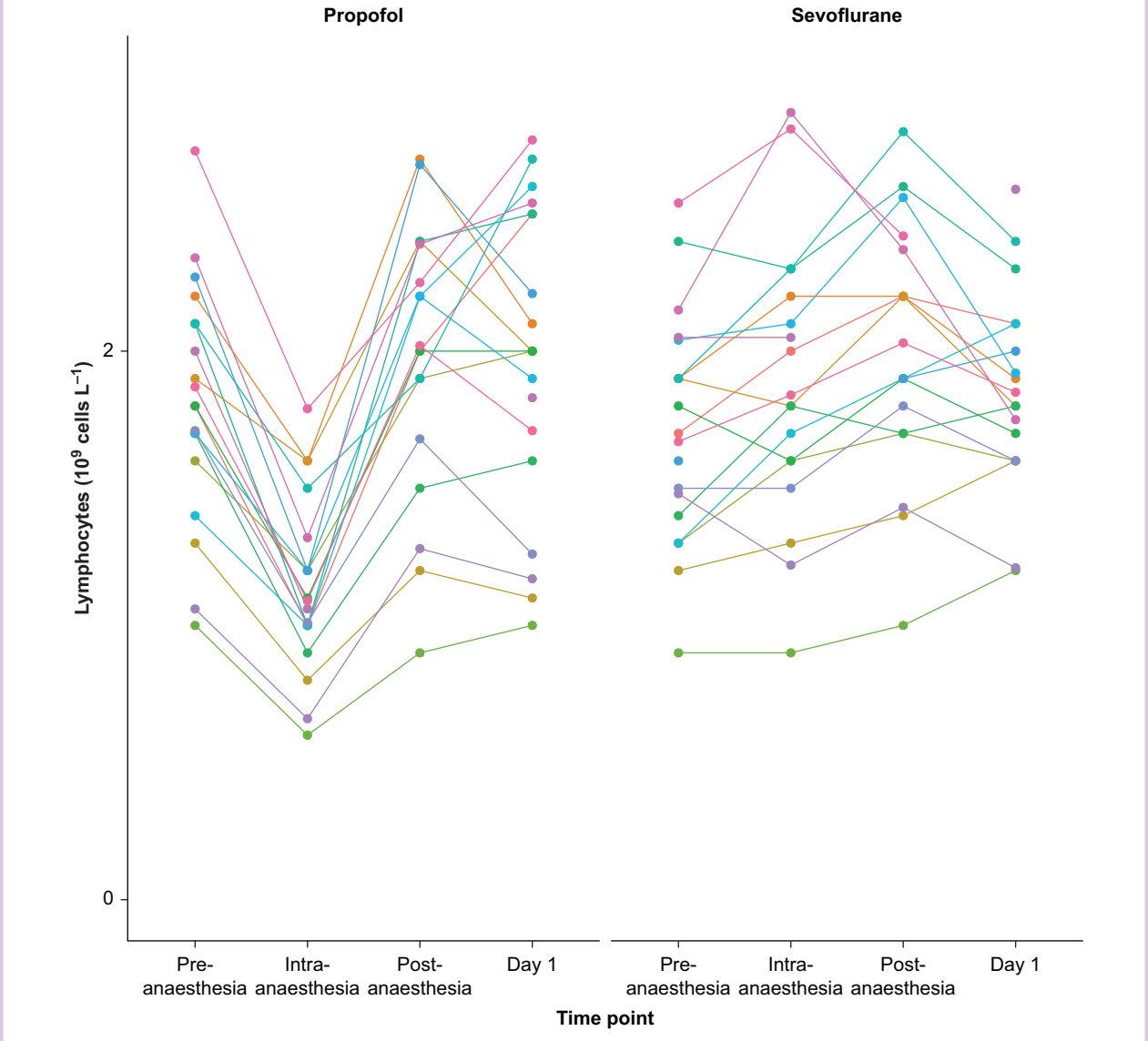

Fig 3. Lymphocyte counts for healthy individuals undergoing sevoflurane or propofol anaesthesia.

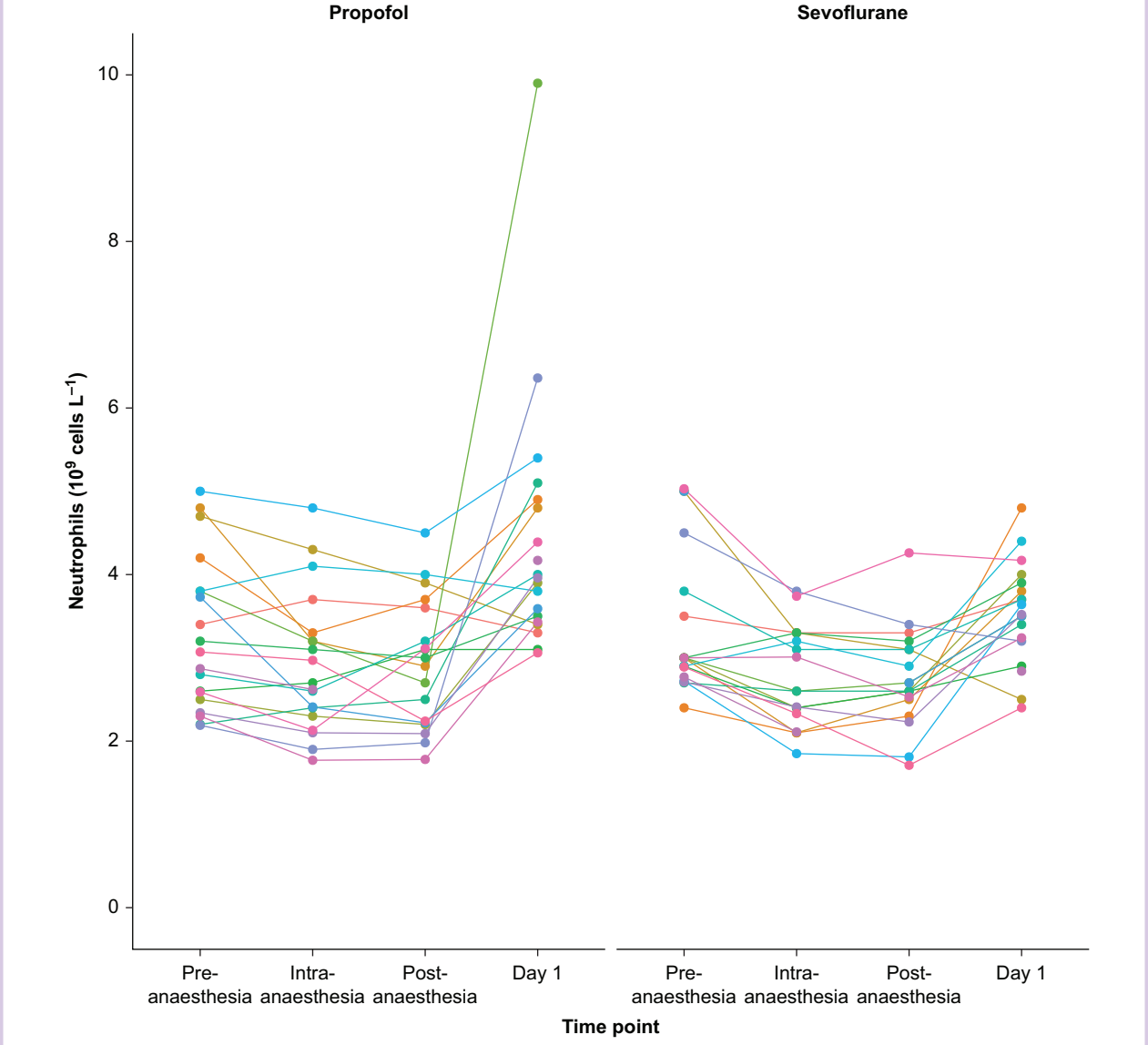

Fig 4. Neutrophil counts for healthy individuals undergoing sevoflurane or propofol anaesthesia.

in the propofol group. Although increased neutrophil counts were not observed in all participants after propofol anaesthesia, the decreased lymphocyte counts during propofol anaesthesia were consistent for all participants. Thus, the consistency of the transient decrease in lymphocyte counts during propofol anaesthesia suggests a biological mechanism triggered by propofol. Conversely, the increased neutrophil-to-lymphocyte ratio 1 day after propofol anaesthesia may be attributed to outliers with increased neutrophil responses caused by factors other than propofol anaesthesia.

Propofol has been suggested to stimulate T-cell responses.[26] A phenomenon known as *lymphopaenia-induced homeostatic proliferation* is characterised by transient lymphopaenia that causes T-cell activation.[27] During the transient lymphopaenia, lymphocytes travel to the extravascular space, where it is believed that they are presented for antigens. In turn, this causes naive T-cells to proliferate and become specific to the antigens.[28] The phenomenon is initiated by interferon Type 1 and interleukin-7.[29] A study of propofol anaesthesia in healthy volunteers supports this hypothesis of propofol-induced T-cell stimulation. Kallioinen and colleagues[30] reported increased cytokines, including interleukin-7, related to the adaptive immune response after propofol anaesthesia without surgery. Our study included only healthy volunteers without underlying pathology and surgical trauma; therefore, no antigens, which are usually released during surgery, were present in our anaesthesia setting. Relevant antigens could initiate a T-cell response, resulting in increased T-cell proliferation.[28] In studies of patients undergoing hysterectomy and breast cancer surgery, propofol anaesthesia has led to increased postoperative lymphocyte counts and lower neutrophil-to-lymphocyte ratios compared

with sevoflurane anaesthesia.[31,32] Thus, our finding may represent the physiological initiation of a T-cell response caused by propofol anaesthesia.

Although our study design facilitated the exploration of the isolated effects of anaesthetics on immune function *in vivo*, essential limitations should be considered. First, our setting with healthy volunteers does not match the clinical setting of patients requiring surgery, and the changes in white blood cell counts were small. Patients presenting for surgery are heterogeneous, where comorbidities and physiological derangement influence immune function.[33] Our study participants all had normal preoperative immune function, which may not be present in patients scheduled for surgery. Moreover, our study did not include any surgical stimulation. It is reasonable to believe that the surgical stress response modifies the effect of sevoflurane and propofol on the immune system. It is likely that T-cells in healthy volunteers are more robust against external stress than in patients with comorbidities undergoing surgery. Additionally, although our study focused on the effects of hypnotics alone, modern anaesthesia includes other drugs, such as neuromuscular blocking agents, opioids, and vasoactive agents.[34] The balance between the various drugs used during anaesthesia may play an important role in the perioperative immune response. Because sevoflurane and propofol likely have different effects on all organ systems, it is possible that the differences in lymphocyte counts during anaesthesia were mediated by effects on other systems, such as cardiovascular changes or the adrenergic responses, instead of direct effects on the immune system. Lastly, the neutrophil-to-lymphocyte ratio is perhaps an over-simplistic representation of the immune response. In future studies, there is a need to characterise the immune response in greater detail to better examine the effects of anaesthesia. Considering the complexity of the immune system, multiple pathways and mechanisms should be explored using advanced techniques (e.g. by whole-blood gene expression profiling, whole-blood *in vitro* immune stimulations, cytokine measurements, and flow cytometry).

Potentially, optimised anaesthesia can modulate the surgical stress response and preserve immunological homeostasis in the perioperative phase. Preserved immune function may lead to improved clinical outcomes after surgery. Nevertheless, more studies on the effects of anaesthesia on the immune system are required to understand the impact of anaesthesia on immune function. Further, large randomised trials investigating the effect of anaesthesia on postoperative cancer recurrence after surgery are ongoing and will provide insights on the impact of anaesthesia on cancer recurrence (NCT01975064, NCT03034096, NCT0266041, and NCT04316013).

In conclusion, in this randomised crossover study in healthy individuals, we found different neutrophil-to-lymphocyte ratios with sevoflurane *vs* propofol anaesthesia. The difference in the neutrophil-to-lymphocyte ratio was attributed to transient lymphopaenia during propofol anaesthesia. The impact of propofol-induced lymphopaenia on perioperative immune function warrants further investigation.

Authors' contributions

Study design: all authors.
Recruitment of patients: SSM.
Data collection: RPH, SSM, MSA.
Data analysis: RPH.
Writing of first draft of paper: RPH.
Critical revision of paper: SSM, KM, IG, MSA.

Declarations of interest

The authors declare no conflicts of interest.

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Data sharing

A research biobank of blood samples from this study has been established. Researchers who have interest in partnerships regarding further explorative studies using these data are encouraged to contact the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2022.100005.

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