Cytokine 169 (2023) 156290

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Short communication

# Plasma cytokine levels in spinal surgery with sevoflurane or total intravenous propofol anesthesia – A post hoc analysis of a randomized controlled trial

Stephanie Franzén [a,*], Egidijus Semenas [a], Anders Larsson [b], Michael Hultström [a,c], Robert Frithiof [a]

[a] Department of Surgical Sciences, Division of Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden
[b] Department of Clinical Chemistry, Uppsala University, Uppsala, Sweden
[c] Department of Medical Cell Biology, Division of Integrative Physiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

*Keywords:*
Acute kidney injury
Interleukin-6
Propofol
Sevoflurane
Surgery

ABSTRACT

Surgical tissue trauma stimulates an inflammatory response resulting in increased levels of cytokines which could contribute to acute kidney injury (AKI). It is not clear if anesthetic modality affects this response. We aimed to investigate the role of anesthesia in a healthy surgical population on the inflammatory response and the correlation to plasma creatinine.

This study is a post hoc analysis of a published randomized clinical trial. We analyzed plasma from patients who underwent elective spinal surgery randomized to either total intravenous propofol anesthesia (n = 12) or sevoflurane anesthesia (n = 10). The plasma samples were collected before anesthesia, during anesthesia, and 1 h after surgery. Plasma cytokine levels after surgery were analyzed for correlations with duration of surgical insult and change in plasma creatinine concentration.

The cytokine interleukin-6 (IL-6) was increased after surgery compared with preoperatively. IL-6 was higher in the sevoflurane group than the propofol group after surgery. No patient developed AKI, but plasma creatinine was increased postoperatively in the sevoflurane group. There was a significant association between surgical time and plasma IL-6 postoperatively. No significant correlation between change in plasma creatinine and IL-6 was detected. The cytokines IL-4, IL-13, Eotaxin, Interferon γ-Induced Protein 10 (IP-10), Granulocyte Colony-Stimulating Factor (G-CSF), Macrophage Inflammatory Protein-1β (MIP-1β), and Monocyte Chemoattractant Protein 1 (MCP-1) were lower postoperatively than before surgery independent of anesthetic modality.

This post hoc analysis revealed that plasma IL-6 was increased after surgery and more so in the sevoflurane group than the propofol group. Postoperative plasma IL-6 concentration was associated with surgical time.

## 1. Introduction

Surgical tissue trauma causes release of proinflammatory cytokines. [1] It is still unclear if anesthetic agents affect the inflammatory response to surgery. When investigated in children, the postoperative systemic inflammatory response is weaker after propofol anesthesia compared with the volatile anesthetic sevoflurane suggesting a protective effect of propofol compared with sevoflurane. [2] On the other hand, sevoflurane protects against the postoperative inflammatory response and myocardial injury after cardiopulmonary bypass surgery. [3] A recent *meta*-analysis summarized the effect of anesthetic modality on inflammation, and concluded that neither propofol nor sevoflurane impact inflammation. [4] Even though this *meta*-analysis did not reveal any significant impact of anesthetic modality on the inflammatory response to surgery, other studies show that both propofol and sevoflurane have properties that could modulate inflammation. [2,5].

The proinflammatory cytokine interleukin-6 (IL-6) has been suggested to be a predictor of acute kidney injury (AKI) when increased after surgery. [6] Moreover, sevoflurane has previously been associated with attenuated renal excretory function and increased plasma

* Corresponding author at: Department of Surgical Sciences, Division of Anesthesiology and Intensive Care Uppsala University Uppsala University Hospital, Entrance 40, Hedenstierna Laboratory, 751 85 Uppsala, Sweden.
*E-mail address:* stephanie.franzen@uu.se (S. Franzén).

https://doi.org/10.1016/j.cyto.2023.156290
Received 1 December 2022; Received in revised form 13 June 2023; Accepted 24 June 2023
Available online 1 July 2023

creatinine concentration. [7,8] It is therefore possible that sevoflurane *per se* may contribute to the pathogenesis of postoperative AKI by modulating the release of cytokines. [6].

We hypothesized that anesthesia *per se* alters plasma levels of cytokines and modulates the inflammatory response to surgery, and that this reaction is more pronounced in sevoflurane anesthesia compared with propofol anesthesia. We also aimed to test the hypothesis that postoperative plasma IL-6 concentration is associated with the duration of surgical insult and renal function as estimated by plasma creatinine concentration.

## 2. Methods

### 2.1. Study design

A retrospective post hoc analysis was performed on samples collected from the *Renal function during sevoflurane or total intravenous propofol anesthesia* randomized controlled trial (Clinicaltrials.gov: NCT0333680, EudraCT: 2017–001646-10). [8] Patients were randomized to receive propofol or sevoflurane anesthesia. Blood samples were collected before anesthesia, 30 min into anesthesia, and 1 h after surgery. Patient inclusion criteria were men and women, 18–65 years old, scheduled for elective spinal surgery. Exclusion criteria were breast feeding/pregnancy, renal impairment, liver impairment, American Heart Association class 3–4, American Society of Anesthesiologists class 3–5, genetic malignant hyperthermia, allergies to anesthesia-related substances, body mass index > 37, inadequacy to give informed consent.

### 2.2. Cytokine analysis

Plasma levels of 27 cytokines were analyzed with the Bio-Plex Pro Human Cytokine Grp I Panel 27-plex kit (batch 64363180) on the Luminex MAGPIX reader (Bio-Rad Laboratories AB, Sundbyberg, Sweden) according to the manufacturer's instructions. The assay included quantification (pg $ml^{-1}$) of Interleukin-1 beta (IL-1β), Interleukin-1 receptor antagonist (IL-1ra), Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-5 (IL-5), Interleukin-6 (IL-6), Interleukin-7 (IL-7), Interleukin-8 (IL-8), Interleukin-9 (IL-9), Interleukin-10 (IL-10), Interleukin-12 (IL-12), Interleukin-13 (IL-13), Interleukin-15 (IL-15), Interleukin-17 (IL-17), Fibroblast Growth Factor basic (FGF-b), Interferon gamma (IFN-γ), Granulocyte Colony-Stimulating Factor (G-CSF), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), Platelet Derived Growth Factor BB (PDGF-BB), Interferon gamma-Induced Protein-10 (IP-10), Monocyte Chemoattractant Protein 1 (MCP-1), Macrophage Inflammatory Protein-1 alpha (MIP-1α), Macrophage Inflammatory Protein-1 beta (MIP-1β), Eotaxin, RANTES, Tubular Growth Factor beta (TGF-β), and Vascular Endothelial Growth Factor (VEGF).

### 2.3. Statistical analysis

The software Statistica (version 13.5.0.17, StatSoft, Tibco, Uppsala, Sweden) was used for statistical analysis. The Friedman ANOVA & Kendall's concordance test was used to analyze changes over time independent of subgroup and within each subgroup. For intergroup differences, the Kruskal-Wallis ANOVA was used with three dependent variables together with the subgrouping variable (propofol vs sevoflurane) to analyze multiple comparisons for mean ranks in all groups. Significance level was set at 95%. General linear regression analysis was performed to correlate postoperative IL-6 concentration with surgical time and change in plasma creatinine and IL-6 concentration from preoperative to postoperative. Raw data are presented as median (interquartile range), and box plot is presented with log transformed data.

## 3. Results

### 3.1. Inclusion

Plasma cytokine levels were analyzed in samples from 22 healthy individuals (n = 12, propofol and n = 10, sevoflurane) preoperatively, 30 min into anesthesia and 1 h postoperatively.

### 3.2. Cytokine detection

The assay quantified (pg $ml^{-1}$) plasma levels of the cytokines IL-1β, IL-1ra, IL-4, IL-6, IL-8, IL-9, IL-13, IP-10, MIP-1α, MIP-1β, MCP-1, RANTES, Eotaxin, G-CSF, TNF-α, and IFN-γ (Table 1). The remaining cytokines from the panel were below the detection range of the assay (IL-2, IL-5, IL-7, IL-10, IL-12, IL-15, IL-17a, GM-CSF, PDGF-bb, FGF-b, and VEGF).

### 3.3. Plasma cytokine levels during anesthesia and after surgery

Plasma samples were taken 30 min into anesthesia and compared with the preoperative values. No statistically significant changes of anesthesia were revealed. One hour after surgery in the postoperative ward, IL-6 levels (Fig. 1) were significantly higher than preoperatively for both anesthetic modalities. However, patients anesthetized with sevoflurane had higher concentrations of IL-6 compared with the propofol modality (Fig. 1). Moreover, IL-4, IL-13, G-CSF, MCP-1, MIP-1β and Eotaxin were significantly lower after surgery than preoperatively in all patients (Table 1). Even though IP-10 was significantly lower after surgery compared with before, this effect was more pronounced in the sevoflurane group than the propofol group (Table 1). In contrast, IFN-γ was lower after surgery than before in the propofol group. Meanwhile, TNF-α was lower after surgery than before in the sevoflurane group (Table 1).

### 3.4. Association of preoperative to postoperative change in plasma IL-6 and creatinine concentration

Plasma creatinine concentration was higher in the sevoflurane group than the propofol group after surgery (68 [59–73] vs 80 [68–95], $p = 0.015$). However, the analysis showed no significant association between the preoperative to postoperative change in plasma IL-6 and creatinine concentration ($R^2 = 0.0005$, $p = 0.920$). When separating the two modalities, the correlation remained not statistically significant (propofol: $R^2 = 0.0005$, $p = 0.823$; sevoflurane: $R^2 = 0.0005$, $p = 0.950$).

### 3.5. Association of postoperative plasma IL-6 levels and surgical time

Surgical time was significantly longer in the sevoflurane group compared with the propofol group (82 [44–129] vs 174 [111–202] min, $p = 0.005$). Plasma concentration of IL-6 after surgery was significantly associated with surgical time ($R^2 = 0.47093$, $p = 0.0004$). Like the aforementioned association, the propofol group had plasma IL-6 concentrations which were significantly associated with the duration of surgery ($R^2 = 0.44317$, $p = 0.018$). However, a statistically significant correlation was not seen in the sevoflurane group ($R^2 = 0.28598$, $p = 0.111$).

## 4. Discussion

The main finding from this study was that only the proinflammatory IL-6 was increased after surgery and that this effect was more pronounced in the sevoflurane group. Interestingly, numerous chemokines and anti-inflammatory cytokines were significantly decreased postoperatively. The investigation furthermore revealed a significant association between postoperative IL-6 levels and surgical time, but not between the preoperative to postoperative change in plasma creatinine

**Table 1**
Summary of cytokines detected by the assay (mean [95%CI] in pg/ml) in all patients (n = 22), propofol group (n = 12), and sevoflurane group (n = 10) before anesthesia, during anesthesia, and 1 h after surgery. * Denotes $p < 0.05$ compared with preoperative values. P vs S (p): p-value for propofol vs sevoflurane comparison. Data are presented as median (interquartile range).

| Table 1 | ALL | PROPOFOL | SEVOFLURANE | P vs S (p) |
|---|---|---|---|---|
| **Interleukin 1β** | | | | |
| Before | 0.9 (0.0–1.4) | 0.6 (0.0–1.6) | 0.9 (0.0–1.4) | 0.869 |
| During | 0.5 (0.0–1.3) | 0.8 (0.0–1.3) | 0.3 (0.0–1.2) | 0.692 |
| After | 0.4 (0.0–1.7) | 0.5 (0.0–1.3) | 0.2 (0.0–3.0) | 0.817 |
| **Interleukin 1ra** | | | | |
| Before | 312 (208–398) | 312 (285–422) | 312 (127–398) | 0.448 |
| During | 312 (250–576) | 350 (267–609) | 300 (153–576) | 0.717 |
| After | 285 (127–447) | 246 (63–447) | 317 (151–492) | 0.291 |
| **Interleukin 4** | | | | |
| Before | 2.3 (1.0–2.9) | 2.5 (1.0–2.9) | 1.9 (0.9–3.0) | 0.895 |
| During | 1.7 (0.7–2.4) | 1.7 (1.0–2.4) | 1.7 (0.0–2.7) | 0.895 |
| After | 1.0 (0.3–1.6) * | 1.0 (0.3–1.6) * | 1.0 (0.3–1.6) | 0.767 |
| **Interleukin 6** | | | | |
| Before | 0.0 (0.0–2.3) | 0.0 (0.0–1.1) | 0.0 (0.0–2.3) | 0.843 |
| During | 0.0 (0.0–0.0) | 0.0 (0.0–0.3) | 0.0 (0.0–0.0) | 0.999 |
| After | 4.9 (0.0–12.9) * | 0.5 (0.0–9.6) | 12.3 (4.0–19.9) * | **0.018** |
| **Interleukin 8** | | | | |
| Before | 2.0 (0.0–3.2) | 1.5 (0.0–4.7) | 2.4 (0.0–3.2) | 0.717 |
| During | 2.6 (0.0–8.2) | 4.6 (0.0–14.2) | 1.3 (0.0–4.0) | 0.307 |
| After | 1.5 (0.0–4.0) | 1.5 (0.5–13.2) | 1.0 (0.0–4.0) | 0.742 |
| **Interleukin 9** | | | | |
| Before | 319 (153–519) | 354 (203–515) | 313 (143–523) | 0.717 |
| During | 295 (215–488) | 273 (196–498) | 299 (215–394) | 0.742 |
| After | 303 (101–495) | 273 (112–485) | 334 (8–495) | 0.974 |
| **Interleukin 13** | | | | |
| Before | 1.5 (0.0–2.5) | 1.3 (0.0–2.3) | 1.9 (0.0–4.4) | 0.742 |
| During | 1.2 (0.0–2.1) | 1.2 (0.0–2.7) | 1.1 (0.0–1.7) | 0.767 |
| After | 0.9 (0.0–1.7) * | 0.6 (0.0–1.7) | 0.9 (0.0–3.6) | 0.843 |
| **Interferon γ** | | | | |
| Before | 1.3 (0.0–3.4) | 1.3 (0.0–3.6) | 0.8 (0.0–3.1) | 0.621 |
| During | 0.3 (0.0–3.1) | 0.1 (0.0–3.2) | 1.0 (0.0–3.1) | 0.692 |
| After | 0.0 (0.0–2.2) | 0.0 (0.0–1.0) * | 1.8 (0.0–5.9) | 0.086 |
| **Tumor necrosis factor α** | | | | |
| Before | 33 (12–48) | 40 (10–49) | 27 (15–38) | 0.448 |
| During | 39 (10–54) | 24 (8–53) | 47 (35–54) | 0.176 |
| After | 17 (14–29) | 19 (14–29) | 14 (11–39) * | 0.598 |
| **Eotaxin** | | | | |
| Before | 44 (31–54) | 46 (30–53) | 39 (31–54) | 0.895 |
| During | 34 (29–54) | 38 (20–56) | 34 (29–54) | 0.999 |
| After | 28 (20–41) * | 29 (22–41) * | 25 (19–41) * | 0.531 |
| **Granulocyte Colony-Stimulating Factor** | | | | |
| Before | 59 (40–64) | 55 (35–75) | 59 (50–60) | 0.843 |
| During | 65 (42–76) | 62 (42–67) | 70 (50–86) | 0.199 |
| After | 35 (30–60) * | 36 (26–48) * | 35 (30–60) | 0.668 |
| **Interferon γ-Induced Protein 10** | | | | |
| Before | 345 (217–482) | 446 (266–576) | 261 (214–379) | 0.129 |
| During | 350 (246–482) | 368 (233–506) | 350 (269–443) | 0.791 |
| After | 232 (172–357) * | 309 (234–443) | 178 (162–230) * | **0.024** |
| **Monocyte Chemoattractant Protein 1** | | | | |
| Before | 24 (18–37) | 22 (16–29) | 26 (18–48) | 0.199 |
| During | 24 (17–28) | 25 (17–28) | 22 (17–44) | 0.869 |
| After | 13 (10–22) * | 13 (7–17) * | 13 (10–23) | 0.307 |
| **Macrophage Inflammatory Protein 1α** | | | | |
| Before | 1.9 (1.4–2.6) | 1.9 (1.6–2.3) | 1.7 (1.2–2.6) | 0.598 |
| During | 1.9 (1.7–2.3) | 1.9 (1.5–2.3) | 1.9 (1.7–2.6) | 0.921 |
| After | 1.4 (1.1–2.0) | 1.3 (1.1–1.5) * | 1.9 (1.2–2.3) | 0.147 |
| **Macrophage Inflammatory Protein 1β** | | | | |
| Before | 190 (99–250) | 199 (133–150) | 180 (97–266) | 0.621 |
| During | 188 (129–223) | 178 (122–238) | 190 (129–215) | 0.742 |
| After | 174 (71–248) * | 169 (75–233) | 197 (14–255) | 0.621 |
| **RANTES** | | | | |
| Before | 2520 (779–4471) | 2575 (1635–4861) | 2116 (732–4471) | 0.598 |
| During | 2471 (1505–3304) | 2440 (1297–2973) | 2608 (1541–3304) | 0.692 |
| After | 1820 (1126–3159) | 1884 (879–2221) | 1630 (1520–3402) | 0.644 |

and IL-6. Therefore, this study demonstrates that not anesthesia, but the duration of surgical insult affects plasma levels of cytokines. However, sevoflurane anesthesia seems to augment the IL-6 response to surgical insult which subsequently could be a contributor to postoperative AKI.

Surgery *per se* causes trauma to the local tissue and generates an inflammatory response. [1] Interleukin-6 has been associated with surgical trauma and is a potent proinflammatory signal peptide with various functions to stimulate the innate immune response. [9] In this study, IL-6 was increased postoperatively yet this increase was significantly higher in the sevoflurane group than the propofol group. It has been demonstrated that propofol can suppress the production of IL-6 suggesting a favorable outcome regarding postoperative inflammation compared with sevoflurane. [5] Postoperative IL-6 could be associated with surgical severity or duration however, it has been reported that open surgery does not cause higher IL-6 levels compared with laparoscopic surgeries [10]. Although, in this study we report that the prolonged surgical insult is associated with increased concentration of plasma IL-6.

Here we also report that the preoperative to postoperative increase in plasma IL-6 and creatinine levels are not significantly correlated. This is in contradiction with the suggestion that IL-6 is a predictor of AKI. [6] Since no patient in this study developed AKI, increased levels of IL-6 do not have to translate into AKI. Since this study only assessed one-hour postoperative changes and outcome, postoperative morbidity after a longer time period can therefore not be excluded. Clinical interest in IL-6 as a biomarker and as a therapeutic target has increased after the success of the IL-6 blocker tocilizumab in severe covid-19, which also could be beneficial in non-covid inflammation. [11,12].

The role of anesthesia in postoperative inflammation has been discussed to some extent and seem to be different depending on both type of surgery and sometimes anesthetic modality. Propofol has been suggested to have both anti-inflammatory and antioxidative properties. [2] Studies have shown that propofol can attenuate the endotoxemic inflammatory response via toll-like receptor 4 and that propofol is protective against septic acute kidney injury. [13] Meanwhile, sevoflurane preconditioning has been shown to be a beneficial methodology in cardiopulmonary surgical settings to improve postoperative outcome. [3] However, volatile agents does not appear to protect against renal injury. [14] It should however be noted that anesthetic modality *per se* could impact study outcome in clinical or experimental studies targeting inflammation and IL-6, since we demonstrate that propofol and sevoflurane affect postoperative IL-6 levels differently.

In this study, several chemokines and IL-4 were lower after surgery compared with preoperatively which indicates that this type of surgery causes some kind of immunosuppression independent of anesthetic modality. Another explanation could be that anesthesia and surgery causes a shift in fluid distribution which hypothetically could dilute the plasma and therefore translate to reduced plasma concentrations. If this were to be the case, plasma creatinine and IL-6 would then also be affected by this. The specific roles of sole cytokines are complicated and highly advanced depending on several mechanisms which makes it hard to conclude the actual role of this decrease in plasma cytokine levels.

### 4.1. Strengths and limitations

This study has some strengths and limitations. The major strength is that we provide data on plasma cytokine levels in anesthetized patients without the impact of surgical trauma. Also, the study was conducted during a controlled perioperative setting regarding fluid administration, use of vasopressors, and normal blood pressure. One limitation of this study is the small sample size. The sample size makes it difficult to provide firm conclusion on the correlations between surgical time and plasma IL-6 concentrations in the separate subgroups of anesthetic modality. Yet, the clinical trial was conducted in a controlled setting and still provides robust data. Another limitation is the lack of endpoints in the clinical trial. No patients in this study developed AKI however,

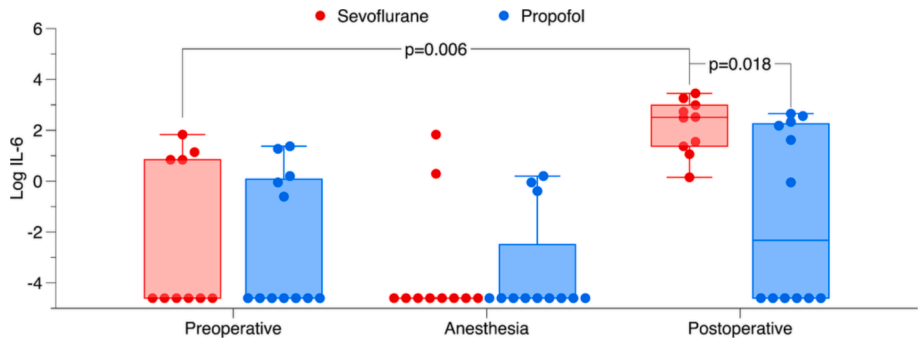


**Fig. 1.** Log transformed plasma levels of interleukin (IL)-6 (pg/ml) in sevoflurane (red) and propofol (blue) before surgery, 30 min into anesthesia, and after surgery. Data are presented as individual scatter plot of log transformed values together with box-whiskers (median and interquartile range). P-values are derived from statistical non-parametric analyses on raw data (Methods section 2.3).

plasma creatinine concentrations were still increased after surgery which indicates a significant effect on renal function by the sevoflurane modality. Moreover, we lack a prolonged postoperative follow-up period to associate the increased IL-6 levels with long-term postoperative morbidity. However, the main aim of the study was to assess the acute inflammatory response by anesthesia and surgery. Even so, a clinical trial demonstrated that sevoflurane anesthetized patients had significantly higher plasma IL-6 levels and morbidity rate at postoperative day 7 when compared with propofol anesthesia. [15].

### *4.2. Conclusion*

Anesthesia *per se* did not significantly alter plasma cytokine concentrations. However, IL-6 was increased after surgery and this effect was more pronounced in sevoflurane anesthesia compared with propofol anesthesia. Additionally, there was a significant correlation between postoperative plasma IL-6 and surgical time, but not between preoperative to postoperative change in plasma IL-6 and creatinine concentration. In conclusion, our data suggests that sevoflurane anesthesia augments the postoperative inflammation through the IL-6 pathway when compared with intravenous propofol anesthesia.

Funding.

This study was funded by the Swedish Research Council to RF (2014–02569 and 2014–07606).

## CRediT authorship contribution statement

**Stephanie Franzén:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Egidijus Semenas:** Investigation, Resources, Data curation, Writing – review & editing. **Anders Larsson:** Methodology, Resources, Writing – review & editing. **Michael Hultström:** Conceptualization, Formal analysis, Writing – review & editing, Supervision. **Robert Frithiof:** Conceptualization, Formal analysis, Writing – review & editing, Supervision, Funding acquisition.

## 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.

## Data availability

Data can be provided upon reasonable request.

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