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The effect of general *versus* spinal anesthesia on perioperative innate immune function in patients undergoing total hip arthroplasty

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Abstract

Background Increasing evidence shows that postoperative innate immune dysregulation is associated with delayed recovery and infectious complications. The aim of this study was to compare the effects of general versus spinal anesthesia on innate immune function during and after total hip arthroplasty (THA).

Methods This comparative matched cohort study used data from two single-center randomized-controlled trials. Patients from the control group of the HIPPO study received general anesthesia and were matched to control patients from the MAGIC study who received spinal anesthesia in a 2:1 ratio (general($n=18$); spinal($n=9$)). Immune function was assessed by determination of ex vivo cytokine production capacity upon whole blood stimulation with *E. coli* lipopolysaccharides (LPS) and measurement of plasma cytokines and danger-associated molecular patterns (DAMPs).

Results In the general anesthesia group, ex vivo cytokine production capacity of IL-1β was significantly lower shortly after induction ($p=0.02$) and both IL-1β and IL-6 were significantly lower at the end of surgery compared to the spinal anesthesia group ($p=0.002$ and $p=0.02$, respectively). On postoperative day 1 (POD1), no differences were observed. Plasma cytokine concentrations did not differ between the spinal and general anesthesia group at most timepoints, except for IL-10 at the end of surgery ($p=0.04$) and TNF on POD1 ($p=0.04$), which were higher in the general anesthesia group. Plasma concentrations of DAMPs did not differ between the groups.

Conclusions General anesthesia has a transient impact on innate immune function in patients undergoing THA, but the clinical significance of anesthesia-induced innate immune dysregulation might be limited as no differences were observed on POD1.

Trial registration The HIPPO study (NCT05562999, date of registration 2022-10-03) and MAGIC study (NCT05723406, date of registration 2023-02-10) are registered at ClinicalTrials.gov.

Keywords Anesthesia, Total hip arthroplasty, Innate immune function

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Introduction

Globally, over 1 million total-hip arthroplasties (THAs) are performed each year [1], and the number of procedures is expected to grow substantially in the coming decades [2]. THA can greatly improve patients' quality of life and has a very high rate of post-surgical satisfaction [3]. However, the operation is not without risks and complications, such as periprosthetic joint infections (PJIs). The incidence of PJI is relatively small, approximately 1% [4], but the impact of this complication can be devastating. An increased susceptibility to infections after surgery, such as PJIs, has been associated with postoperative innate immunosuppression [5, 6].

The degree and duration of postoperative immune dysregulation are believed to be determined by the amount of admitted surgical trauma [6]. Surgical trauma induces the release of danger-associated molecular patterns (DAMPs). These DAMPs bind to receptors on immune cells of the innate immune system, which causes a predominantly anti-inflammatory response characterized by an increase in circulating interleukin (IL)-10, resulting in immunosuppression [5, 7]. Pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF), IL-6 and IL-1β, are also elevated shortly after trauma [8, 9]. In addition to surgical trauma, anesthetics commonly used in surgery may have a direct effect on the functions of immunocompetent cells [10]. In general, the effects of intravenous (IV) anesthetics on postoperative immune function appear to be moderate compared to the effects of surgical trauma in healthy patients undergoing short procedures [11]. However, the extent of this effect remains only scarcely investigated.

Patients undergoing THA are mostly offered either spinal or general anesthesia [12], but, when possible, spinal anesthesia is deemed superior [13]. Whether spinal anesthesia results in a favorable postoperative outcomes remains a topic of debate [14–17]. Possible beneficial effects of spinal anesthesia on postoperative outcomes, specifically infectious complications, might be due to the effects of general and spinal anesthesia on immune function. Due to the complexity of clinical studies, present knowledge regarding the effects of anesthetics on the innate immune system has been derived mostly from in vitro studies [11].

As the effects of spinal and general anesthesia on perioperative innate immune function have only been scarcely investigated, the aim of this study was to compare the effects of general and spinal anesthesia on perioperative innate immune function in patients undergoing THA.

Methods

Study design and population

This comparative matched cohort study used data from the control groups of two single-center randomized-controlled trials (RCTs) conducted at Radboud University Medical Center (Radboudumc, Nijmegen, the Netherlands) to compare the effects of general and spinal anesthesia on perioperative immune function. Permission for the trials was granted by the Medical Research Ethics Committee 'METC Oost-Nederland' (NL81931.091.22 and NL82808.091.22) and all patients provided written informed consent prior to any study-related procedures. The RCTs were enrolling simultaneously and were performed in accordance with de Declaration of Helsinki. The MAGIC study (NCT05723406) was performed to determine the effect of sugammadex administered during total hip arthroplasty under spinal anesthesia on postoperative immune suppression. Patients in the control group of this study received placebo (NaCl 0.9%) and were all included in the spinal anesthesia group of this matched cohort. Additionally, appropriate patients from the control group of the HIPPO study (NCT05562999) were identified for the general anesthesia group. The HIPPO study was initiated to compare the effects of moderate versus deep neuromuscular blockade (NMB) on perioperative immune function in patients undergoing total hip arthroplasty under general anesthesia. Patients in the control group of the HIPPO study only received an induction dose of 0.6 mg/kg rocuronium for tracheal intubation with an additional bolus of 10–20 mg rocuronium when the train of four (TOF) count exceeded 2. They were matched to the patients from the MAGIC study in a 2:1 ratio (general: spinal) based on type of surgery (primary THA). This study adheres to CONSORT guidelines. For detailed information regarding the study design and procedures of the MAGIC and HIPPO trials, we refer to the articles that report on these studies [18, 19].

In- and exclusion criteria

Adult patients scheduled for primary THA under spinal or general anesthesia were included. Exclusion criteria comprised insufficient control of the Dutch language, known or suspected hypersensitivity to sugammadex, deficiency of vitamin K-dependent clotting factors or coagulopathy, severe renal (creatinine clearance < 30 mL/min) or liver (Child-Pugh classification C) disease, mentally incapacitated patients, and chronic use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), steroids, or immunosuppressive drugs. Women were also excluded if they were currently pregnant or breastfeeding or if they were in childbearing potential without use of adequate contraception.

Additional exclusion criteria for the spinal anesthesia group were severe vertebral column disorder, chronic use of psychotropic drugs, known hypertrophic obstructive cardiomyopathy, and severe aortic or mitral valve stenosis.

Anesthesia

In the spinal anesthesia group, neuraxial anesthesia was obtained with bupivacaine 0.5% 10–20 mg combined with sufentanil. Sedation was achieved by 1.5–4.5 mg/kg/hr propofol infusion upon the patient's request. Additionally, esketamine was administered. In the general anesthesia group, induction of anesthesia was achieved with propofol (1–3 mg/kg), sufentanil (0.1–0.5 µg/kg), esketamine (2.5–10 mg), and rocuronium (0.6 mg/kg) prior to tracheal intubation. General anesthesia was maintained with continuous propofol (6–10 mg/kg/h) and esketamine (2.5–10 mg/h) perfusion. In both groups, perioperative administration of dexamethasone was avoided because this might influence postoperative immune function. Total hip replacement surgery was performed with cemented prostheses via posterolateral approach. Multimodal postoperative analgesia was administered according to the local protocol.

Sample and data collection

Blood samples (Lithium heparin (LH) and ethylenediaminetetraacetic acid (EDTA) anticoagulated) were drawn before surgery, after induction of general or spinal anesthesia (before incision), at the end of surgery, and on postoperative day 1. First, the LH and EDTA anticoagulated blood tubes were centrifuged at 2,970 RCF at room temperature for 10 min. EDTA anti-coagulated plasma samples were centrifuged again at 16,000 RCF at room temperature for 10 min. Subsequently, plasma was stored at -80 °C until further analysis. Baseline characteristics and perioperative parameters were obtained from digital patient files in the programme Epic Systems Corporation (Epic).

Ex vivo cytokine production

Leukocyte cytokine production capacity was determined ex vivo by stimulation of whole blood with *Escherichia coli* lipopolysaccharides (*E. coli* LPS (serotype O55:B5 Sigma Aldrich, St Louis, MO, USA)) to effectively assess the functionality of the immune system. 0.5 mL LH anticoagulated blood was added to prefilled tubes with 2 mL Dutch-modified Roswell Park Memorial Institute (RPMI) culture medium (negative control) or culture medium supplemented with 12.5 ng/mL *E. coli* LPS (final concentration 10 ng/mL) as described previously [5, 20]. The tubes were incubated at 37 °C with 5% CO_2. After 24 h, they were centrifuged at 2,970 RCF at room temperature for 10 min and supernatant was stored at -80 °C until analysis. Concentrations of pro-inflammatory cytokines IL-6, IL-1β, TNF and anti-inflammatory cytokine IL-10 were measured batchwise using Human Bio-Techne R&D enzyme-linked immunosorbent assays (ELISAs) according to the manufacturer's instructions (R&D systems, Minneapolis, MN, USA, catalogue numbers DY206, DY201, DY210, and DY217B).

Plasma DAMP and cytokine concentrations

Plasma concentrations of DAMPs were measured batchwise using ELISAs. The Human High Mobility Group Protein B1 (HMGB-1) ELISA (invitrogen, catalogue number EEL047; Thermo Fisher Scienficic, Waltham, Massachusetts, USA) was used according to the manufacturer's instructions to measure plasma concentrations of HMGB-1. Plasma concentrations of S100A8/A9 and S100A12 were measured using Human S100A8/S100A9 Heterodimer and Human EN-RAGE DuoSet ELISAs (R&D systems, Minneapolis, MN, USA, catalogue numbers DY8226-05 and DY1052-05 respectively). Plasma concentrations of pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF), as well as anti-inflammatory cytokine IL-10, were measured in plasma obtained from EDTA-anticoagulated blood using a simultaneous Luminex assay according to the manufacturer's instructions (Milliplex; Millipore, Billerica, MA, USA).

Statistical analysis

Continuous data in tables and figures are expressed as mean ± standard deviation (SD) and median ± interquartile range (IQR), respectively. Categorical data are presented as numbers with percentages. Differences at baseline between the groups were determined using independent samples T-test or Chi-square tests as applicable. Mann-Whitney U test was used to determine differences in cytokine concentrations between groups and Friedman tests followed by Dunn's post-hoc tests with Bonferroni correction were conducted to determine differences between timepoints within each group. ANCOVA was used to correct for statistically significant differences in baseline characteristics for the primary outcome (ex vivo cytokine production). Plasma cytokine concentrations below the detection limit as determined by Luminex assay were considered equal to the lowest detectable concentrations. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS statistics version 29 (IBM Corporation, Armonk, NY, USA) and RStudio version 2023.12.1 (Posit, PBC, Boston, MA, USA) and figures were created using Graphpad Prism version 9 (Graphpad Software, NY, USA).

Table 1 Baseline characteristics. Differences were determined using independent samples T-test or chi-square test as applicable. Data are presented as mean (SD) or number (%) unless specified otherwise. ASA: American Society of Anesthesiologists

		Spinal anesthesia (*n* = 9)	General anesthesia (*n* = 18)	*P*-value
Patient characteristics	Age	61.7 (18.9)	60.4 (16.9)	0.87
	Male sex	5 (55.6)	8 (44.4)	0.59
	Body mass index (BMI)	27.5 (6.1)	29.1 (6.9)	0.57
	ASA classification	3 (33.3%)	0 (0%)	**0.006**
	I	2 (22.2%)	14 (77.8%)	
	II	4 (44.4%)	4 (22.2%)	
	III			
	History of smoking	5 (55.5%)	9 (50.0%)	0.62
	Side of hip replacement, L/R	4 / 5	11 / 7	0.41
Comorbidities	Cardiovascular disease	5 (55.6%)	10 (55.6%)	1.00
	Pulmonary disease	6 (66.7%)	14 (77.8%)	0.54
	Renal insufficiency	0 (0%)	1 (5.6%)	0.47
	Neurological disease	3 (33.3%)	2 (11.1%)	0.24
	Liver insufficiency*	1 (11.1%)	0 (0%)	0.15

* Auto-immune hepatitis

Table 2 Intraoperative parameters and postoperative outcomes. Data are presented as mean (SD) or number (%). PACU: Post Anesthesia care unit

		Spinal anesthesia (*n* = 9)	General anesthesia (*n* = 18)	*P*-value (T-test)
Intraoperative parameters	Duration of surgery (minutes)	102 (15)	124 (39)	0.12
	Blood loss (mL)	429 (175)	605 (317)	0.14
	Propofol (mg)	404 (279)	1672 (535)	**< 0.001**
	Esketamine (mg)	13.5 (11.4)	27.9 (19.2)	**0.049**
	Bupivacaine (mg)	13.7 (1.3)	/	/
	Sufentanil (µg)	3.9 (5.2)	28.7 (16.7)	**< 0.001**
Postoperative outcomes	PACU stay (minutes)	76 (54)	114 (68)	0.16
	Time until first mobilization (hours)	25 (21)	32 (34)	0.60
	Hospital stay (days)	2.7 (2.3)	3.3 (3.0)	0.57
	Re-admission	0 (0%)	1 (5.6%)	0.47
	Infectious complications	1 (11.1%)	2 (11.1%)	1.00

Results

Patient characteristics and intra- and post-operative parameters

Nine patients were included in the spinal anesthesia group, and eighteen patients were included in the general anesthesia group. All patients selected for this matched cohort study were recruited between November 2022 and October 2023 and were included in the analyses. Baseline characteristics were similar between the groups except for ASA classification (Table 1). Significant differences in intraoperative anesthesia (propofol, esketamine, and sufentanil) were found as expected due to the different anesthesia techniques used in the two groups. Postoperative outcomes did not differ between the groups (Table 2). In total, three patients developed an infectious complication. One patient in the spinal anesthesia group received antibiotic treatment for a superficial wound infection. In the general anesthesia group, one patient had a periprosthetic joint infection (PJI), and one patient suffered from a urinary tract infection. Mortality did not occur and no patients experienced postoperative delirium.

Ex vivo cytokine production

Ex vivo cytokine production of IL-1β was significantly lower in the general anesthesia group compared to the spinal anesthesia group (Fig. 1) after induction and at the end of surgery ($p=0.02$ and $p=0.002$, respectively). At the end of surgery, also ex vivo cytokine production of TNF was significantly lower in patients who received general anesthesia ($p=0.02$). At POD1, no significant differences were found between the groups. ANCOVA with correction for American Society of Anesthesiologists (ASA) score showed the same statistically significant differences between the groups (suppl. Table S1).

After induction and at the end of surgery, cytokine production capacity of IL-1β and IL-6 was significantly decreased compared to baseline levels in the general anesthesia group. The same applied to the production

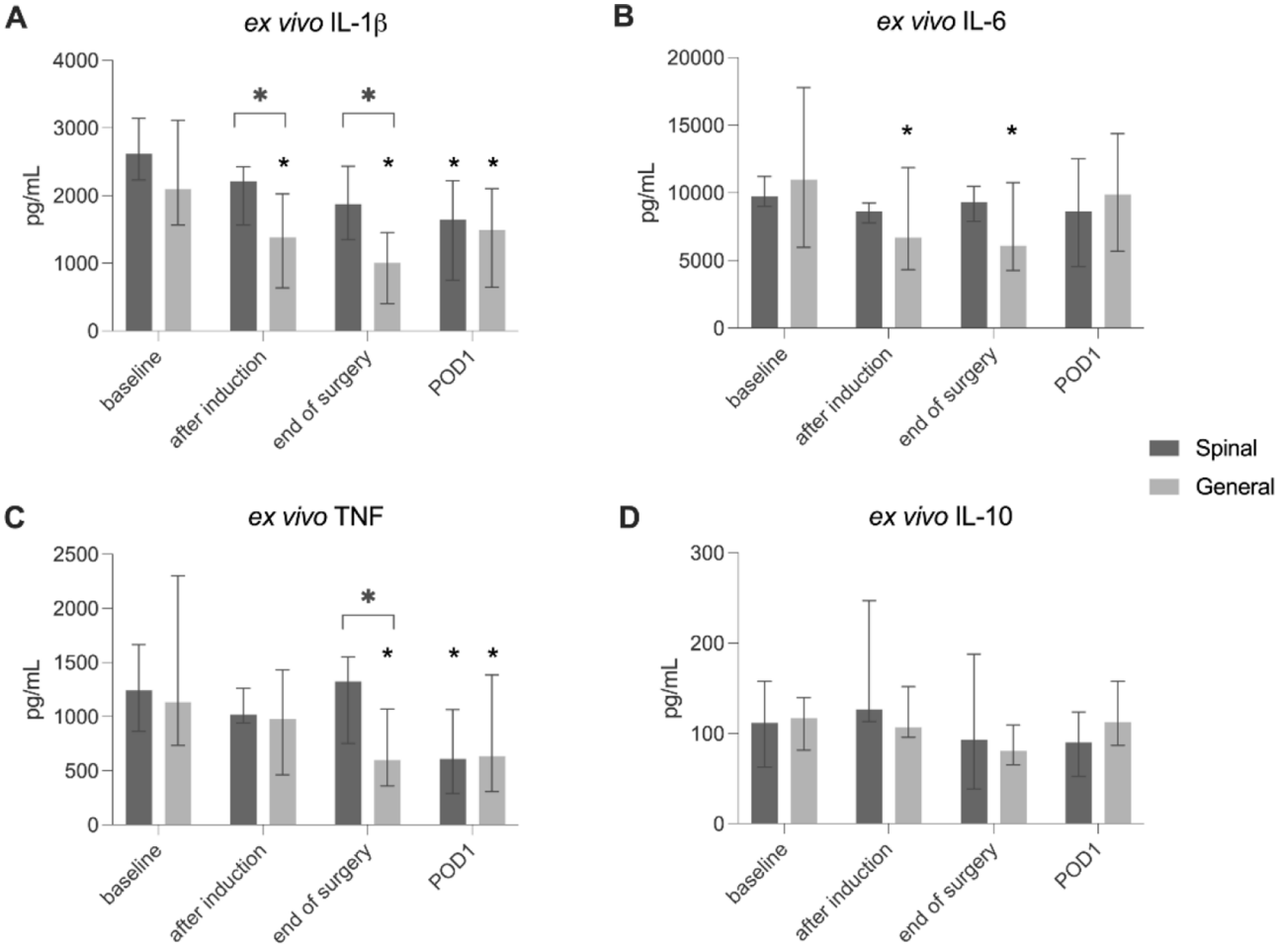

Fig. 1 **A-D** Cytokine production capacity of leukocytes upon ex vivo stimulation with *Escherichia Coli* lipopolysaccharides of pro-inflammatory cytokines interleukin (IL)-1β, IL-6, and tumour necrosis factor alpha (TNF) and anti-inflammatory cytokine IL-10 at baseline, after induction (before first incision), at the end of surgery, and on postoperative day 1 (POD 1) in patients undergoing total hip arthroplasty under spinal ($n=9$) versus general ($n=18$) anesthesia. Data are expressed as median ± interquartile range (IQR)

of TNF at the end of surgery after general anesthesia. At POD1, cytokine production of both IL-1β and TNF were significantly decreased compared to baseline in both groups. No differences between groups and over time were observed regarding ex vivo cytokine production of the anti-inflammatory cytokine IL-10. Details on the total white blood cell count and the concentrations of different leukocyte populations can be found in supplemental Table S2.

Plasma DAMP and cytokine concentrations

Plasma concentrations of DAMPs (HMGB1, S100A8/A9, and S100A12) were similar in the spinal and general anesthesia groups at all timepoints (Fig. 2). In both groups, levels of HMGB1 decreased during surgery while concentrations of the S100A8/A9 heterodimer increased. Concentrations of both aforementioned DAMPs had returned to baseline levels on POD1, while S100A12 was increased.

Plasma TNF concentrations on POD1 were higher in the general anesthesia group compared to the spinal anesthesia group ($p=0.04$). IL-10 was also higher at the end of surgery in patients who received general anesthesia ($p=0.04$). No other differences in plasma cytokine concentrations were found between the groups (Fig. 3). Plasma levels of IL-6 were significantly increased on POD1 compared to baseline in both groups. Plasma concentrations of IL-10 were only significantly elevated in the general anesthesia group on POD1.

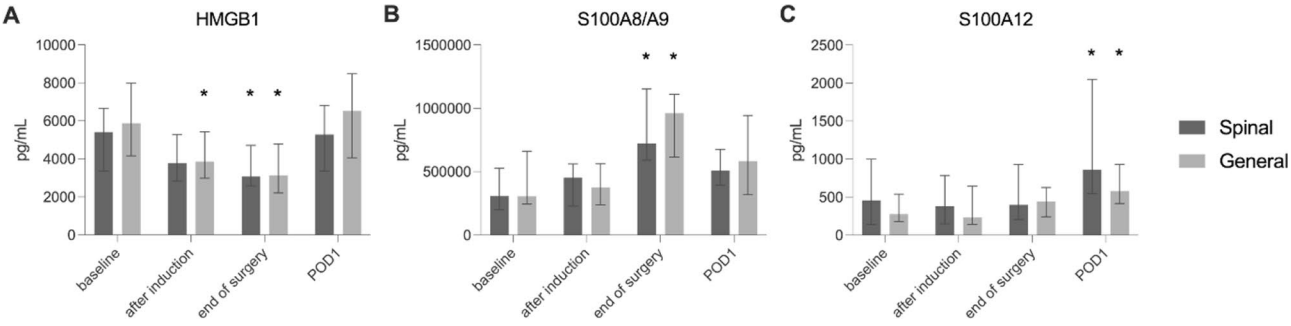

Fig. 2 **A-C** Plasma concentrations of danger-associated molecular patterns (DAMPs) at baseline, after induction (before first incision), at the end of surgery, and on postoperative day 1 (POD1) in patients undergoing total hip arthroplasty under spinal ($n = 9$) versus general ($n = 18$) anesthesia. Data are expressed as median ± interquartile range (IQR). * = significant difference from baseline determined by Friedman tests with Bonferroni correction ($p < 0.05$); No significant differences between groups were found as assessed by Mann-Whitney U test. HMGB1: high mobility group box 1

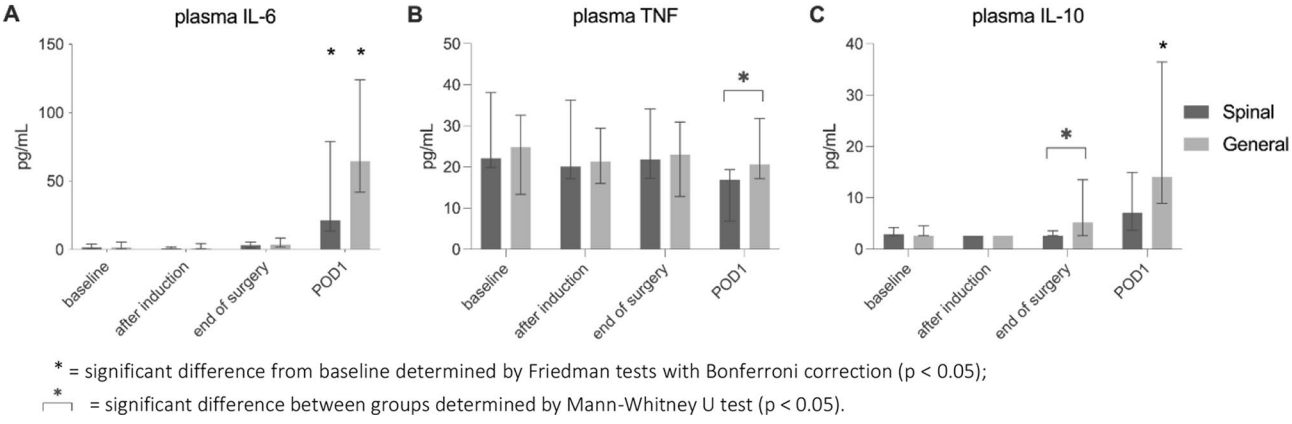

Fig. 3 **A-C** Plasma cytokine concentrations of pro-inflammatory cytokines interleukin (IL)-6 and tumour necrosis factor alpha (TNF), and anti-inflammatory cytokine IL-10 at baseline, after induction (before first incision), at the end of surgery, and on postoperative day 1 (POD1) in patients undergoing total hip arthroplasty under spinal ($n = 9$) versus general ($n = 18$) anesthesia. Data are expressed as median ± interquartile range (IQR)

Discussion

This comparative matched cohort study was designed to differentiate between the effects of spinal and general anesthesia on perioperative immune function in patients undergoing THA. Ex vivo cytokine production was affected more in the general anesthesia group compared to the spinal anesthesia group. However, on POD1 no differences in ex vivo cytokine production capacity between the groups were observed. Overall, plasma concentrations of cytokines and DAMPs did not differ between the spinal and general anesthesia.

The current study showed a moderately higher impact of general anesthesia on intraoperative ex vivo cytokine production capacity compared to spinal anesthesia. In the general anesthesia group, ex vivo cytokine production capacity of IL-1β was significantly lower after induction of anesthesia compared to the spinal anesthesia group. Furthermore, ex vivo cytokine production capacity of IL-1β and IL-6 was significantly reduced compared to baseline already shortly after induction of general anesthesia, even before incision. At the end of surgery, ex vivo cytokine production of all three pro-inflammatory cytokines was reduced only in the general anesthesia group, and production capacity of IL-1β and TNF was significantly lower compared to the patients receiving spinal anesthesia. Measurement of ex vivo cytokine production capacity (predominantly TNF) is a commonly used method for quantification of innate immune function in critical illness and low production capacity has been associated with adverse outcomes [21]. To our knowledge, no previous study has been performed comparing general and spinal anesthesia regarding ex vivo cytokine production capacity. Van Deuren et al. [22]. did show decreased ex vivo production of cytokines in a combined general and spinal anesthesia group starting at 3 h after surgery, but not immediately after induction of anesthesia. This finding is in line with our results as we did not find an effect of spinal anesthesia, although a mixed group might not give a true representation of the effect of anesthesia. In our study, on POD1 the difference between general and spinal anesthesia in ex vivo IL-1β and TNF production had disappeared. This suggests a transient effect of general anesthesia on perioperative immune function and that the biological impact

of surgery on the inflammatory response may outweigh the impact of the anesthetic technique.

The temporary differences in immune function after administration of general versus spinal anesthesia might be explained by the effect of the different anesthetic drugs in each of the groups. In our study, bupivacaine was used to achieve spinal anesthesia. A potential effect of bupivacaine on the immune system is the inhibition of natural killer (NK) cells, which – in addition to macrophages - are crucial in the innate immune response [23]. Local anesthetics have also been shown to impair function of polymorphonuclear leukocytes which can theoretically increase the risk of postoperative infections [24]. On the other hand, local anesthetics can reduce the inhibitory effect of stress on the immune system. Normally, the hypothalamic-pituitary-adrenal axis (HPA) of patients is activated during surgery, resulting in a change in neuroendocrine function which inhibits the immune system [23]. These opposing effects might explain the lack of an immunosuppressive effect of spinal anesthesia in the current study.

Our findings suggest that the drugs used for general anesthesia have immunosuppressive effects. Propofol was used for the induction and maintenance of general anesthesia. Propofol is a gamma-aminobutyric acid (GABA) receptor agonist [25]. GABA serves as an important inhibitory neurotransmitter in the brain and spinal cord [26]. GABA receptors are also widely distributed in immune cells such as neutrophils, monocytes, and macrophages. Administration of GABA or drugs that mimic GABA have been shown to result in decreased cytokine secretion [25, 27]. Propofol has a prominent anti-inflammatory effect by regulation of macrophage function. Propofol can exert its anti-inflammatory effect by reducing the production of inflammatory cytokines by macrophages. Additionally, immunosuppression of macrophages may be caused by inhibition of mitochondrial membrane potential and adenosine triphosphate (ATP) biosynthesis [25]. In our cohort, sufentanil and esketamine were also administered in significantly larger amounts to the general anesthesia group. Sufentanil is an effective opioid analgesic with immunosuppression as an important side effect [28, 29]; fentanyl impairs the function of macrophages, NK cells, and T-cells in vitro. Furthermore, high doses of opioids have been correlated with a higher risk of infectious diseases [28]. However, controlled clinical randomized trials to support these correlations are lacking. Esketamine may also have an immunomodulatory effect, but results from previous studies are contradictory. Zhang et al. described that in Asian patients undergoing modified radical mastectomy, esketamine had a systemic anti-inflammatory effect and attenuated immunosuppression [30]. On the contrary, Cho et al.. found that low-dose intraoperative ketamine administration did not result in favorable impacts on postoperative NK cell activity and inflammatory responses [31] after laparoscopic colorectal cancer surgery. Future clinical studies investigating the effects of each individual drug could provide further understanding of the contributions of individual drugs in the observed immunosuppression.

The type of anesthesia did not have a clear effect on plasma cytokine and DAMP concentrations in our study. No differences between the groups were found in plasma concentrations of IL-6, but TNF was significantly higher in the general anesthesia group compared to the spinal anesthesia group on POD1. In women undergoing cesarian section, serum TNF levels were also higher in the general anesthesia group compared to the spinal anesthesia group 30 min after entering the recovery room [32]. In our study, levels of IL-6, TNF, and IL-10 were not increased or decreased after administration of anesthesia and at the end of surgery compared to baseline. Høgevold et al.. also measured changes in plasma cytokines after THA in general or regional anesthesia. They did not find significant differences between the groups in concentrations of IL-6 and TNF during and after surgery [33]. Additionally, in the previously mentioned study by van Deuren et al. [22]. , plasma concentrations of IL-6 after induction of anesthesia did not differ from baseline.

Concentrations of DAMPs did not differ between the spinal and general anesthesia group at all timepoints, and no clear differences were observed after induction of anesthesia compared to baseline. A previous study found significantly higher concentrations of S100A8/A9 and S100A12 three days after mastectomy compared to breast-conserving surgery [34]. As these differences were present at a later timepoint which was not included in the current study, we cannot rule out the possibility of differences between the spinal and general anesthesia groups at later timepoints. DAMPs are released upon cellular stress and damage. They induce the expression of proinflammatory cytokines and participate in immune regulation [35]. In our cohort, an increase in S100A8/A9 and S100A12 was seen at the end of surgery and on POD1 respectively, but without differences between the two groups. The absence of diversity in DAMPs, produced as a result of surgical trauma, between the spinal and general anesthesia group suggest that the detected differences in plasma cytokines and ex vivo cytokine production capacity might be due to the direct effect of anesthesia on innate immune function instead of indirectly via surgical tissue injury.

This study has some limitations that warrant consideration for a comprehensive understanding of our findings. Most importantly, as propofol was used in the spinal anesthesia group to achieve sedation, it is not possible to make an unbiased distinction between spinal

and general anesthesia. Differences in immune function might be more distinguished between patients under general anesthesia and patients with only spinal anesthesia without sedation due to the considerable effect of propofol on immune function as described earlier. However, as administration of propofol for sedation upon patient's request is standard practice, we believe our cohort gives a true representation of the THA population. Additionally, our small sample size limited the statistical power of our analyses, potentially resulting in an inability to detect existing differences. Still, a clear trend was observed especially for ex vivo cytokine production, which shows that a larger sample size was not crucial to obtain meaningful effects. Lastly, the groups differed in ASA scores at baseline. The spinal anesthesia group contained more patients with ASA I or ASA III, while the general anesthesia group mainly consisted of patients with ASA II. However, as demonstrated, correction for ASA score during statistical analysis resulted in the same outcome. The findings of this study give an indication of the potential effect of anesthesia on postoperative innate immune function, but mainly allow for further investigations with a larger sample size to size to assess associations with postoperative clinical outcomes such as (infectious) complications. Additionally, as this study specifically focuses on the effects of anesthesia on innate immune function, the effects of on the adaptive immune system—which become more prominent in the later stages of the immune response — were not addressed and represent an important area for future research.

Conclusion

General anesthesia has a transient impact on innate immune function as reflected by a lower ex vivo cytokine production capacity shortly after induction and at the end of surgery. As no differences in innate immune function were observed on POD1, the clinical significance of anesthesia-induced innate immune dysregulation might be limited.

Abbreviations

ATP	Adenosine triphosphate
DAMPs	Danger-associated molecular patterns
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
GABA	Gamma-aminobutyric aci
HMGB-1	High Mobility Group Protein B1
HPA	Hypothalamic-pituitary-adrenal
IL	Interleukin
IQR	Interquartile range
IV	Intravenous
LH	Lithium heparin
LPS	Lipopolysaccharides
NK	Cell natural killer cell
NMB	Neuromuscular blockade
PJI	Periprosthetic joint infection
POD1	Post operative day 1
RCF	Relative centrifugal force
RCT	Randomized controlled trial
RPM	Rounds per minute
SD	Standard deviation
THA	Total hip arthroplasty
TNF	Tumor necrosis factor alpha

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02883-1.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

LMCJ, VB, LTE, LABJ, CK, JV, and MCW contributed to the study conception and design. Material preparation, data collection and analysis were performed by LMCJ and VB. The first draft of the manuscript was written by LMCJ. VB, LTE, LABJ, CK, JV, and MCW commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies were performed in accordance with the Declaration of Helsinki and approved by the Medical Research Ethics Committee 'METC Oost-Nederland' (NL81931.091.22 and NL82808.091.22). All participants provided written informed consent prior to any study-related procedures.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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