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Comparison of inhalation and total intravenous anesthesia on inflammatory markers in microdiscectomy: a double-blind study

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Abstract

Background The choice of anaesthetic technique has the potential to exert a significant influence on the perioperative stress response, immune modulation and inflammation which are critical factors in surgical recovery. The primary objective of this study was to compare 24-h postoperative IL-6 levels between patients undergoing lumbar microdiscectomy under TIVA or sevoflurane anesthesia. Secondary outcomes included perioperative changes in CRP, NLR and PLR.

Methods This prospective, randomised, double-blind study included 40 patients classified as American Society of Anesthesiologists (ASA) I-II and scheduled for elective lumbar disc herniation surgery. Patients were randomly assigned to receive either TIVA with propofol or inhalational anaesthesia with sevoflurane. Interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), neutrophil-to-lymphocyte ratio (NLR) levels were measured at preoperative, intraoperative and postoperative time points.

Results Postoperative IL-6 levels were significantly lower in the TIVA group than in the sevoflurane group ($p < 0.05$), with a blunted increase in IL-6 levels from the preoperative to the postoperative phases. Postoperative CRP levels were significantly lower in the TIVA group ($p < 0.05$), whereas PCT levels remained stable across groups. There were no significant differences between groups in NLR values.

Conclusion The results of this study indicate that TIVA with propofol may offer a superior modulation of inflammatory responses compared to sevoflurane in patients undergoing lumbar microdiscectomy. These findings indicate that TIVA may be a preferred anaesthetic technique for surgical procedures that require precise control of the perioperative inflammatory response. Further studies are required to validate these findings in larger populations and diverse surgical contexts.

Trial registration ClinicalTrials.gov, NCT 06386965.

Keywords Propofol, Sevoflurane, Interleukin 6

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Background

Surgical procedures induce neuroendocrine, metabolic and inflammatory responses as a result of surgical stress [1, 2]. Significant disturbances in the inflammatory process have the potential to result in a number of complications, including delayed wound healing, an increased risk of infection, impaired stress response, failure of multiple organs, and an elevated likelihood of metastatic progression [3]. These responses are influenced by factors such as the severity of tissue damage, the duration of the procedure, intraoperative blood loss, postoperative pain levels, and the choice of anaesthetic technique [4–6]. The level of stress experienced during surgery can significantly affect the patient's recovery and impose additional demands on the healthcare system, potentially resulting in prolonged hospital stays [7].

General anaesthesia may be administered via inhalational anaesthetics, intravenous medications, or a combination of both. It has been demonstrated that all of these forms of anaesthesia modulate the immune system, exerting effects on both innate and adaptive immunity [8–10]. Propofol has been reported to enhance infiltration of natural killer (NK) cells, T cells and T helper (Th) cells into tissues without altering total T cell counts or leukocyte apoptosis, while modulating innate immune function. Sevoflurane has been associated with inducing apoptosis in T and B lymphocytes, altering the Th1/Th2 lymphocyte ratio, reducing blood lymphocyte and NK cell counts, and increasing neutrophil levels [11].

In contrast to many previous studies that have focused on oncologic or major abdominal surgeries the present study is specifically focused on a minimally invasive surgical procedure, lumbar microdiscectomy, which is associated with less tissue trauma and minimal postoperative complications [12]. This methodological approach enabled the assessment of the effects of anaesthetic techniques on inflammatory markers, with reduced interference from surgical trauma or disease-related inflammation. By selecting this procedure, the study aims to provide clearer insights into the differential effects of TIVA and inhalational anaesthesia under controlled surgical conditions. Furthermore, meticulous care was taken in the handling of blood samples to minimise pre-analytical variation and guarantee the reliability of the data obtained.

The objective of this study was to compare the impact of TIVA with propofol and inhalation anaesthesia with sevoflurane on inflammatory markers during the preoperative, intraoperative, and postoperative periods in patients undergoing lumbar microdiscectomy surgery.

Methods

This prospective, randomized, double-blind, single-centre study was approved by the Institutional Ethics Committee (Decision number: 010.99/15, Date: 28/02/2024) and was performed in accordance with the Declaration of Helsinki. It was registered on ClinicalTrials.gov. (ref. no: NCT06386965) on May 22,2024 and adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from the participants.

Between May and July 2020, 40 patients were randomly assigned in a 1:1 allocation ratio to two groups (sevoflurane and TIVA, 20 patients per group) using a computer-generated random number sequence to ensure an unpredictable allocation process. No restrictions, such as blocking or stratification, were applied to the randomization process. To maintain allocation concealment, a series of sequentially numbered, opaque, sealed envelopes was prepared, each containing the assigned intervention based on the randomization sequence. These envelopes were opened only after participant enrollment, ensuring strict adherence to the concealment protocol. The random allocation sequence was generated by an independent researcher not involved in the enrollment or treatment of participants. The principal investigator enrolled participants and assigned groups according to the sealed envelopes. Anesthesia was maintained with sevoflurane in one group and propofol in the other. Both patients and outcome assessors were kept unaware of group assignments to adhere to the double-blind study protocol. All surgeries were performed by the same surgeon.

Inclusion criteria were patients aged 18 to 65 years, classified as ASA I-II, undergoing elective lumbar disc herniation surgery with L4-5 or L5-S1 level disc herniation, extruded disc, or motor deficit. Patients classified as ASA IV or higher, those aged 65 years and older or under 18 years, and those with a history of recurrent disc surgery, spinal stenosis, trauma, infection, endocrine disorders, or immune diseases were excluded from the study.

Intervention and anesthesia protocol

Upon arrival in the operation room, all patients were monitored with a three-lead electrocardiogram, non-invasive blood pressure measurement and finger pulse oximetry. After intravenous (iv) cannulation patients were premedicated with 1 mg iv midazolam. All patients received 1 g of IV cefazolin within 30 min prior to skin incision as part of standard surgical prophylaxis.

In the sevoflurane group anesthesia was induced with 1 µg/kg iv fentanyl, %6–8 sevoflurane with %100 O2 via face mask and 0.5 mg/kg iv rocuronium. In the TIVA

group anesthesia was induced with 1 µg/kg iv fentanyl, 2 mg/kg iv propofol and 0.5 mg/kg iv rocuronium.

After intubation, both groups were ventilated mechanically with oxygen-air mixtures. The lungs were ventilated to maintain end tidal CO2 value between 30–35 mmHg. Anesthesia was maintained by continuous infusion of propofol 6–8 mg/kg/h in the TIVA group and with sevoflurane 0.8–1 MAC in the inhalation group. The administration of remifentanil was conducted via continuous intravenous infusion at a dose of 0.1–0.2 µg/kg/min. The dosage was adjusted according to haemodynamic parameters, and the depth of anaesthesia was monitored using the bispectral index (BIS). The BIS was maintained between 40 and 60. Surgery was performed in prone position.

Patients received 1 mg/kg iv tramadol and 1 g iv paracetamol for postoperative analgesia. 20 mg iv metklopramid were given to the patients for postoperative nausea. Multimodal adjuvant agents including dexmedetomidine, magnesium sulfate, ketamine and nonsteroidal anti-inflammatory drugs (NSAIDs) were intentionally excluded from the study to minimise potential confounding effects on inflammatory marker levels. All the patients were extubated in the operating room and transferred to postanesthesia care unit. Pain levels were routinely assessed by nursing staff in the ward and paracetamol was administered every 6 h. Patients with a VAS score exceeding 4 were administered 100 mg of tramadol as rescue analgesia within the first 24 h.

Measurements

Data recorded included demographic characteristics, duration of surgery, blood transfusion requirements, time to discharge and complications.

Venous blood samples were collected on the ward prior to transfer to the operating room (T1), 30 min after the start of surgery (T2, following extruded disc removal) and at 24 h postoperatively (T3). Blood samples were drawn from the arm that did not receive intravenous fluids or any medications. Samples for IL-6 assays were centrifuged at 2500 rpm for 10 min at the bedside and stored at −20°C until analysis. Blood samples collected for analyses other than IL-6 were sent to the laboratory for immediate processing upon collection. Serum IL-6 and PCT levels were measured using the Roche Cobas e 801 analyzer (Roche Diagnostics, Penzberg, Germany) with electrochemiluminescence immunoassay technology. CRP concentrations were assessed on the Roche Cobas c 701 analyzer using an immunoturbidimetric method. NLR values were calculated from complete blood count parameters obtained via a Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan), which utilizes fluorescent flow cytometry. Laboratory personnel were blinded to the study groups and were not involved in the administration of anaesthesia.

Sample size

A review of previous studies did not provide sufficient data to calculate the sample size accurately. Therefore a pilot study was conducted, which indicated that 24-h IL-6 levels had an average of approximately 30 pg/mL, with a standard deviation (SD) of 25 pg/mL, reflecting a wide range of variability. Based on these pilot results we used Statulator (statulator.com) to calculate the required sample size. Assuming a pooled SD of 25 units, a power of 80% and a two-sided significance level of 5%, it was determined that 19 participants per group (38 in total) would be necessary to detect a true difference of 23 units in mean IL-6 levels between the intervention and control groups. To account for an expected 10% dropout rate, the study was initiated with 20 patients per group, resulting in a total sample size of 40 participants. The pilot dataset was internally generated, unpublished, and used exclusively for the calculation of the sample size for the present study.

Statistical analysis

Descriptive statistics included the mean, standard deviation, median, minimum, maximum and percentage values. The distribution of variables was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For normally distributed independent quantitative variables, the independent samples t-test was applied, while the Mann–Whitney U test was used for non-normally distributed independent quantitative variables. The Wilcoxon signed-rank test was employed for the analysis of dependent quantitative variables. Independent qualitative variables were analyzed using the chi-square test. All statistical analyses were conducted using SPSS software version 27.0 (IBM Corp., Armonk, NY).

Outcomes

The primary outcome of the study was the serum IL-6 level at 24 h postoperatively, which also served as the basis for the sample size calculation in the power analysis. Secondary outcomes included perioperative changes in CRP, NLR and PLR. Surgery duration, blood transfusion needs and time to discharge also recorded. No changes to the trial outcomes were made after the study commenced.

Results

Forty-three patients were assessed for eligibility for lumbar disc herniation surgery. Two patients declined to participate and one did not meet the inclusion criteria. Forty patients were randomized into two groups as shown in

Fig. 1. Two patients refused postoperative blood sampling and a total of 38 patients completed the study (Fig. 1).

Baseline characteristics including age, gender distribution, weight, height, body mass index, ASA score and duration of surgery were comparable between the sevoflurane and TIVA groups, with no statistically significant differences ($p > 0.05$) (Table 1). No patients required blood transfusion and all patients were discharged on the first postoperative day.

There were no statistically significant differences in preoperative or intraoperative IL-6 levels between the sevoflurane and TIVA groups ($p > 0.05$). Postoperative IL-6 levels were significantly lower in the TIVA group compared to the sevoflurane group ($p < 0.05$) (Table 2). In

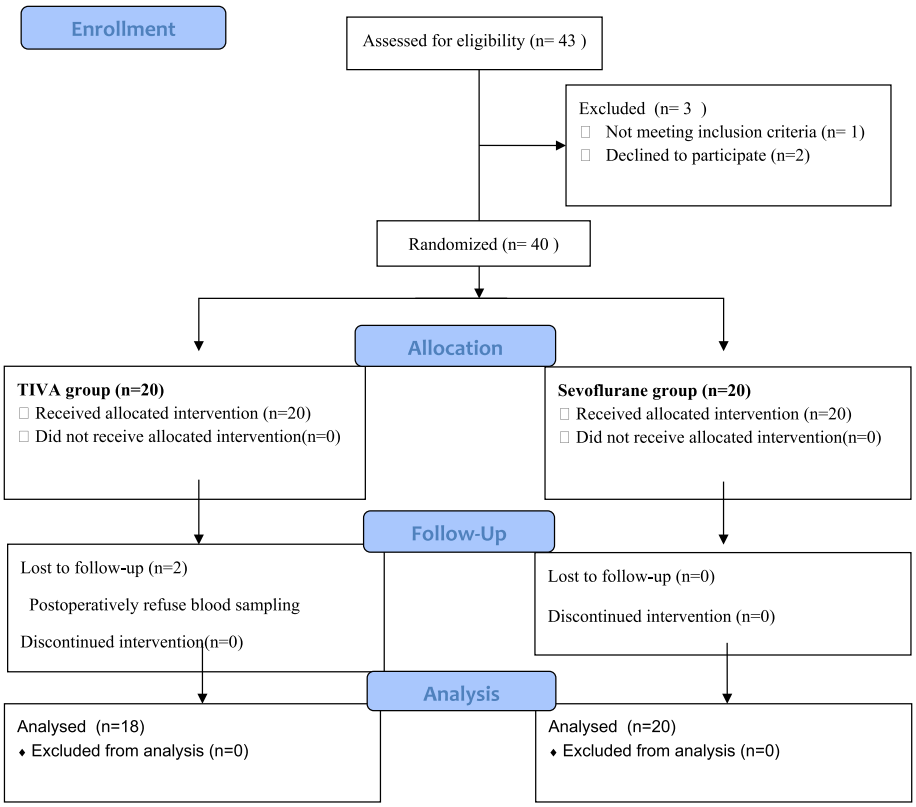

Fig. 1 CONSORT diagram

Table 1 Patient demographics and perioperative characteristics

		Sevoflurane group (n = 20)			TIVA group (n = 18)			p Value
		Mean (± SD)	Median	I.Q-3.Q	Mean (± SD)	Median	I.Q-3.Q	
Age (years)		41,7 ± 10,2	40,0	32,8—50,5	41,8 ± 11,3	43,0	31,0—49,5	0,970 [t]
Gender	Female	12			11			0,944 [X2]
	Male	8			7			
Weight (kg)		68,9 ± 10,5	69,0	59,0—75,0	68,9 ± 11,7	68,0	56,5—80,3	0,991 [t]
Height (cm)		167,0 ± 7,1	166,0	164,3—169,5	167,8 ± 9,6	165,0	163,8—170,5	0,724 m
BMI		24,6 ± 2,8	25,4	22,0—26,7	24,5 ± 3,6	24,2	21,2—26,1	0,882 [t]
ASA	I	9			6			0,463 [X2]
	II	11			12			
Surgery time (min)		135,8 ± 15,6	137,5	125,0—145,0	131,9 ± 14,5	130,0	120,0—136,3	0,160 m

TIVA total intravenous anaesthesia, *BMI* body mass index, *ASA* American society of anesthesiologist

[t] Independent sample t test/[m] Mann–whitney u test/[X2] Chi-square test

Table 2 IL-6 levels in sevoflurane and TIVA groups before the surgery (T1), 30 min after the surgery (T2) and 24 h after the surgery (T3)

	Sevoflurane group(n = 20)			TIVA group (n = 18)			p Value
	Mean (± SD)	Median	I.Q-3.Q	Mean (± SD)	Median	I.Q-3.Q	
IL-6							
T1	3,8 ± 2,0	3,2	1,8—6,3	4,7 ± 2,7	3,4	2,4—6,8	0,219 m
T2	4,3 ± 2,9	3,7	2,2—5,6	4,5 ± 3,4	3,8	1,5—6,0	0,849 m
T3	54,8 ± 45,4	41,3	19,0—84,3	20,1 ± 23,5	12,6	6,4—16,0	0,000 m
T1/T2	0,4 ± 3,8	0,4	−1,9—2,5	−0,2 ± 3,7	−1,3	−1,7—0,1	0,183 m
within group variation p	0,687	w		0,136	w		
T1/T3	51,0 ± 45,2	37,4	15,0—82,5	15,5 ± 24,5	5,5	2,6—10,3	0,000 m
within group variation p	0,000	w		0,000	w		

m Mann–whitney u test/w Wilcoxon test

both groups postoperative IL-6 levels were significantly increased compared to preoperative levels ($p < 0.05$). The increase in IL-6 levels from preoperative to postoperative was significantly higher in the sevoflurane group than in the TIVA group ($p < 0.05$) (Fig. 2).

There were no significant differences in preoperative, intraoperative or postoperative PCT levels between the two groups ($p > 0.05$) (Table 3). Postoperative CRP levels were significantly lower in the TIVA group ($p < 0.05$) (Fig. 3, Table 3).

In the TIVA group the preoperative NLR value was significantly lower than in the sevoflurane group ($p < 0.05$), while intraoperative and postoperative NLR values did not differ significantly between the two groups ($p > 0.05$) (Table 3).

Discussion

This study has attempted to investigate that the effects of two anesthetic techniques—propofol based TIVA and sevoflurane-based inhalation anesthesia—on inflammatory parameters in patients undergoing surgery due to lumbar disc herniation. TIVA showed a reduced inflammatory response with lower post-operative IL-6 and CRP levels compared to sevoflurane.

IL-6 is the principal cytokine responsible for the induction of the systemic changes collectively known as the acute phase response [13]. In a study. on patients with colorectal cancer, no significant difference was found between IL-6 results for the fist 24-h postoperatively in patients under propofol-remifentanil and isoflurane-remifentanil anaesthesia [14]. Another study revealed no statistically significant difference in IL-6 values between patients undergoing propofol-remifentanil and sevoflurane-fentanyl anaesthesia during the initial 24-h postoperative period following colorectal cancer surgery [15]. These findings indicate that both anaesthetic approaches may exert comparable effects on inflammatory responses. Similarly, a study reported that there was no significant difference between TIVA and sevoflurane with regard to early postoperative IL-6 levels in patients undergoing radical cystectomy for bladder cancer [16]. Discrepancies in findings across studies may stem from variations

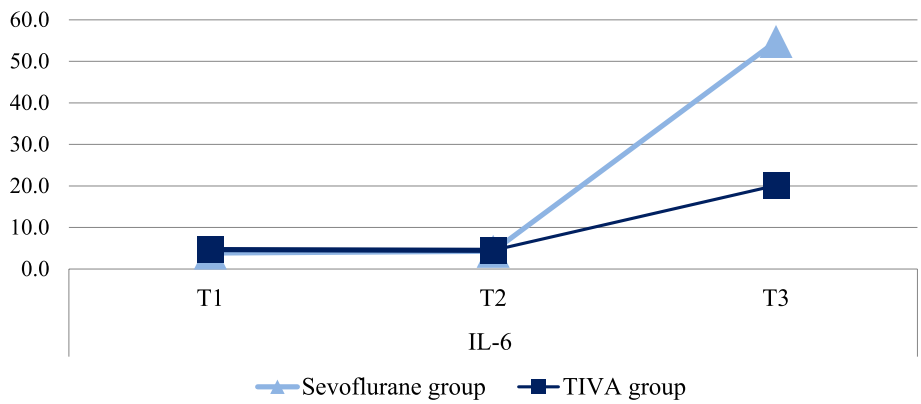

Fig. 2 Comparison of the effect of sevoflurane and TIVA on IL-6 levels before the surgery (T1), 30 min after the surgery (T2) and 24 h after the surgery (T3). (IL-6 = Interleukin 6; TIVA = total intravenous anesthesia)

Table 3 PCT, CRP AND NLR levels in sevoflurane and TIVA groups before the surgery (T1), 30 min after the surgery (T2) and 24 h after the surgery (T3)

	Sevoflurane group (n = 20)			TIVA group (n = 18)			p Value
	Mean (± SD)	Median	I.Q-3.Q	Mean (± SD)	Median	I.Q-3.Q	
PCT							
T1	0,03 ± 0,01	0,02	0,0—0,0	0,03 ± 0,02	0,02	0,0—0,0	0,769 [m]
T2	0,03 ± 0,01	0,03	0,0—0,0	0,03 ± 0,02	0,02	0,0—0,0	0,537 [m]
T3	0,05 ± 0,02	0,04	0,0—0,1	0,05 ± 0,03	0,04	0,0—0,1	0,314 [m]
CRP							
T1	2,45 ± 3,45	1,23	0,5—2,5	4,94 ± 9,29	1,68	1,1—4,6	0,140 [m]
T2	2,93 ± 3,85	1,80	0,6—4,1	6,04 ± 9,79	1,32	0,7—9,4	0,682 [m]
T3	25,3 ± 20,6	21,1	10,5—31,7	15,3 ± 18,6	8,5	3,8—19,1	0,016 [m]
NLR							
T1	2,88 ± 2,46	3,35	0,0—4,6	0,00 ± 0,00	0,00	0,0—0,0	0,000 [m]
T2	2,50 ± 0,99	2,65	1,6—3,2	3,64 ± 5,00	2,33	1,4—4,0	0,953 [m]
T3	5,77 ± 3,80	4,51	3,2—7,9	7,33 ± 5,88	5,44	2,6—11,8	0,650 [m]

PCT Procalcitonin, *CRP* C-reactive protein, *NLR* neutrophyl-lympocte ratio

m Mann–whitney u test

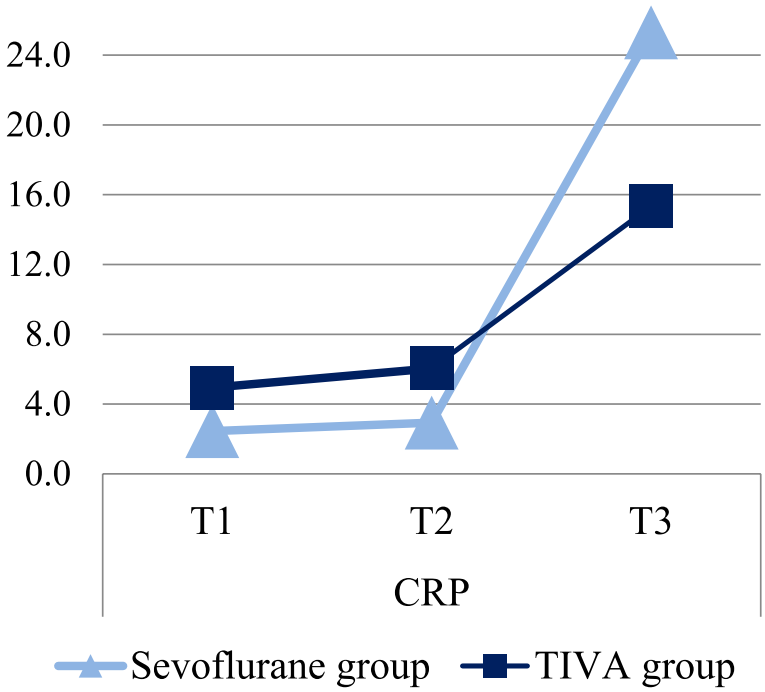

Fig. 3 Comparison of the effect of sevoflurane and TIVA on CRP levels before the surgery (T1), 30 min after the surgery (T2) and 24 h after the surgery (T3). (CRP = C reactive protein; TIVA = total intravenous anesthesia)

in surgical procedures, patient populations, and timing of biomarker measurements. For instance, oncological surgeries may elicit a more robust inflammatory response compared to minimally invasive procedures, potentially explaining divergent outcomes in IL-6 levels. Additionally, Mazoti et al. discovered that IL-6 levels exhibited a notable elevation during the postoperative period in both the isoflurane and propofol groups, with no statistically significant distinction between the two groups in relation to otorhinological surgery [17]. Moreover, O'Bryan and colleagues observed no significant differences in IL-6 levels between patients receiving propofol or sevoflurane

during the perioperative period in a meta-analysis [18]. The analysis indicated that the choice of anaesthetic agent may not be a significant factor in the perioperative levels of inflammatory markers [18]. However, this finding may be related to the heterogeneity of the patient groups in O'Bryan's meta-analysis.

The literature also contains conflicting results. Some studies reported significantly elevated IL-6 levels and a more pronounced increase in patients who received inhalational anaesthesia compared to those who received intravenous anaesthesia particularly in minor surgical procedures [19, 20]. In our study there were no significant differences in preoperative and intraoperative IL-6 levels between the groups. However, postoperative IL-6 levels were significantly lower in the TIVA group. Furthermore, the increase in IL-6 from preoperative to postoperative levels was significantly less pronounced in the TIVA group in comparison to the sevoflurane group. These findings indicate that propofol's immunomodulatory effects may be the underlying mechanism responsible for the reduced inflammatory response observed in the TIVA group. It has been demonstrated that propofol exerts an inhibitory effect on nuclear factor kappa B (NF-κB), a pivotal mediator of the inflammatory cascade [21]. This mechanism may provide an explanation for the reduced IL-6 levels observed in the present study. This lends support to the notion that inhalational anaesthesia may give rise to a more pronounced inflammatory response than intravenous anaesthesia.

PCT levels essentially remain stable unless there is a significant infectious trigger [22]. Conversely, CRP is a more generalised marker of systemic inflammation that may be more sensitive to anaesthetic types. In a study by Kadantseva et al., who indicated that CRP levels were higher postoperatively in the inhalation anesthesia group than in the TIVA group, particularly in patients with resected breast cancer [23]. These findings lend support to the hypothesis that TIVA may have beneficial effects with regard to the attenuation of perioperative inflammatory stress. But a meta-analysis reported no significant differences in CRP levels between propofol and sevoflurane, indicates that such benefits may not be universal and could depend on specific clinical or procedural contexts [18]. No statistically significant difference was observed in the levels of PCT between the propofol and sevoflurane groups during the preoperative, intraoperative or postoperative period in our study. Nevertheless, the postoperative CRP level was significantly lower in the TIVA group. This may indicate a potential beneficial role for TIVA with propofol in reducing the systemic inflammatory response following surgery.

NLR is a straightforward marker in peripheral blood, employed to evaluate the inflammatory response and physiological stress during the perioperative period, also is a reliable marker of systemic inflammation [24, 25]. Variations in the anesthetic technique can impact NLR levels, potentially affecting the inflammatory response and influencing surgical outcomes. In patients with gastric cancer who underwent minimally invasive gastrectomy, the postoperative NLR was lower in the propofol group [26, 27]. Studies evaluating the difference between propofol and sevoflurane in patients with breast cancer and gastric cancer found no difference between intraoperative and postoperative NLR values [23, 28] In this study preoperative NLR value was found to be significantly lower in the propofol group compared to the sevoflurane group indicating a potentially more favourable inflammatory profile in patients receiving TIVA. However, there were no significant differences in intraoperative and postoperative NLR values between the groups ($p > 0.05$), indicating that this advantage did not persist throughout the perioperative period. This finding highlights the necessity of interpreting NLR results within the broader context of additional inflammatory markers and their temporal patterns.

With regard to the clinical outcomes, no significant postoperative complications were observed in either group. Furthermore, the time to hospital discharge did not differ significantly between patients receiving TIVA and those receiving sevoflurane-based anaesthesia. While these parameters were not designated as primary endpoints, they were recorded as part of routine perioperative follow-up and offer additional context for the clinical interpretation of our findings. It is suggested that future studies with larger sample sizes may be better suited to detect more subtle differences in postoperative recovery profiles between anesthetic techniques.

Although this study offers compelling evidence for the perioperative advantages of TIVA, it is important to acknowledge certain limitations. Further research is required in the form of larger, multicentre studies in order to validate these results. Furthermore, the study did not assess long-term outcomes, such as postoperative recovery and chronic pain. In addition, this study does not include the length of stay, cost analysis or an assessment of the ecological footprint. A further key limitation is the baseline discrepancy in preoperative NLR values between the groups, despite randomisation. This imbalance is likely attributable to chance variation associated with the limited sample size and should be considered when interpreting perioperative inflammatory responses. In order to enhance the generalisability and robustness of these findings, it is recommended that future studies involve larger, multicentre trials with comprehensive outcome assessments.

Conclusions

Most of the studies on this topic have been conducted in cancer patients, and our study is one of the few that has been conducted in both healthy patients and patients undergoing minimally invasive surgery. Nevertheless, further research is necessary to corroborate these findings in a broader range of surgical populations and with longer-term follow-ups.

TIVA exhibited a diminished inflammatory response, as evidenced by reduced postoperative IL-6 levels and a more modest elevation in IL-6 levels relative to sevoflurane. These findings indicate that TIVA may be a promising anaesthetic option for reducing perioperative inflammation. Based on the results of this study we believe it is important to increase the use of TIVA in patients who need to reduce their inflammatory burden.

Abbreviations

TIVA	Total intravenous anaesthesia
ASA	American Society of Anesthesiologists
IL-6	Interleukin-6
CRP	C-reactive protein
PCT	Procalcitonin
NLR	Neutrophil-to-lymphocyte ratio
NK	Natural killer
Th	T helper
Iv	Intravenous
BIS	Bispectral index
SD	Standard deviation
NF-κB	Nuclear factor kappa B

Supplementary Information

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Supplementary Material 1

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Disclosures

All authors declare that they have no conflicts or interest.

Authors' contributions

M.B.Y, H.Y.A, I.D contributed to the consept of the study. M.B.Y, H.Y.A, E.A contributed to study design. M.B.Y, I.D, H.Y.A, K.T, M.A.D.C contributed to data collection. M.B.Y, K.T and H.Y.A contributed data analyses. M.B.Y, H.Y.A, I.D contributed to preparation of the final draft. M.B.Y, Y.Y, B.Ç, E.A contributed to critical revision of the article. All authors participated in the revision of the manuscript, and revised the manuscript critically for important intellectual content. All of the authors have read and approved the final version of this manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The database management in accordance with privacy legislation and the presented study in accordance with the ethical principle of the Declaration of Helsinki. Ethical approval for this study was obtained by the Research Ethics Committee (Decision number: 010.99/15, Date: 28/02/2024). Written and verbal informed consent was obtained from all study participants. Trial is registered on ClinicalTrials.gov (ref. no: NCT06386965). The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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