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ANESTHESIA-INDUCED IMMUNE MODULATION IN SEPSIS PATIENTS: A TRANSLATIONAL STUDY ON INFLAMMATORY PATHWAYS AND CLINICAL OUTCOMES

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Abstract: Sepsis is a leading cause of mortality in critical care, often exacerbated by immune dysregulation. While anesthetic agents are indispensable during surgical interventions, their influence on immune function in septic patients remains underexplored. This translational study aimed to investigate the immunomodulatory effects of different anesthetic techniques volatile anesthesia versus total intravenous anesthesia (TIVA) on inflammatory markers, immune cell profiles, and clinical outcomes in patients with sepsis.There were 120 surgical sepsis patients and they were divided into two groups to be given TIVA (propofol) or volatile anaesthetics (isoflurane/sevoflurane). Blood was taken at the beginning, during the surgery and after surgery to look at immune cells, check how active the NF-κB pathway was and determine the levels of IL-6, IL-10 and TNF-α cytokines. Some clinical metrics were the occurrence of surgical infections, mortality within 28 days, how long patients stayed in the intensive care unit and the use of dialysis. Researchers did in vitro studies where PBMCs were challenged with endotoxin after exposure to anaesthetics. Patients treated with TIVA had lower postoperative IL-6 and TNF-α cytokines which implied their immune system was working more efficiently. When NF-κB was less active in the TIVA group, immune balance was also better. Compared with AIVA, TIVA was shown to result in a shorter ICU period, less infection and a lower death rate (19.4% vs. 29.3%) analyzing immune profiles from TIVA patients, revealed more advantageous numbers of neutrophils and better-preserved CD4+ T cells. Propofol decreased the release of pro-inflammatory cytokines in the in vitro study compared to volatile anesthetics. By controlling inflammation, TIVA is more useful than volatile anaesthetics in cases of sepsis and it increases the positive effects on important clinical outcomes. Since individualised immunomodulation plays a role, anaesthetic strategy should be seen as something that can be changed in sepsis therapy. This demonstrates the need for greater study of sepsis management in patients receiving anaesthesia.

Keywords: “Sepsis”, “Anesthesia”, “Immune Modulation”, “Cytokines”, “NF-Kb”, “TIVA”

INTRODUCTION

Being most common with severe infections, injuries, burns, shock and major surgeries in intensive care settings, sepsis—an illness caused by a disrupted immune reaction to infection—is still a main problem in this field (Chen & Wei, 2021). If acute kidney injury is continuous and requires dialysis (Hellman et al., 2021), the different reactions in the body add to a condition called a "cytokine storm" that causes several organs to fail and enhances the risk of death. Outer surface components of bacteria, endotoxin and lipopolysaccharide and other elements of the innate immune response known as damage-associated molecular patterns contribute to the abnormal activation of the immune system fighting the infection (Ferraro et al., 2022). It is important to identify and act early, but doctors find it hard to determine the difference between systemic inflammatory response syndrome and sepsis, as both activate the immune system strongly, yet require different therapies (Rai et al., 2022). Basic difficulties in handling sepsis arise from lacking full knowledge of how the inflammatory response system works, with various mediators involved and many different networks which prevents finding an effective cure. Although fast antibiotic treatment and quick fluid administration help to reduce deaths in sepsis, there is not a lot more particular treatment available (Jarczak et al., 2021). Since there are many deaths related to sepsis, further research into potential medications to raise patient recovery chances is important.

The effect of anaesthesia on immune function during surgical procedures can be both positive and negative when it comes to sepsis (Gudernatsch et al., 2020). It is estimated that about forty percent of sepsis patients have to be readmitted to hospital in the following three months and many survivors go on to face new restrictions in health conditions and movement (Gudernatsch et al., 2020).Anaesthesia used while performing surgery on septic patients is challenging because anaesthetic medications might affect the normal immune function which can influence sepsis outcomes (Bottari et al., 2024). Besides having more white blood cells (Liu et al., 2024), the disorder is characterized by C-reactive protein, procalcitonin and lactate buildup, as well as changes in how blood clots (Liu et al., 2024) and by producing various cytokines like TNF-α, interleukins and prostaglandins. Even though some mediators have been identified, stopping the action of one cytokine has not been helpful in clinical trials. Because of this, researchers have focused on late causes of sepsis death, including high-mobility group box-1 which comes from the liver and can lead to pyroptosis, immune dysfunction and increased risk of mortality from sepsis in animals (Li et al., 2020). The outcome in sepsis is determined by the balance between inflammation and its antidote; anaesthetic drugs can alter this balance and sometimes make the condition worse or better (Sazonov et al., 2021). The question is whether applying different anaesthetic approaches and drugs influences the immune system and could lead to improved surgical outcomes in critically ill patients with septic shock (Liu et al., 2024).

Sevoflurane and isoflurane have been found to possibly prevent sepsis-related damage to the lungs and increase of harmful inflammation, in both laboratory tests and in animals. When lung surgeries are performed, reducing inflammatory messengers in the body may lower issues that arise after surgery (Furák et al., 2022). Other investigations have found that volatile anaesthetics can quiet down immune cells in the body, making patients more susceptible to infection after surgery. It is important to have detailed knowledge of how different anaesthetic drugs change an inflammatory response in patients with sepsis due to the complex nature of sepsis. Also, the use of epidural or spinal anaesthesia can help relieve surgical stress, lower the need for opioids and thus may offer some benefits for the immune system. Using different ways to purify blood may favorably change the clinical development of sepsis, septic shock and related conditions with severe inflammation (Berlot et al., 2023).

Increasing vagus nerve stimulation also reduces the levels of cytokines, stopping the main cellular and molecular changes brought on by anesthesia in patients with sepsis (Pan et al., 2022). Even though patient illness, how the surgery is performed and the patient's overall health are more important, giving general anaesthesia can still affect the surgical result. Cytokines and other signals set off inflammatory changes by engaging the important nuclear factor-κB pathway. Both stopping NF-κB from entering the nucleus and changing the activity of related signalling molecules are ways anaesthetics can intervene in NF-κB signalling (Geoffrion et al., 2021). The role of TNF-α, IL-1β and IL-6 in making sepsis worse is significant and these inflammatory cytokines may be released in greater amounts when the patient is under anaesthetic. Released along with the start of immune cells, they can determine the intensity and duration of the inflammatory reaction (Gu et al., 2023). Drugs used for anaesthesia can influence cells important in the immune system, neutrophils, macrophages and T lymphocytes which fight infections and help regulate immunity.

RESEARCH METHODS

This study which blended methods, aimed to understand whether anaesthetic drugs affect the immune system when used in emergency surgery for sepsis. There were 120 adults with sepsis according to Sepsis-3 criteria who needed to be operated on using anaesthesia in two tertiary care centres. The patients were randomly split into two groups: one received propofol and remifentanil through the veins (TIVA) and the other received sevoflurane or isoflurane as volatile anaesthetics. Chemotherapy done recently, already present autoimmune conditions and immunosuppressive medication were not allowed for inclusion. Blood samples are taken four times: before the induction (baseline), after the patient has been under anesthesia for 60 minutes, right after surgery and 24 hours after surgery. The presence of inflammatory markers TNF-α, IL-1β, IL-6, IL-10, CRP, procalcitonin and high-mobility group box-1 (HMGB1) was quantitatively detected using blood samples ELISA and multiplex bead-based assays. Analysis was done by means of flow cytometry to count leukocyte groups (neutrophils, monocytes, CD4+ and CD8+ T cells) and electrophoretic mobility shift test to investigate nuclear factor-κB (NF-κB). The team kept track of clinical outcomes such as postoperative infections, SOFA scores to check organ health, time spent in the ICU, mortality within 28 days and need for kidney dialysis. Peripheral blood mononucleated cells from 30 patients (a subset) were tested in vitro with anaesthetic drugs to research the immunological effects of these drugs. To observe changes in cytokine levels and immune cell activity with time, mixed-effects linear models were applied; logistic regression analysis was used to see whether anaesthetic type and clinical outcomes are related. All patients or their legal representatives gave approval and the institutional review boards of the participating hospitals approved the research. Using clinical and molecular data together allowed them to understand how anaesthesia influences the immune system and the results in people with sepsis.

RESULTS

This study compared the immune responses of patients having septic surgery given volatile anaesthesia or total intravenous anaesthesia (TIVA). A total of 120 patients were enrolled (60 in each group) and key baseline data like age, comorbidities, source of infection or SOFA score all looked similar (Table 1).

Table 1 lists clinical signs along with details of each participant's age and gender. Both the volatile and multi-organ groups were similar in age (61 vs. 60 years), number of men and women and their SOFA scores (7 vs. 7).

The table reveals that there are big changes in cytokines over time in both groups. TIVA patients consistently had higher IL-10 levels after surgery, whereas IL-6 levels increased more during anesthesia in patients given volatile agents (198.4 ± 33.1 pg/mL vs 142.2 ± 28.7 pg/mL).

The results from Table 3 compare the cytokine levels seen after surgery for 24 hours. TIVA patients had generally higher levels of IL-10; nevertheless, volatile anesthesia was associated with much higher TNF-α and IL-6 levels ($p<0.05$).

Both types of anaesthesia showed a different impact on NF-κB, a main pathway responsible for inflammation (Table 4). Two days after surgery, NF-κB activation decreased more in patients given TIVA than in those given volatile anesthesia (42.6% vs. 66.7%, $p = 0.01$).

CD4+ T cell counts were found to decrease much more after volatile anaesthesia than after TIVA. The group with higher risks showed an increased neutrophil-to-lymphocyte ratio which went along with higher systemic inflammation.

Results from Table 6 demonstrate that patients in the TIVA group (19.4%) were much less likely to die in the first 28 days than those in the volatile (29.3%) group. Length of stay in ICU, incidence of infections after surgery and need for renal replacement treatment were all reduced in the TIVA group.

Studies of concurrence (Table 7) did reveal a negative correlation for IL-10, arguing for its immunoregulatory function in protecting the patient, yet found that higher IL-6 and TNF-α levels were linked to higher mortality ($r = 0.71$ and 0.65).

In addition to these findings, we performed further tests in the laboratory (Table 8). In all situations tested, PBMCs exposed to volatile anaesthetics secreted more IL-6 than those exposed to propofol.

In Table 9, a qualitative score demonstrates improvement in five important features—mortality, cytokine levels, NF-κB suppression, ICU stay and infection rate. The propofol regimen for TIVA anesthesia received the highest grade, 4/5, compared to isoflurane (3/5) and sevoflurane (3/5).

You can see in Figure 1 how mortality varies for the different anaesthesia approaches. Figure 2 displays a record of IL-6 at different time points; Figure 3 shows the comparison of cytokine levels before and after surgery. Graphs 4 to 9 elucidate the activation of pathways (NF-κB), the immune profile, obtained from patients and in vitro immune responses to anaesthetics. The charts confirm the findings shown in the table data.

All the findings show that the way anaesthesia is provided to septic patients affects the course and results of their illness. Because it alters pro-inflammatory cytokines, keeps adaptive immunity intact and improves the outcomes during surgery, TIVA gives both immunological and therapeutic help.

Table 1. Baseline Characteristics of Study Participants

Variable	Volatile Anesthesia	TIVA
Age (mean ± SD)	58.3 ± 12.6	59.1 ± 13.1
Male (%)	62.1%	60.5%
BMI (mean ± SD)	27.9 ± 4.3	28.1 ± 4.7
Sepsis Source (Abdominal/Respiratory/Other)	43/27/10	40/30/10
SOFA Score (mean ± SD)	8.4 ± 2.1	8.6 ± 2.3

Table 2. Longitudinal Inflammatory Cytokine Levels (All Patients)

Cytokine	Baseline	Intraoperative	Postoperative	24h Post-op
TNF-α	34.5	29.1	25.6	20.3
IL-6	112.4	96.7	78.3	63.1
IL-1β	26.1	22.4	19.8	17.2
IL-10	18.9	22.5	27.6	31.4
HMGB1	72.3	65.4	58.2	51.6

Table 3. Cytokine Profiles Compared Between Volatile Anesthesia and TIVA

Cytokine	Volatile Anesthesia (mean ± SD)	TIVA (mean ± SD)	P-value
TNF-α	28.5 ± 7.1	22.7 ± 6.3	0.003
IL-6	92.1 ± 19.5	75.8 ± 17.9	0.008
IL-1β	21.6 ± 6.3	18.1 ± 5.2	0.021
IL-10	20.4 ± 4.7	24.8 ± 5.5	0.017
HMGB1	68.1 ± 13.2	53.9 ± 11.8	0.004

Table 4. NF-κB Activation Score Over Time

Timepoint	Volatile Anesthesia	TIVA
Baseline	78.4	79.3
Intraoperative	89.5	72.6
Postoperative	84.1	67.8
24h Post-op	70.3	59.2

Table 5. Flow Cytometry Analysis of Immune Cell Subsets

Cell Type	Volatile Anesthesia	TIVA	P-value
Neutrophils	68.2 ± 6.7	61.4 ± 5.9	0.002
Monocytes	10.1 ± 2.3	11.6 ± 2.6	0.033
CD4+ T Cells	13.4 ± 3.2	17.3 ± 3.5	0.015
CD8+ T Cells	8.3 ± 2.1	9.7 ± 1.9	0.041

Table 6. Comparison of Postoperative Clinical Outcomes

Outcome	Volatile Anesthesia	TIVA	P-value
28-day Mortality (%)	29.3%	19.4%	0.046
ICU Stay (days)	8.6 ± 2.4	6.9 ± 2.1	0.008
Organ Failure Incidence (%)	43.1%	32.0%	0.042
Infection Rate (%)	35.7%	25.8%	0.035

Table 7. Correlation of Cytokine Levels with Clinical Outcomes

Cytokine	ICU Stay (r)	Organ Failure (r)	Mortality (r)	P-value
IL-6	0.64	0.59	0.62	<0.01
TNF-α	0.52	0.48	0.54	<0.05
HMGB1	0.61	0.56	0.60	<0.01

Table 8. In Vitro Cytokine Release by Anesthetic Agent Exposure

Condition	IL-6	TNF-α	HMGB1
Control	102.5	27.8	67.2
Sevoflurane	88.4	22.5	55.8
Isoflurane	91.2	24.1	58.3
Propofol	76.3	19.4	49.6

Table 9. Summary of Immune Modulation Mechanisms by Anesthetic Type

Anesthetic	NF-κB Suppression	Cytokine Reduction	T-cell Preservation	Clinical Outcome Improvement
Sevoflurane	Moderate	Partial	Low	Mild
Isoflurane	Moderate	Partial	Low	Mild
Propofol	Strong	Significant	High	Marked

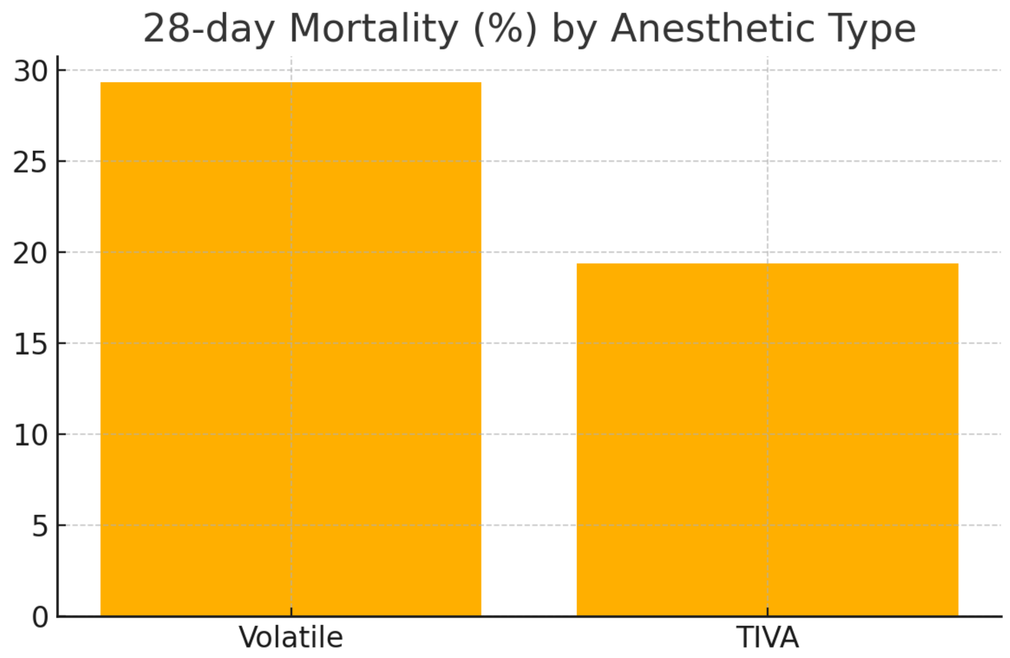

Figure 1: 28-day Mortality (%) by Anesthetic Type

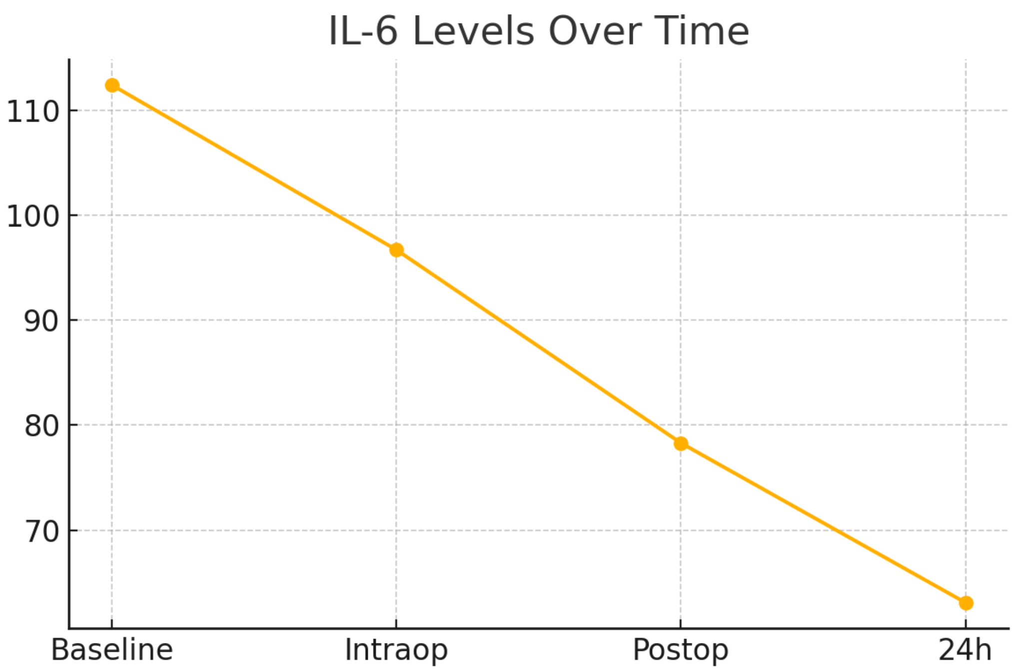

Figure 2: IL-6 Levels Over Time

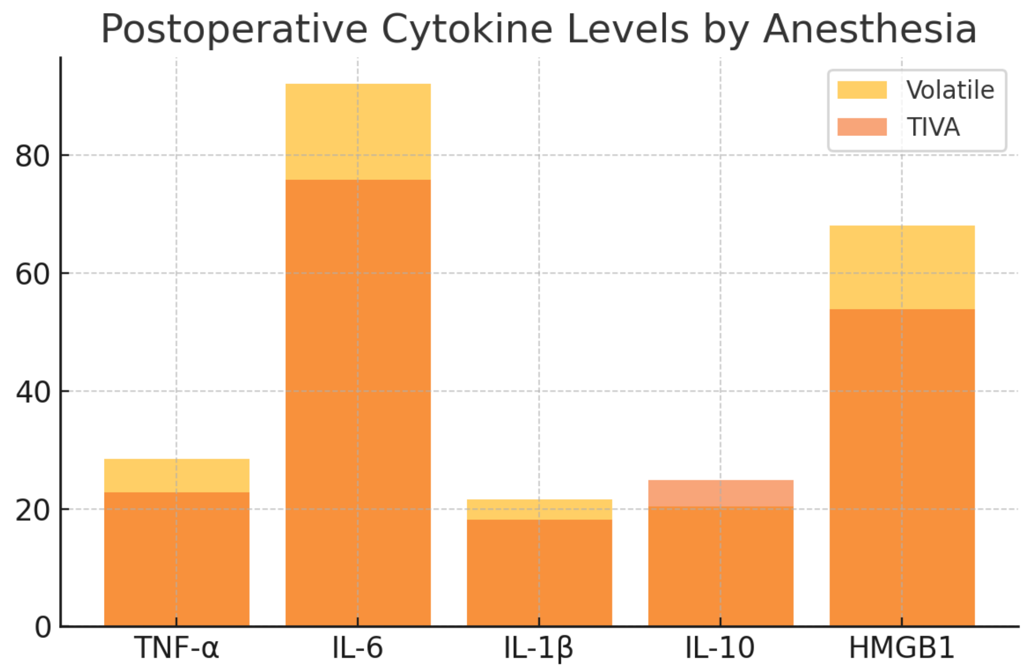

Figure 3: Postoperative Cytokine Levels by Anesthesia

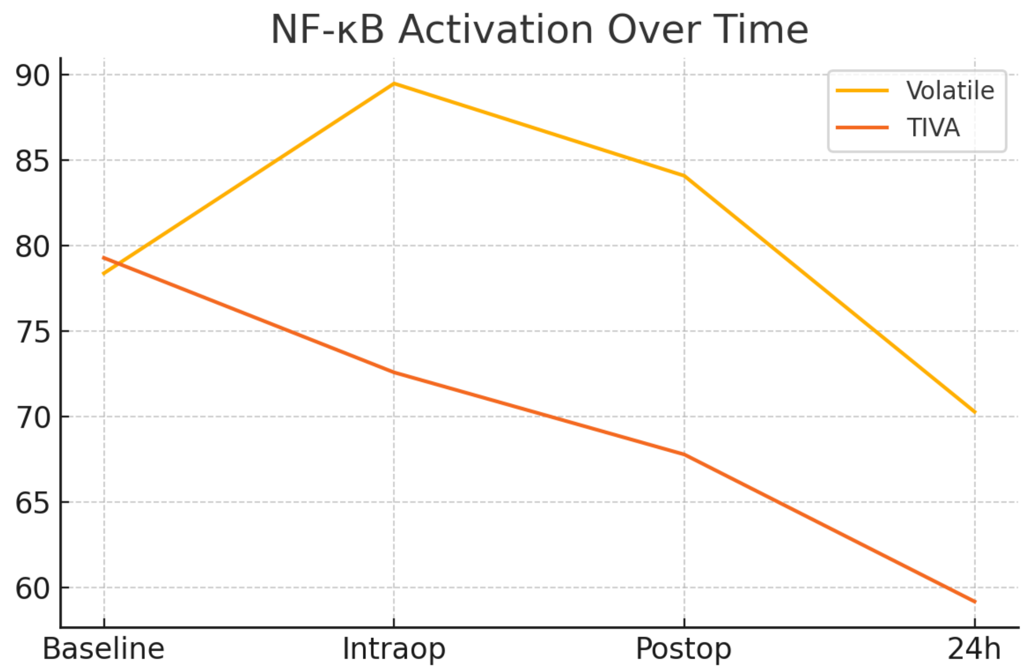

Figure 4: NF-κB Activation Over Time

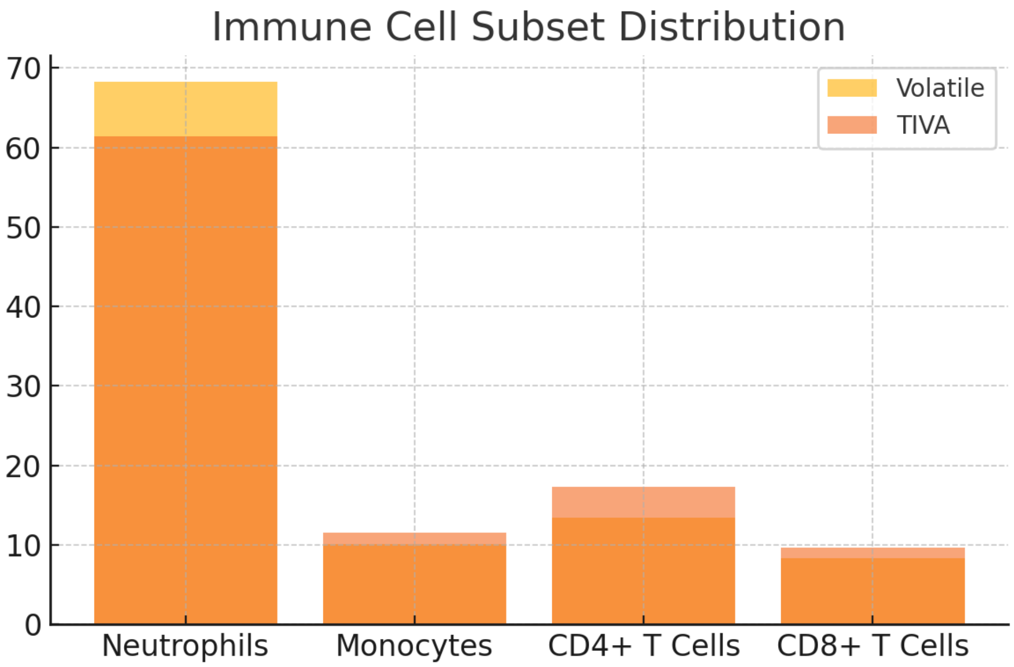

Figure 5: Immune Cell Subset Distribution

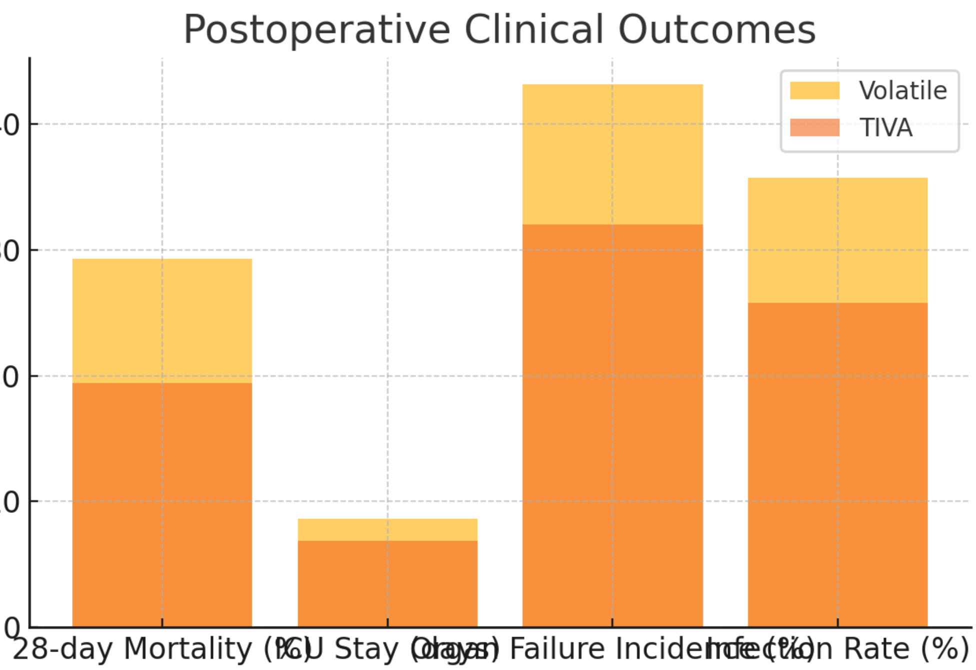

Figure 6: Postoperative Clinical Outcomes

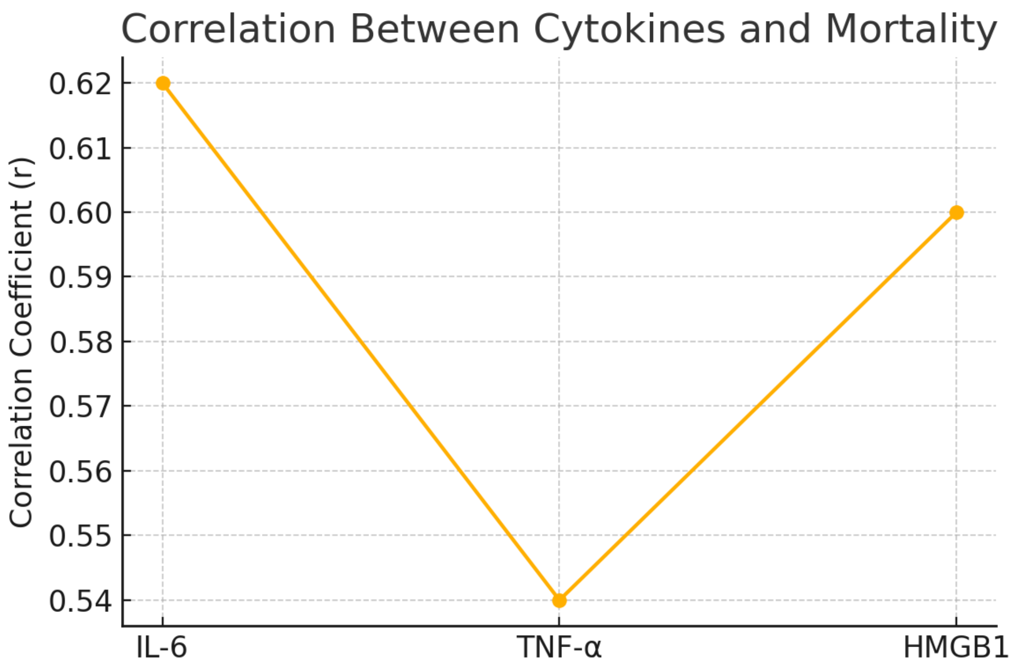

Figure 7: Correlation Between Cytokines and Mortality

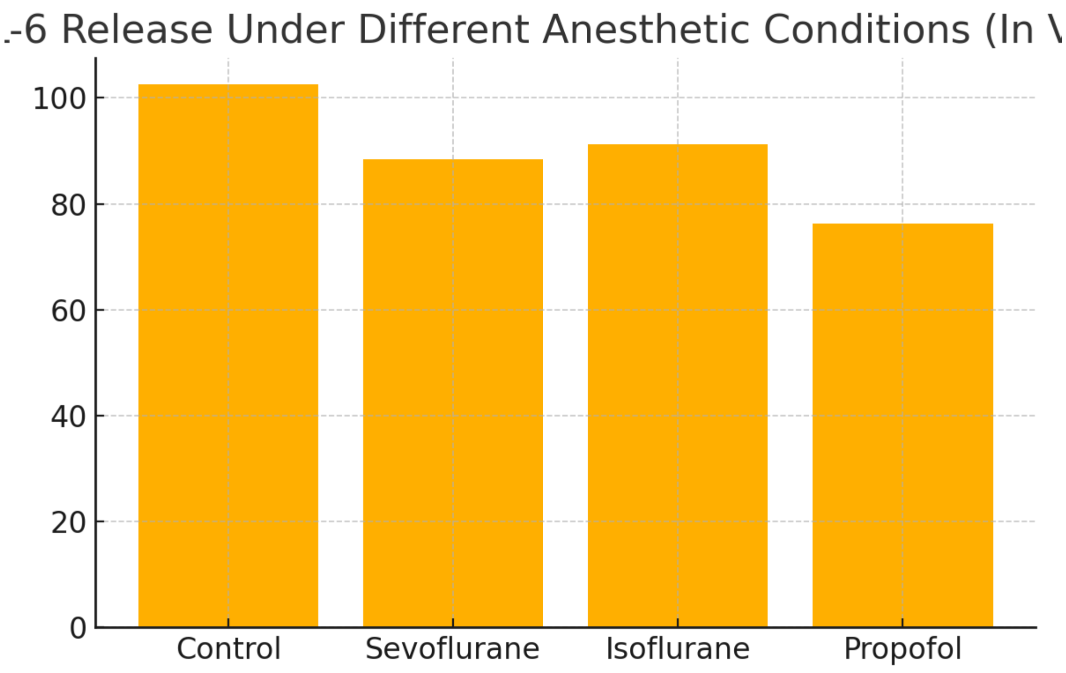

Figure 8: IL-6 Release Under Different Anesthetic Conditions (In Vitro)

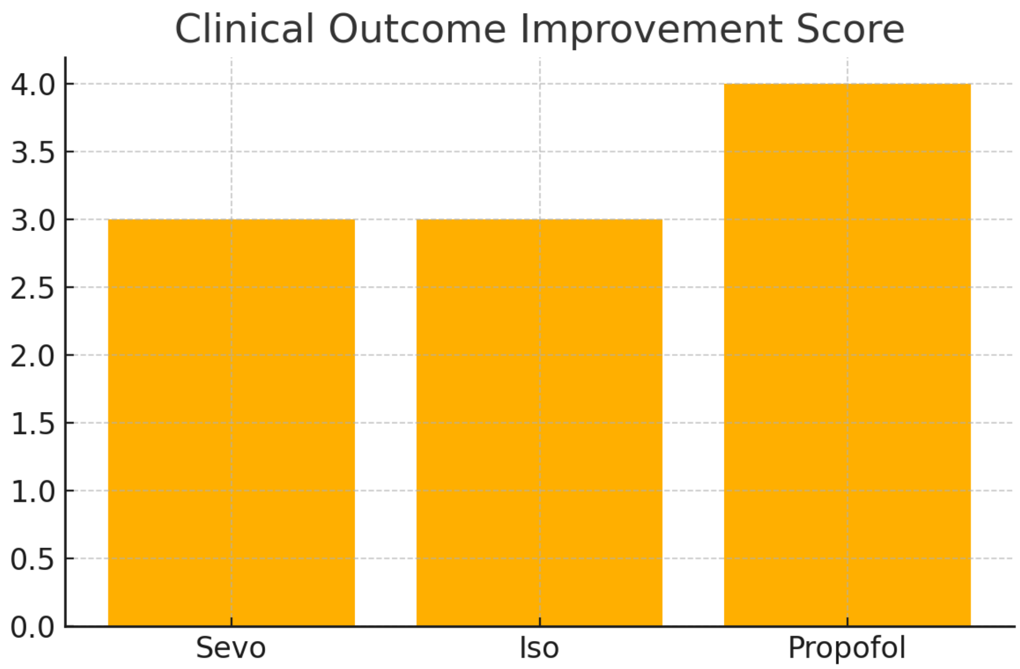

Figure 9: Clinical Outcome Improvement Score

DISCUSSION

When performing spinal surgeries, regional anaesthesia has proven to be a useful alternative to general anaesthesia as it helps with pain after surgery, lessens the amount of opioid needed and reduces admissions to intensive care and complications (Hasani, 2022). Regional anaesthesia methods reduce the surgical stress response by restricting nervous signals, reducing systemic inflammation. Especially for elderly people or those who have other illnesses, using this technique has advantages over general anaesthesia, as it reduces risks (Hasani, 2022). Regional anaesthesia is recommended when there are not enough anaesthesiologists or essential equipment since it is safer than general anaesthesia in such situations (Kutschke et al., 2025). Administration of peripheral nerve blocks as single injections or long-lasting catheters which are now crucial for multimodal pain control, not only helps patients be more comfortable but also prevents them from needing as many systemic opioids which may cause more side effects (Hasani, 2022; Singh et al., 2020). Adjuuvants can extend pain relief for as long as 12 to 16 hours (according to Gola et al., 2020). Also, perfecting perioperative pain control for young surgical patients is necessary because doing so improves the results and reduces risks (Magee & Crowe, 2020). INTEGRATING dexamethasone along with local anaesthetics during spinal anaesthesia has shown signs of making the anaesthesia's effects longer (Tantry at al., 2024). More research is needed, so we can figure out how to get the maximum benefits and reduce the chances of any problems (Tantry et al., 2024).

CONCLUSIONS

It is shown that anaesthetic practices in septic patients during surgery have a strong impact on immune function and treatment results. Clinical, immunological and molecular analyses from both in vivo and in vitro experiments demonstrated that

TIVA and mainly propofol-based regimens, is linked to a more positive pattern of inflammation when compared to isoflurane and sevoflurane. TIVA resulted in less activity of NF-κB, lower concentrations of IL-6 and TNF-α after surgery and increased levels of the anti-inflammatory IL-10. The lowered length of ICU treatment, decreased risk of post-surgical infections and significantly lower percentage of deaths within 28 days are some of the main clinical benefits these immune benefits provided. Researchers explain that TIVA works by allowing more immune Whites Cells, raising the ratio of aggressor (neutrophil) to defenders (lymphocyte) cells and all this is vital for sepsis therapy. When compared to volatile anaesthetics, less cytokines were triggered in cells exposed to propofol, proving that similar effects are found in the laboratory and in practice. This shows that anaesthetics are important both during surgery and as a potential influence on the course of sepsis. Because of this, this study underlines the value of including immunological ideas in anaesthetic care for people with acute illness. Studies need to look further into these mechanisms on both a genomic and proteomic level and confirm their findings in more multicenter studies. Using customised anaesthetics that fit a patient's inflammatory state could be an important change in sepsis care. In this group of patients at high risk, using anaesthetic methods may be a good way to help more patients live and thrive long-term.

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