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Review

Medicine

Influence of anaesthetic drugs on immune response: from inflammation to immunosuppression

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Abstract

Introduction

The immune system protects us from infections through coordinate action of its components. Patients and animals undergoing anaesthesia and surgery show alterations in the immune response. In this paper, we review the effects of some of the most common anaesthetic drugs on the immune system, in particular the effects within 24 hours after their administration, describing their effects on cells and cytokines of the innate and acquired immune system.

Discussion

As it is difficult to isolate the effects of anaesthetic drugs in the case of surgery, diverse *in vitro* studies with human immune cells or *in vivo* with animal models have been used to study the effect of anaesthetic drugs on the immune system. These studies have demonstrated diverse effects, such as changes in immune cell counts and functionality, and on the secretion patterns of diverse cytokines affecting the inflammatory response in the postoperative period.

Conclusion

Effects of anaesthetic drugs on the immune system are clinically important because the amount and function of the immune cells, as well as the balance between pro- and anti-inflammatory cytokines secretion, are related to postoperative infections and tissue injury.

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Introduction

The immune system is vital for survival because our environment has plenty of potentially deadly microbes and immune system protects us from infectious pathogens. The immune system recognises and eliminates pathogens with the induction of innate and then adaptive immune responses. Innate immunity, also called natural or native immunity, is the firstline of defence and refers to protective mechanisms that are present even before infection. Principal components of innate immunity are epithelial membranes that block the entry of microbes, phagocytic cells (neutrophils and macrophages), dendritic cells, natural killer (NK) cells, and several plasma proteins, including the complement system. Most important cellular reactions of innate immunity are inflammation–the process in which phagocytic cells are recruited and activated to eliminate microbes–and virus elimination, mediated by dendritic and NK cells. Adaptive immunity, also called acquired or specific immunity, consists of mechanisms that are induced by microbes and are capable of specifically recognising microbial and nonmicrobial molecules called antigens. The adaptive immune system consists of lymphocytes and their products, including antibodies and cytokines. The receptors of lymphocytes are much more diverse than those of the innate immune system, and they are capable of recognising a vast array of foreign substances. There are two types of adaptive immunity: humoral immunity, which is mediated by B lymphocytes and their secreted antibodies, which protect against extracellular microbes and their toxins, and cell-mediated or cellular immunity, which is mediated by T lymphocytes which mainly protect against intracellular microbes. Both types of acquired immunity are linked by a broad family of proteins called cytokines, which play an important role in immune cell activation, regulation and communication.

Patients or experimental animals submitted to anaesthesia and surgical procedures suffer diverse immunological alterations, which are difficult to determine if they are induced by anaesthetic drugs or by surgical procedure stress. Anaesthetics comprise a heterogeneous group of drugs whose mechanism of action is not yet fully clarified. It is known that anaesthetic drugs can alter synaptic transmission by two mechanisms. A nonspecific membrane perturbing action and a specific action on membrane receptors, primarily acting as an agonist on the inhibitory $GABA_A$[1] receptor, which is the major inhibitory nervous system receptor. Indeed, the specific mechanisms by which anaesthetic drugs affect the immune system still remain unclear, but anaesthetic drugs induce analgesia affecting the transmission of nerve impulses, and they modulate surgical stress by acting on the hypothalamus–pituitary–adrenal axis, affecting catecholamines and glucocorticoid secretion[2]. Thus, part of the effect of anaesthetics on the immune system would be due to its action on the well-known immunomodulatory effect of glucocorticoids[3].

Diverse *in vitro* experiments with human immune cells[4], *ex vivo*[5–7], *in vivo*[8–10] or animal models have been used to study the effect of anaesthetic drugs on the immune system.

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These studies have demonstrated diverse effects, such as changes in immune cell counts and functionality, and effect on the secretion patterns of diverse immune mediators, affecting the inflammatory response through the cytokine release in the postoperative period[3]. These effects are clinically important because the balance between the pro- and anti-inflammatory cytokines secretion is related to postoperative infections and tissue injury[11,12]. Here, we review the effects of some of the most common anaesthetic drugs (Table 1) on the immune system. Although some studies have showed effects of anaesthetic drugs on immune response even several days after their administration[9,13,14], we will focus mainly on the effects within 24 hours after procedure, describing their effects on cells and cytokines of the innate and acquired immune systems.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines

Effects of anaesthetic drugs on immune cells

Anaesthetic drugs generally induce an increase in leucocytes counts[9,13–17] exerting diverse effects on each of different immune cell subpopulation (Table 2). In the next section, most significant functions of each immune cell type and the effect of specific anaesthetic drugs are described.

Neutrophils

Neutrophils are the most abundant population of circulating leucocytes. These cells are significant participants in the earliest phase of the inflammatory response. Neutrophils rapidly migrate to sites of infection, where they identify, ingest (phagocytosis) and destroy microbes (respiratory burst, lysosome degranulation). The neutrophil cytoplasm contains granules with microbicidal substances. Activated neutrophils release cytokines [tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-8 and transforming growth factor (TGF)-β], prostaglandins, thromboxanes and leukotrienes. Anaesthetic drugs affect both count and functionality of neutrophils. Thiopental and midazolam inhibit phagocytosis; and propofol, isoflurane, bupivacaine and lidocaine inhibit both phagocytosis and respiratory burst[16,18]. Propofol and desflurane increase neutrophil counts in peripheral circulating blood[13,14], although several studies have reported contradictory effects of sevoflurane on neutrophil count[13,14,19].

Mononuclear phagocytes

The mononuclear phagocytic system consists of cells whose primary function is phagocytosis and plays central role in both the innate and adaptive immune responses. Monocytes are circulating cells which are incompletely differentiated until they migrate to tissues, where they mature and become macrophages. Despite their primary function being phagocytosis, these cells also produce and release cytokines that stimulate inflammation (IL-1, IL-6, IL-12 and TNF-α). Anaesthetic drugs affect both monocyte circulating levels and functionality. Sevoflurane decreases circulating monocytes[10] without affecting their phagocytic activity[20]. Experiments carried out with halothane have contributed to understand the tissue specialisation of macrophages. Halothane does not have an effect on spleen macrophage phagocytic activity[21], but enhance peritoneal macrophage phagocytosis and respiratory burst[6]. Intravenous anaesthetics, such as propofol, midazolam and thiopental, inhibit both phagocytosis and respiratory burst[15,18]. Halothane and lidocaine decrease mononuclear cell counts by enhancing their apoptosis[10].

Lymphocytes

This subpopulation of leucocytes has a common cell precursor and has several subtypes: NK cells, T cells (CD3), CD4 and CD8, and B cells (CD19) among others. Anaesthetic drugs exert effects on these cells. Some studies have reported a decrease in lymphocyte counts after anaesthesia with propofol[7,14]. Inhalational anaesthetics induced different effects on lymphocytes. Some studies have showed an increase in lymphocyte counts after sevoflurane, halothane and desflurane anaesthesia[6,13,19], while others showed lower counts[10,20]. Sevoflurane and isoflurane induced lymphocyte apoptosis[22] *in vitro*. Ketamine[23] and local anaesthetics, such as bupivacaine and lidocaine[24], inhibited proliferation after mitogen stimuli. These are the reported effects of anaesthetic drugs in each lymphocyte subtype.

Natural killer cells

NK cells are large lymphocytes with abundant cytoplasmic granules and specific membrane markers. They are participants of the innate immune response, and essentially recognise

Table 1 Classification of anaesthetics

General anaesthetics		Local anaesthetics
Intravenous anaesthetics	Inhalational anaesthetics	
Ketamine Thiopental Propofol Fentanyl Remifentanil Midazolam Opioids	Halothane Sevoflurane Desflurane Isoflurane Enflurane	Lidocaine Bupivacaine Levobupivacaine

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Table 2 Anaesthetic drugs and their effect on immune cells

Immune cells	Effect of anaesthetic drugs
Leucocytes	Sevoflurane ↑cell counts[13] Desflurane ↑ cell counts[13] Propofol ↑ cell counts[14] Isoflurane ↑ cell counts[14] Levobupivacaine ↑ cell counts
Neutrophils	Thiopental ↓ phagocytosis[16,18] Propofol ↓ phagocytosis and respiratory burst and ↑ cell counts[13,14,16,18] Isoflurane ↓ phagocytosis and respiratory burst[16,18] Bupivacaine ↓ phagocytosis and chemotaxis[16,18] Lidocaine ↓ phagocytosis and chemotaxis[16,18] Desflurane ↑ cell counts[13,14]
Mononuclear phagocytes	Sevoflurane ↓ monocyte counts[14] Halothane ↑ peritoneal macrophage phagocytosis and respiratory burst[4] ↓ cell counts[10] Propofol ↓ phagocytosis and respiratory burst[15,18] Midazolam ↓ phagocytosis and respiratory burst[15,18] Thiopental ↓ phagocytosis and respiratory burst[15,18] Lidocaine ↓ cell counts[10]
Lymphocytes	Propofol ↓ cell counts[7,14] Sevoflurane ↓ cell counts[22] Isoflurane ↓ cell counts[22] Ketamine ↓ proliferation[23] Bupivacaine ↓ proliferation[24] Lidocaine ↓ proliferation[24]
NK cells	Propofol ↑cell counts[7,14], ↓ cytotoxic activity[7] Sevoflurane ↑ cell counts[13] Desflurane ↑ cell counts[13] Isoflurane ↓ cell counts[25] Halothanes ↓ cytotoxic activity[7]
CD4 Helper T lymphocytes	Halothane ↓ cell counts[21] Sevofluranes ↓ cell counts[13], ↓ Th1 and ↑ Th2[17] Isoflurane ↓ cell counts[25] Propofol ↑ cell counts[14] and ↓ Th1[17]
CD8 Cytotoxic T lymphocytes	Propofol ↓ cell counts[14,21] Sevoflurane ↓ cell counts[14,21] Halothane ↓ cell counts[14,21] Isoflurane ↑ cell counts[13,25] Desflurane ↑ cell counts[13,25] Isoflurane ↑ apoptosis[24]
CD19 B lymphocytes	Isoflurane ↑ cell counts[13,25] Desflurane ↑ cell counts[13,25] Halothanes ↑ antibody titre[8] Sevoflurane ↑ Primary and secondary immune responses[5,8,9,20,21,27] Opioids ↓ proliferation and antibody production[15]

virus-infected and stressed cells, and respond by direct cell killing and secretion of inflammatory cytokines [interferon (IFN)-γ]. An antibody receptor on the NK surface, called CD16 (FcγRIIIa), recognises the Fc regions of IgG1 and IgG3 antibodies. Thus, NK cells kill target cells that have been coated with antibody molecules (antibody-dependent cell-mediated cytotoxicity). The anaesthetic drug propofol induces an increase in NK

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Table 3 Effects of anaesthetic drugs on innate immune response cytokines

Cytokines	Effect of anaesthetic drugs
IL-1	Propofol ↓ plasmatic levels[15] Ketanime ↓ plasmatic levels[15] Thiopental ↓ plasmatic levels[15] Isoflurane ↑ plasmatic levels[28] Sevoflurane ↓ plasmatic levels[15] Desflurane ↓ plasmatic levels[15] Opioids ↓ plasmatic levels[15] Lidocaine ↓ release[5] Bupivacaine ↓ release[29]
IL-6	Propofol ↑ plasmatic levels[14,18,29,31] Ketamine ↓ plasmatic levels[15] Thipontal ↓ plasmatic levels[15] Remifentanil ↑ plasmatic levels[30] Fentanil ↑ plasmatic levels[30] Sevoflurane ↑ plasmatic levels[14] Isoflurane ↑ plasmatic levels[4,28,31] Opioids ↓ plasmatic levels[15] Levobupivacaine ↑ plasmatic levels[29] Bupivacaine ↑ plasmatic levels[4]
IL-8	Ketamine ↓ plasmatic levels[15] Propofol ↑ plasmatic levels[31] Thiopental ↓ plasmatic levels[15] Midazolam ↓ plasmatic levels[15] Isofluranes ↑ plasmatic levels[31] Propofol *in vitro* ↓ release from neutrophils[18]
IL-10	Ketamine ↑ plasmatic levels[15] Propofol ↑ plasmatic levels[14,15] Thiopental ↑ plasmatic levels[15] Fentanil ↑ plasmatic levels[30] Remifentanil ↑ plasmatic levels[30] Isoflurane ↑ plasmatic levels[4] Sevoflurane ↑ plasmatic levels[14] Bupivacaine ↑ plasmatic levels[4]
TNFα	Ketamine ↓ plasmatic levels[15] Propofol ↓ plasmatic levels[15] Thiopental ↓ plasmatic levels[15] Fentanil ↑ plasmatic levels[30] Remifentanil ↑ plasmatic levels[30] Isoflurane ↑ plasmatic levels[4,25] Sevoflurane ↓ plasmatic levels[15] Enflurane ↓ plasmatic levels[15] Opioids ↓ plasmatic levels[15] Bupivacaine ↑ plasmatic levels[4]

cell count and decreases cytotoxic activity[7,14]. Inhalational anaesthetics such as sevoflurane and desflurane enhance NK cell counts[13] and isoflurane decreases them[25]. Halothane reduces NK cytotoxic activity[7].

T lymphocytes (CD3)

T lymphocytes are produced in the bone marrow and their precursors migrate to and mature in the thymus. Two major T-cell subsets are helper T lymphocytes (CD4) and cytotoxic T lymphocytes (CD8), which express in the membrane of the CD3 molecule that is part of the antigen receptor complex. Both CD4 and CD8 are involved in adaptive immune response. The effects of anaesthetic drugs depend on the T cell type. Isoflurane, sevoflurane and halothane enhance both CD4 and CD8 apoptosis not only by upregulation of the Fas/FasL system but also by affecting the expression of other anti-apoptotic and pro-apoptotic factors[10,22,26].

Helper T lymphocyte (*CD4*): CD4 lymphocytes are key mediators directing the adaptive immune response either to a cellular response (Th1) or humoral response by activating B cells (Th2). Repeated anaesthesia with halothane[21] and desflurane[13] decreases CD4 cells. Propofol increases cells counts[14], while, depending on the model, sevoflurane may increase[14] or decrease[14,20] CD4 cell counts. Regarding the type of response, propofol decreases Th1 and sevoflurane diminishes Th1 and enhances Th2 responses[17].

Cytotoxic T lymphocytes (*CD8*): The main function of these cells of the adaptive immune response is their specific cytotoxic activity against infected cells with intracellular organisms or neoplastic cells. CD8 cells are activated by cytokines (IL-2 and IFN-γ) secreted by Th1 lymphocytes. Anaesthesia with propofol, sevoflurane and halothane decreases CD8 cell numbers[14,21], while isoflurane and desflurane increases CD8 cell numbers[13,25].

B lymphocytes (CD19)

B cells are able to recognise soluble antigens by membrane antibodies. This recognition induces B-cell activation, proliferation and differentiation to plasma cells that secrete antibodies. The effect on the number of B lymphocytes depends on the drug type. Isoflurane and desflurane increase the cell numbers[13,25], while sevoflurane and propofol can increase[13,14,27] or decrease[18,20] it. Anaesthetics also affect B lymphocyte

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Table 4 Effects of anaesthetic drugs on adaptive immune response cytokines	
Cytokines	**Effect of anaesthetic drugs**
IL-2	Propofol ↓ production[29] Ketanime ↓ release[15] Morphine ↓ plasmatic levels[15]
IFN-γ	Propofol ↑ plasmatic levels[15] Thiopental ↓ plasmatic levels[15] Remifentanil ↓ plasmatic levels[15] Opioids (morphine) ↓ plasmatic levels[15]
IL-4	Thiopental ↓ plasmatic levels[15] Morphine ↓ plasmatic levels[15]
TGF-β	Sevoflurane ↑ plasmatic levels[14] Morphine ↑ plasmatic levels[15]

activation. Halothane increases the antibody titre[8], and, as sevoflurane does, it increases the primary and secondary responses[5,8,9,20,21,27]. Opiates decrease B-cell proliferation and antibody production[15].

Effect of anaesthetic drugs on cytokines

Many interactions and effector functions of leucocytes are mediated by short-acting secreted mediators called cytokines, a heterogeneous group of molecules mainly produced by leucocytes, although, under certain conditions, they are also mediated by other cell types. Cytokine expression is highly regulated, and cell activation is necessary for their synthesis to exert their biological activity. They can act in autocrine, paracrine or endocrine way and their functions are also pleiotropic and redundant. Some of them are considered as innate immune response regulators and others regulate the adaptive immune response. In the following section, we describe the effects of anaesthetic drugs on cytokines; in fact, these are the better studied effects of anaesthetics on the immune system.

Cytokines of innate immunity

Cytokines such as IL-1, IL-6, IL-8, IL-10 and TNF-γ are produced and released mainly by cells of the innate immune response, such as activated macrophages and monocytes. Lymphocytes and endothelial cells can also produce these cytokines (Table 3). The production of these cytokines can be affected by anaesthetic drugs.

IL-1: It is produced by monocytes, macrophages, dendritic and NK cells. There are two forms: IL-1α and IL-1β. IL-1 has significant inflammatory effects, such as histamine release induction, fever and the synthesis of acutephase proteins. Isoflurane induces high mRNA expression, and enhances IL-1 levels[28]. Anaesthetic drugs such as ketamine, thiopental, sevoflurane, enflurane, propofol and opiates decrease IL-1 plasmatic levels[15]. *In vitro*, local anaesthetics such as lidocaine and bupivacaine inhibit IL-1 release[29].

IL-6: It is produced mainly by monocytes, macrophages and T lymphocytes; and among other functions, it stimulates acutephase protein synthesis. IL-6 also affects adaptive immune response, stimulates antibodies production and enhances IL-2. Anaesthetic drugs such as propofol, remifentanil, fentanil, sevoflurane, isoflurane, levobupivacaine and bupivacaine increase IL-6 levels[4,14,18,28–32], while ketamine, thiopental and opiates decrease IL-6 concentration[15]. The mechanism is not clear, but it is known that isoflurane increases mRNA expression[28] and sevoflurane enhances the level of the alarmin homeobox protein 1[32].

IL-8: It is actually a chemokine produced by leucocytes that stimulates neutrophil chemotaxis and degranulation. Propofol and isoflurane increase IL-8[31], whereas ketamine, thiopental and midazolam inhibit its liberation[15]. *In vitro* experiments have demonstrated that propofol inhibits neutrophil IL-8 liberation[18].

IL-10: It is produced by monocytes, macrophages, T-regulatory cells and B lymphocytes. It is the main anti-inflammatory cytokine because it inhibits the synthesis of IFN-γ, TNF-α, IL-2 and IL-12. IL-10 also induces IgG synthesis. Many anaesthetic drugs such as ketamine, thiopental, propofol, fentanil, remifentanil, isoflurane, sevoflurane and bupivacaine increase IL-10 levels[4,14,15,30].

TNF-α: It is produced by NK cells, T and B lymphocytes, mastocytes, monocytes and macrophages in response to bacterial antigens. TNF-α is the main pro-inflammatory cytokine and is responsible for septic shock. This cytokine favours extravasation with endothelial cell stimuli to produce IL-8 and adhesion molecules. Isoflurane raises mRNA[28] expression and increases TNF-α levels, and is the same with fentanil, remifentanil and bupivacaine[4,25,28,30]. Sevoflurane, enflurane, ketamine, thiopental, propofol and opiates inhibit its liberation from mononuclear cells[15].

Cytokines that regulate adaptive immune response

T CD4 lymphocyte activation, proliferation and differentiation after antigenic stimuli lead to an adaptive immune response towards Th1 or Th2 immunity. Th1 lymphocytes produce IL-2, IFN-γ and TNF-α, while Th2 lymphocytes mainly produce IL-4, IL-10 and IL-13 cytokines (Table 4). In fact, some of these cytokines are produced by the innate and adaptive immune responses; those that are specific for the adaptive response are affected by anaesthetic drugs.

IL-2: It is released by activated T lymphocytes (CD4 and CD8) after

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antigenic stimuli. IL-2 is the main inducer of lymphocyte proliferation (T, B and NK cells). IL-2 also enhances natural (by NK cells) and specific (by CD8) cytotoxicity and increases MHC type II molecule expression. Anaesthetic drugs, through different mechanisms, decrease its effects. Ketamine inhibits its release[15], morphine diminishes its levels[15] and propofol suppresses IL-2 production[29].

IFN-γ: This cytokine is produced mainly by Th1, CD8 and NK lymphocytes. IFN-γ activates macrophages and inhibits Th2 differentiation, so it is considered a proinflammatory cytokine. *In vitro*, propofol increases its concentration[15], whereas thiopental and remifentanil decrease its concentration. The same effect has been observed during chronic opioid administration, such as morphine[15].

IL-4: It is produced by Th2 cells, NK lymphocytes and mast cells. IL-4 promotes Th2 differentiation and inhibits Th1 response. IL-4 also blocks the action of IL-1 inducing the production of IL-1Ra. IL-4 is related to parasitic infections and allergic processes as it enhances IgE production. Thiopental inhibits IL-4 liberation, while morphine increases it[15].

TGF-β: It is produced by activated T-regulatory lymphocytes and macrophages. TGF-β has immunosuppressive effects because it inhibits the synthesis of IFN-γ, TNF-α, IL-1 and IL-2, and it also inhibits NK and CD8 cytotoxic activity. Sevoflurane[14] increases its levels and after chronic administration, morphine[15] favours its production by lymphocytes, monocytes and macrophages.

Effect of anaesthetic drugs on glucocorticoids

Glucocorticoids (GCs) are significant immunomodulatory hormones. They bind to specific receptors that translocate to the nucleus and modulate cytokine expression. The GC–receptor complex binds to and inactivates nuclear factor-κB (NF-κB), one of the most important immune transcription factors. In human blood mononuclear cells in culture, GCs strongly decrease the production of IL-1, TNF-α, IL-2, IL-3, IL-4, IL-5, IL-10, IL-12, IFN-γ, IL-6 and IL-8[3]. Sevoflurane and desflurane increase Gc plasmatic level[13], while propofol decreases it[14].

NF-κB regulates T- and B-lymphocyte activation, and pro-inflammatory cytokine production and release, as well as adhesion molecule expression. NF-κB is located in the cytoplasm in an inactivated form; after specific external signal, it is activated, translocated to the nucleus and promotes cytokine synthesis. Anaesthetic drugs such as ketamine, propofol and morphine inhibit cytokine production by blocking NF-κB activation[15].

Conclusion

Several immune functions are modified after anaesthetic drugs are administered by direct or indirect effects on stress responses. Significant activities such as phagocytosis, respiratory burst, proliferation and cell count are modified after anaesthetic procedures. Anaesthesia also affects the immune response by suppressing or by releasing different cytokines, affecting the inflammatory response. Thus, the type of anaesthetic drug is important to consider the surgical procedures for animal models because they are able to affect diverse immune system functions and should be taken into account when choosing the anaesthetic drug. Regarding the clinical practice, it has been reported that some alterations in the immune system persist several days after the end of the anaesthetic exposure. However, the post-anaesthetic immunological complications are rare in patients with proper immune system function; while in patients with certain immunodeficiency, the choice of appropriate pain therapy should be carefully selected, considering that the interaction between anaesthesia and the immune system can lead to complications. This is the case in HIV-infected patients that in addition to the effects of anaesthetics on the immune system, it is also important to consider the interactions between antiretroviral drugs and anaesthetics. Antiretrovirals increase or decrease the activity of liver enzymes shortening or lengthening, respectively, the effects of anaesthetic drugs. This subject is also important in other conditions, such as in cancer, considering that immunosuppression induced by anaesthetic drugs enhances progression of metastasis after tumour removal surgery. NK cells, through the release of IFN-γ and their cytotoxic activity, are significant factors that contribute for the elimination of neoplastic cells; anaesthetic drugs that affect these functions provoke decreased IFN-γ release or cytotoxic activity impairing the elimination of tumour cells. This is a situation that must be considered in each patient, which includes trying to find the best anaesthetic technique that leads to a better outcome.

Abbreviations list

GC, glucocorticoids; IL, interleukin; INF, interferon; NF-kB, nuclear factor-kB; NK, natural killer; TGF, transforming growth factor; TNF, tumour necrosis factor.

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