PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 62 (2008), No. 4/5 (657/658), pp. 141–147.
DOI: 10.2478/v10046-008-0017-y

Review

ANAESTHESIA AND STRESS RESPONSE TO SURGERY

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Communicated by Jānis Gardovskis

The body reaction to surgery ranges from minor to massive both locally and generally. General response is in the form of widespread endocrinal, metabolic and biochemical reactions throughout the body. Neuro-endocrinal hormone system and inflammation mediators are involved and this process is called "stress response". The response has a compensatory mechanism and provides a maximum chance of survival because of increased cardio-vascular functions, fluid preservation and supply of increased demands for energy generating substrates. If the stress response is prolonged, it may result in exhaustion of essential components of the body, fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality. Suppression of immune defense mechanisms has been demonstrated in the postoperative period. Such immune compromise can affect the postoperative infection rate, healing process, and the rate and size of tumour metastases disseminated during surgery. The mechanism of immunosuppression in the postoperative period is not fully understood. The known mediators of immune depression are neuroendocrine response as well as intravenous opioids and inhalational agents, which have shown to increase the susceptibility to infection through a significant cautions in choosing anaesthetic agents, to minimise harm to the patients. In this paper we review the data about the influence of different anaesthetic agents on neuroendocrine, immune and inflammatory response to surgical stress.

Key words: *anaesthesia, surgical stress, immune response.*

INTRODUCTION

In recent years, the immune response to anaesthesia associated with surgery has caused attention, and knowledge has increased and techniques have been improved in other anaesthesiology-related areas such as endocrine, neuroendocrine, cardiovascular, respiratory and metabolic aspects. Research has led to decreased morbidity and mortality from anaesthesia, but immunologic effects of anaesthesia have been one of the less investigated areas. Both surgical stress and anaesthesia are immunosuppressive. Regional anaesthesia perhaps is less suppressive than general anaesthesia. Some immunologic changes have been reported mainly after major surgical operations (Lennard *et al*., 1985; Procopio *et al*., 2001). Every component of the immunologic profile can be altered during anaesthesia and surgery. It has been clearly shown that anaesthetic agents depress the immune response by compromising phagocytes, lymphocyte transformation, cytotoxicity, antibody response to antigen and chemotactic functions of immune cells. The balance between proinflammatory and anti-inflammatory processes is of key importance in the reaction of the body to infection, injury, and surgical trauma. Drugs commonly used in anaesthesia and intensive care may modulate immunological reactions by influencing intercellular communication through modification of cytokine response and peripheral immune cells such as natural killer cells, B cells, and T lymphocyte subpopulations (Brand *et al.,* 2003). Regarding postoperative consequences, it is generally believed that effective perioperative pain management may result in a more rapid recovery; but the effects of pain relief on postoperative outcome are difficult to measure due to factors such as type and duration of surgery, recovery measures, the analgesics used, their side effects and route of administration (Rosenberg and Kehlet, 1999). The cytokines have a major role in the inflammatory response to surgery and trauma and pain mechanisms. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes that occur. After major surgery, the main cytokines released are interleukin-1 (IL-1), tumour necrosing factor (TNF-α) and interleukin-6 (IL-6). IL-6 is the main cytokine responsible for inducing the systemic changes known as the acute phase response. Within 30–60 min after the start of surgery, IL-6 concentration increases; the change in concentration becomes significant after 2–4 h. Cytokine production re-

flects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures, for example, laparoscopic surgery. The largest increases in IL-6 occur after major procedures such as joint replacement, major vascular and colorectal surgery. After these operations, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively (Sheeran and Hall, 1997). Physical well-being after surgery is influenced by many factors via inflammatory mediators and acute phase proteins. Multiple regression analysis showed that the main predictor of worse physical condition at three days was the size of the C-reactive protein (CRP) response (Hall *et al*., 2002). Walking distances in patients after orthopaedic surgery were more significantly lower in patients with greater IL-6 and CRP concentrations and patients with greater CRP had more severe pain on discharge (Hall *et al.,* 2001). Thus, by promoting IL-6 release we may attenuate overall physical well-being after major surgery. The cytokines IL-1 and IL-6 can stimulate secretion of adrenocorticotropic hormone (ACTH) from isolated pituitary cells *in vitro*. In patients after surgery, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. A negative feedback system exists, whereby glucocorticoids inhibit cytokine production. The cortisol response to surgery is sufficient to depress IL-6 concentrations (Jameson *et al.,* 1997). By carefully choosing agents we may modify the stress response.

MECHANISM OF STRESS RESPONSE

Tissue and peripheral nerve injury leads to local inflammatory reaction, accompanied by elevated concentrations of various biological mediators, including prostaglandins, bradykinins, substance P, calcitonin-G-related protein (CGRP), and cytokines in the injured tissue (McMahon *et al.,* 2005), especially proinflammatory cytokines (Wu *et al.,* 2004; Buvanendran *et al*., 2006). Peripheral injury is associated with inflammatory response at the site of the tissue damage and also in the central nervous system (CNS), including peripheral elevation of TNFα, IL-1, and IL-6, concomitantly with the development of thermal hyperalgesia and mechanical allodynia (Winkelstein *et al.,* 2001; Watkins and Maier, 2002). Proinflammatory cytokines, including IL-1β and IL-6, can induce peripheral and CNS sensitisation, leading to pain augmentation (hyperalgesia) (Watkins *et al*., 1995).

The mechanisms by which IL-1 contributes to central sensitisation are still not fully understood, but several mediating processes have been suggested. Many of the same factors that regulate peripheral hyperalgesia also play a significant role in central sensitisation. Elevated IL-1β in the CNS also leads to the production of COX-2 by neurons in the brain and spinal cord, and promotes synthesis of prostaglandin (PGE) 2, which is known to increase pain sensitivity (Samad *et al*., 2001). Some patients develop very high cytokine response after surgery and they may benefit from cytokine inhibition. This may depend on genetic polymorphism, and particular genotypes can predispose individuals to long-term risks (Masterson and Hunter, 1996)

According to stress response, anaesthetics can be grouped as follows.

GENERAL ANAESTHETICS

The type of general anaesthesia used has no important effect on the stress response, except for high dose opioid anaesthesia which may inhibit intra- but not postoperative catabolic hormonal responses (Desborough and Hall, 1989).

Volatile

In some clinical studies, volatile anaesthetics have been associated with a greater systemic inflammatory response compared to total intravenous anesthetics with adjuvant narcotic infusion (Crozier *et al.,* 1994; Schneemilch and Band, 2001). *In vitro* studies have shown that volatile anesthetics have substantial immunosuppressive effects by inducing programmed cell death in lymphocytes, diminishing lymphocyte function, and altering the distribution of lymphocyte cell subsets (Matsuoka *et al*., 2001; Karabiyik *et al*., 2001). Volatile anaesthetic suppressor lymphocyte activity, which deteriorates host defense, was found to be increased in the sevoflurane group and decreased in the isoflurane group postoperatively. Although the differences were insignificant, these results gave the idea that isoflurane caused less immunosuppression. (Durlu *et al*., 2002). In contrast, in the clinical setting of low stress laparoscopic surgery, the type of volatile anesthetic has been shown to significantly affect the stress response; the changes associated with sevoflurane suggested a more favourable metabolic and immune response compared to isoflurane (Marana *et al.,* 2003). *In vitro* volatile anaesthetics alter relative cytokine concentrations and lymphocyte responses (Woods and Griffits, 1988). Compared with total intravenous anaesthesia (TIVA), the T1/T2 ratio decreases significantly after isoflurane anaesthesia, but not after propofol anaesthesia. The ratio was significantly lower with isoflurane than propofol. Propofol anaesthesia promoted the surgical stress-induced adverse immune response better than isoflurane anaesthesia (Inada *et al*., 2004).

INTRAVENOUS ANAESTHETICS

There are huge differences between intravenous agents. Some of them are given below.

Etomidate

The anaesthetic induction agent etomidate is a carboxylated imidazole which interferes with the production of steroids in the adrenal cortex by reversible inhibition of the enzyme 11β-hydroxylase and cholesterol side-chain enzyme. The synthesis of both aldosterone and cortisol is blocked. A sin-

gle induction dose of the drug will suppress hormone production for 6–12 h (Wagner and White, 1984) while infusion for 1–2 h will block cortisol synthesis for up to 24 h. In healthy patients, there have been observed no adverse cardiovascular effects from such an infusion during surgery, and the only metabolic result of cortisol inhibition seen has been a decrease in the expected glycaemic response. The widespread use of etomidate as a general anaesthesia induction agent further supports the suggestion that low levels of cortisol during surgery are sufficient for surgical survival. At doses commonly administered for induction of general anaesthesia, etomidate has been widely and safely used for decades, often in severe ill patients, despite clear documentation that it lowers cortisol concentrations in peripheral blood for 8–10 h and that it may continue to inhibit adrenocortical synthetic activity for up to 24 h and adrenal responsiveness to ACTH even longer (Duthie *et al*., 1985; Absalom *et al.,* 1999). Intraoperative cortisol concentrations commonly decrease after etomidate induction to less than 10 mg/dl, documenting that the rapid elevation of cortisol ordinarily seen during surgery is not necessary for normal recovery and survival. (Yeager *et al.,* 2005).

Ketamine

There is a growing body of evidence that low-dose ketamine may play an important role in improving postoperative pain management when used as an adjunct to opioids or local anaesthetics. Single intraoperative injection of ketamine (0.15 mg/kg) improved analgesia and passive knee mobilisation twenty-four hours after arthroscopic anterior cruciate ligament surgery and improved the postoperative functional outcome after surgery (Tverskoy *et al*., 1996; Menigaux *et al.,* 2000)

Addition of small doses of ketamine before induction of anaesthesia resulted in attenuation of secretion of the proinflammatory cytokines IL-6 and TNF-α, and in preservation of IL-2 production at its preoperative level. It is suggested that this anaesthetic may be of value in preventing immune function alterations in the early postoperative period (Beilin *et al.,* 2007).

Propofol

Propofol has earned a prominent place in anaesthesiology by rapid and profound induction and easy following, useful secondary properties such as reduction of postoperative nausea and vomiting. Unfortunately, propofol also has many side effects, including directly related to the Intralipid vehicle: the ability to support bacterial growth, pain on injection, hypertriglyceridemia with prolonged infusions, and the potential for intralipid to compromise the immune response (Bowdle and Hines, 2002). Data suggest that anaesthesia with propofol and fentanyl promotes proinflammatory immune responses and influences peripheral lymphocyte composition in patients, which may subsequently affect pathophysiological processes during opioid-based anaesthesia (Brand *et al.,* 2003).

Benzodoazepines

The benzodiazepine, midazolam, which has an imidazole ring in addition to the basic benzodiazepine structure, suppresses the cortisol responses to both peripheral and upper abdominal surgery. Midazolam and diazepam both inhibit cortisol production from isolated bovine adrenocortical cells *in vitro.* Although Crozier and colleagues showed that subjects produced cortisol in response to exogenous ACTH, thus confirming that the site of action of the benzodiazepine is at the hypothalamic–pituitary level, a direct inhibitory effect on steroid production cannot be excluded (Crozier *et al.,* 1987).

Opioids

It is unclear whether opioids in the perioperative period promote or attenuate surgery-induced immunosuppression. It has been known for many years that opioids suppress hypothalamic and pituitary hormone secretion. It was demonstrated that therapeutic doses of morphine have the suppressant effect on the hypothalamic–pituitary–adrenal axis in humans. Morphine suppressed the release of corticotrophin and, consequently, cortisol in normal and stress conditions, although the adrenals were found to respond to exogenous administration of ACTH (Yardeni *et al.,* 2008). In upper abdominal surgery, systemic opioids are relatively ineffective in preventing the stress response to upper abdominal surgery (Desborough, 2000). Opioids in the perioperative period can modulate host-defense mechanisms and can either enhance (Shavit *et al.,* 1984) or suppress tumour metastases. Several factors may account for these conflicting results. Immune suppressive effects of opioids have been observed in pain-free individuals (Yeager *et al*., 1995) or after the administration of relatively moderate to large doses (Beilin *et al*., 1996), whereas the beneficial effects of opioids were observed when administered in an analgesic dose to a host experiencing postoperative pain. Understanding of endogenous peripheral opioid analgesia has promoted the development of clinically useful peripherally acting opioid drugs. The aim is to produce substances that activate peripheral opioid receptors, but which do not cross the blood–brain barrier, thus producing analgesia with less central adverse effects. Buprenorfin and tramadol are opioids with potential favourable immune effects.

REGIONAL ANAESTHESIA

During lower extremity or lower abdominal surgical trauma, for example, epidural block of spinal afferent signals, is associated with a minimal circulating cytokine response since neural blockade prevents or markedly limits hypothalamic-pituitary axis (HPA) activation in these settings (Moller *et al.,* 1984; Naito *et al.,*1992; Moore *et al*., 1994; Lattermann

et al., 2003) However, it fails to limit HPA activation during other types of surgery (upper abdominal or thoracic) that are associated with substantial cytokine release (Naito et al., 1992; Norman and Fink, 1997)

Local anaesthetics can reduce the postoperative inflammatory response in two ways: they block neural transmission at the site of tissue injury and decrease the neurogenic inflammation (Coderre *et al*., 1993); they also have systemic anti-inflammatory properties of their own (Hollmann and Durieux, 2000).

It seems that only regional anaesthesia techniques can lead to long stress response reduction. Preferably we should use continuous techniques, and for example epidural anaesthesia should last at least 24–48 hours (Kehlet, 1998; 2000).

Epidural anaesthesia avoids the depressed mitogen-induced, lymphocyte-proliferative responses normally seen in patients in general anaesthesia (Whelan *et al.,* 1982) There has been observed a significant difference in IL-6 production among the patient controlled analgesia (PCA), patient- controlled epidural analgesia (PCEA) and intermittent opiates regimen (IOR) at 72 hours. IL-6 levels were least increased in the PCEA group, almost returning to preoperative values by 72 h. In contrast, IL-6 levels were most increased in the IOR group and still increasing at 72 h, whereas in the PCA group IL-6 levels were intermediate (Beilin *et al.,* 2003).

An attempt to suppress the markers of the inflammatory response using continuous intense epidural blockade with local anaesthetics has not been successful, showing that neuroaxial blockade with local anaesthetics cannot prevent systemic and local inflammatory reaction (Moore *et al.,* 1994). Some authors have found that nerve blocks, particularly continuous lumbar plexus and sciatic nerve blocks significantly inhibit CRP and IL-6 (Bagry *et al.,* 2008). Other authors have found similar effects of general and spinal anaesthesia on stress response in patients undergoing surgery. Perioperative levels of TNF, IL-6, CRP are comparable in both types of anaesthesia (Buyukkocak *et al*., 2006).

DIFFERENT DRUGS

Glucocorticoids

Recently, glucocorticoids, which block several proinflammatory substances (cytokines, complement, arachidonic acid cascade) have been studied in elective surgery procedures. These results suggest that large preoperative doses of methylprednisolone reduce pain, hyperthermia, IL-6 and PGE responses, and improve pulmonary function (Schulze *et al.,* 1992).

More recent research reported glucocorticoid-induced stimulatory effects on a variety of inflammatory response components. These effects were usually observed at low glucocorticoid concentrations, close to concentrations that are observed *in vivo* during basal, unstimulated states. It seems clear that the long-held clinical view that glucocorticoids act solely as anti-inflammatory agents needs to be reassessed. Varying doses of glucocorticoids do not lead simply to varying degrees of inflammation suppression, but rather glucocorticoids can exert a full range of effects from permissive to stimulatory to suppressive (Munck and Naray-Fejes-Toth, 1992; Yeager *et al*., 2005). Glucocorticoids have been shown to induce or enhance the expression of several cytokine receptors, including those for TNF-a, IL-1, IL-2, IL-6, interferon -γ (IGF) (Almawi *et al.,*1996; Wiegers and Reul, 1998).Glucocorticoid effects on cytokine receptors were shown to be specific to glucocorticoids as the effects are not seen with other steroid molecules (mineralcorticoids). Surgical stress-induced production of brain PGE2 is specifically regulated by glucocorticoid via the mediation of type II corticosteroid receptors. Normal IL-1 signalling is required for the production of brain PGE2 under basal conditions and in response to surgical stress (Beilin *et al.,* 2006).

Clonidine

Clonidine is a centrally acting antihypertensive drug. Injection of the α2-adrenoreceptor agonist clonidin reduces pain behaviour and local tissue proinflammatory cytokine concentration (Romero-Sandoval *et al.,* 2005). Clonidine was observed to change the ratio of T-lymphocyte subpopulations in peripheral blood in favour of a proinflammatory response, which might be favourable for maintaining immune balance after surgery. T1/T2 ratios were significantly lower 6 h after cardiac surgery with clonidine compared to placebo. A possible explanation might be that clonidine, by reducing sympathetic tone via α2-adrenoreceptors, changed the early T-cell subset response in favor of the proinflammatory response after cardiac surgery. This might be important for maintaining immune balance perioperatively. However, the systemic inflammatory response was not affected by clonidine in this study (von Dossow *et al.,* 2006). The effects of intravenous and epidural clonidine, 4 μg/kg, combined with epidural morphine, 40 μg/kg, on the neuroendocrine and immune stress responses to thoracic surgery have been reported. Catecholamines did not change in any of the groups. Total leukocyte and neutrophil counts were increased in all groups at the end of surgery, but increase was least in the epidural clonidine group. The number of lymphocytes was reduced at the end of surgery in the epidural and intravenous group, compared with the control group in which the number of lymphocytes did not change. The effects were more pronounced with epidural than with intravenous administration. We may conclude that clonidine can modulate the immune stress response to thoracic surgery (Novak-Jankovich *et al.,* 2000).

Other authors have found no significant differences in plasma epinephrine or cortisol levels between clonidine and placebo groups. With a clinical dose, clonidine did not prevent postoperative lymphocyte depletion. α2-agonists may not suppress adrenocortical stress responses sufficiently to prevent postoperative immune suppression (Ellis *et al*., 2002).

Clonidine provides haemodynamic stability through its sympatholytic activity, and can reduce anaesthetic and analgesic requirements and provide sedation. By reducing the sympathoadrenal and cardiovascular responses caused by noxious surgical stimuli, the α2-agonists inhibit the stress responses mediated by the sympathetic nervous system (Antaa and Scheinin, 1993).

Physostigmine

Continuous infusion of physostigmine combined with morphine-based PCA in the postoperative period significantly reduced opiate consumption, and enhanced the analgesic response. Patients in the physostigmine group exhibited significantly reduced *ex vivo* production of the proinflammatory cytokine, IL-1β. The finding that patients treated with physostigmine exhibited decreased production of IL-1β may be explained by the fact that physostigmine crosses the blood-brain barrier, elevates acetylcholine levels in the brain, and thereby activates the cholinergic anti-inflammatory pathways (Beilin *et al.,* 2005).

POSTOPERATIVE PAIN MANAGEMENT

Non-steroidal antiinflammatory drugs (NSAID) are used widely for perioperative pain control but have a poor effect on surgical stress responses (Kehlet, 1998). By sparing physiological tissue prostaglandin production, and while inhibiting inflammatory prostaglandin release, cyclooxygenase(COX)-2 inhibitors offer the potential of effective analgesia with fewer side effects than the NSAID, but the desired outcome has been achieved only partially (Power *et al*., 2004; Botting *et al.,* 2003). The mechanism of paracetamol action remains unclear as, respectively, paracetamol has no known endogenous binding sites and does not inhibit peripheral cyclooxygenase activity significantly. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase 'COX-3' that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotinergic pathways (Bonnefont *et al.,* 2003). Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity.

CONCLUSIONS

The neuroendocrine response to stress is an important modifier of immune function, and anxiety, fear, and pain have been shown to be associated with adverse outcomes. There is a lot of data on modification of stress hormone responses by anaesthetic drugs, but very few studies relating hormone levels to long-term outcome have been done. Stress hormones like norepinephrine can trigger a pronounced and immediate activation of pro-inflammatory cells and cytokines. The triggers for stress responses are both psychological and physical, so it seems reasonable that postoperative immune function could be improved by increased attention to perioperative anxiolysis and analgesia.

Table 1

INFLUENCE OF DIFFERENT ANAESTHETIC AND ANALGESIC AGENTS ON STRESS RESPONSE TO SURGERY

Type of analgesia	Endocrine metabolic response	Inflammatory response
Systemic opioids	↓↑	
Epidural opioids	↓	
Lumbar local anaesthetics	↓↓↓	↓
Thoracic local anaesthetics	↓	
Propofol	↓	
Ketamine	↓	
Etomidat	↓↓↓	
NSAID*	↓	↓
Glucocorticoids	↓↓	↓↓↓
Clonidine	↓↓	
Physostigmine	↓	

*NSAID, non-steroidal antiinflammatory drugs; ↓ – weak action; ↓↓ – intermediate action; ↓↓↓ – marked action; ↓↑ – controversial data

The influence of anaesthetic agents on stress response is summarised in Table 1. It will be important to "measure" inflammation by analysis of appropriate serum markers. Measuring inflammation at a preoperative baseline may significantly improve the accuracy with which we stratify patients for operative risk. The markers of inflammation and CRP have a high predictive utility in determining the clinical course. It is also possible that a postoperative profile of these bio-markers may identify patients who would benefit from more sustained anti-inflammatory treatment strategies (Fig. 1).

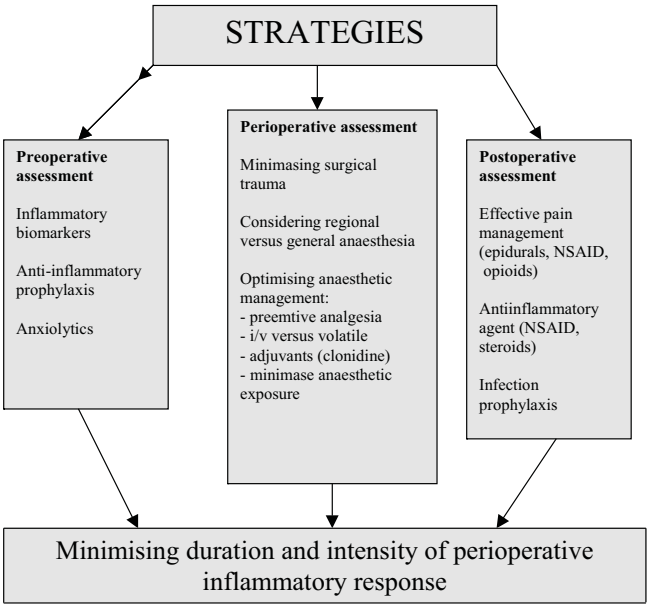

Fig. 1. Strategies minimising perioperative stress response.

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Received 1 July 2008

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ANESTĒZIJAS IETEKME UZ ORGANISMA ATBILDI ĶIRURĢISKAJAM STRESAM

Organisma atbilde uz ķirurģisko iejaukšanos variē no minimālas līdz ļoti izteiktai, ar izmaiņām gan grieziena vietā, gan visās orgānu sistēmās. Viscaur organismā notiek plašas neiroendokrīnās, metabolās un bioķīmiskās reakcijas. Neiroendokrīnās hormonu sistēmas un iekaisuma mediatoru iesaistīšanos šajā procesā sauc par "stresa atbildi". Šai atbildei ir kompensējošs mehānisms, un tas maksimāli palielina izdzīvošanas iespējas, paātrinot kardiovaskulārās sistēmas darbību, palielinot šķidruma uzkrāšanu un enerģētiskās vajadzības. Ja šīs stresa reakcijas ātri nebeidzas, iestājas visu galveno organisma sistēmu izsīkums, attīstās nogurums, samazinās pretestība infekcijām, ir novēlota izrakstīšanās no slimnīcas, pieaug mortalitāte un morbiditāte. Sevišķi gribam uzsvērt imūnsistēmas aizsargmehānismu izsīkumu pēcoperācijas periodā. Tas var ietekmēt infekciozo komplikāciju risku, dzīšanas procesus un audzēju metastāžu diseminmāciju. Imūnsupresijas mehānismi vēl nav līdz galam izpētīti, bet ir pierādīts, ka atsevišķās anestēzijas vielas, kā, piemēram, inhalācijas anestētiķi un intravenozi ievadāmie opioīdi palielina noslieci uz infekciozām komplikācijām, samazinot atbildīgo šūnu citotoksisko aktivitāti. Tātad mums ir jābūt piesardzīgiem, izvēloties anestēzijas veidu un anestētiķus, lai nodarītu iespējami mazāku kaitējumu organismam. Rakstā ir apkopota literatūra par dažādu anestētiķu izmantošanu un to ietekmi uz organisma neiroendokrīno, imūno un iekaisīgo atbildi ķirurģiskajam stresam.