The Impact of Anesthesia and Surgery on Plasma Cytokine Production

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Abstract—Exposure to anesthesia and surgery affects many of the common functions of the immune system. Various examinations have indicated that damage of the immune response could increase perioperative morbidity and mortality rates from infection in exposed patients. The current review summarize the impact of anesthesia and surgery on plasma cytokine production.

Keywords—cytokines, anesthesia, surgery, trauma

Exposure to anesthesia and surgery affects many of the common functions of the immune system.[1] Various examinations have indicated that damage of the immune response could increase perioperative morbidity and mortality rates from infection in exposed patients.[2] Former studies showed the influence of postoperative immunosuppression on the humoral arm as well as the cellular arm of the immune system. Surgery is a major traumatic element in postoperative immunodepression in normal people.[3] A higher degree of surgical trauma determines greater immunodepression.[4] Cytokines are heterogeneous proteins, such as lymphokines, monokines, interleukins and interferons, acting on cell-surface receptors in order to adjust cell growth, evolution and restoration.[5] Cytokines are significant conveyors of the immuno-inflammatory response to impairment and infection, being directly implicated in the symptomatology of sepsis, multiorgan failure and septic shock.[6] From this perspective, the major cytokines are interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-6, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).[7] Surgeries of any kind harm homeostasis and generate various hemodynamic, metabolic and immunologic reactions. Experimental and clinical outcome has demonstrated that surgical trauma is correlated with damaged postoperative immune responses, which could be associated with an impaired generation of proinflammatory cytokines, or with the inhibition of cellular responses.[8] Proinflammatory and anti-inflammatory cytokines proved to be crucial for acute-phase inflammatory and immunological responses triggered following surgical trauma. From this point of view, the most important cytokines are tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6) and interleukin-10 (IL-10).[9] Anesthesia is able to suppress immune function, thus influencing the postoperative course. The combination between general anesthesia and surgical stress may have an impact on the inflammatory responses which are vital for preserving postoperative homeostatic state. Multiple anesthetics have been supposed to harm many of the immune system functions both directly, by altering the performance of immune-competent cells, and indirectly, by adjusting stress response.[10] Various anesthetic techniques may hinder stress response, mainly cytokine activation during and after surgery. There is not clear evidence of the immunomodulatory impact of anesthetics on cytokine production. Anesthetic methods influence adrenergic activity. Recent studies have proved that clinical concentrations of halothane and isoflurane can influence β-adrenoceptor-mediated responses in rat aorta.[11] There is also evidence of correlations between the activity of adrenergic receptors and the production of cytokines. In stress conditions, elevated epinephrine concentrations can trigger IL-6 release by means of adrenergic β2 receptors,[11] whereas activation of α2-adrenergic receptors in macrophage membranes can intensify the secretion of TNF.[12] The described impact of postoperative immunomodulatory on inhalational anesthetics[13-16] also needs to be seriously considered. Changeable restriction of superoxide secretion by human neutrophils was described after exposure to halothane, enflurane and isoflurane.[17-19] Halothane anesthesia also generated higher concentrations of T- and B-lymphocytes, on one side, and lower levels of serum immunoglobulin and a poorer lymphoproliferative response, on the other.[20] Isoflurane proved to activate, rather than restrict, the neutrophil chemotactic response, whereas halothane didn’t have any impact. IL-1β, IL-6 and TNF-α are proinflammatory cytokines. The concentrations of IL-6 and TNF-α in this research were lower than the minimal level where the enzyme-linked immunosorbent assay (ELISA) can accurately identify them and they remained low during the entire period of the study. This could indicate the absence of surgical trauma during minor surgery. IL-1β changes in this study were consistent in both anesthetic groups. IL-1β exhibited an important pre-incision reduction in both groups, indicating the impact of anesthesia alone. There have been elevated serum IL-1, IL-6 and TNF concentrations shown in different types of tissue damage and infection also generated by cells of the immune system following immunological stimulation.[21] IL-1β targets the body’s response to serious damage and endotoxin challenge, stimulating the production of IL-6 and TNF-α. The increase in IL-1β by the end of anesthesia and surgery in this study was probably not enough to determine elevated TNF-α and IL-6.
levels as a result of minor surgical procedures.[22] Studies show the correlation between the increased IL-6 levels detected following trauma or different types of surgery and the intensity of surgical trauma and the length of surgery. Several authors showed the absence of immune damage in case of minor surgery, but its presence when correlated with the trauma of major surgery.[23] In another research, anesthesia used as sole method and minor surgery did not indicate any increase in TNF or IL-6 levels. [24] There are not many studies on the independent impact of anesthetic agents on cytokine levels in humans. In their study, several authors.[24] indicated elevated plasma concentrations of IL-6 when surgery ended and on the first postoperative day, but no discrepancies in IL-6 concentrations between isoflurane and propofol groups. Others [25] observed a decreased release of IL-6 after alfentanil-propofol anesthesia as to isoflurane anesthesia, which was due to alfentanil. IL-2 was the first immunological cytokine to be detected, being vital for the induction of an adequate immune response [26]. In the current study, the design of IL-2 secretion in reaction to anesthesia differed among the two groups. Prior to incision, halothane determined elevated IL-2 levels, while isoflurane determined lower IL-2 levels. By the end of anesthesia and after 24 h, IL-2 levels were reduced in the halothane group and elevated in the isoflurane group, to go back to baseline levels. In another study [27], the reduction in IL-2 secretion was the most powerful deviation detected in trauma-induced immunodeficiency. T-cell dysfunction generates immunosuppression after major trauma, characterized by damaged synthesis of IL-2 and IFN-γ [28]. Faulty production of IL-2 was found in a study conducted following surgery, but without any change in T-helper (Th) cell percentage [29]. IL-2 secretion stimulated by halothane anesthesia as indicated in this research may prevent the restrictive impact of surgical trauma on IL-2 secretion, whereas isoflurane could determine a higher degree of inhibition. The variation in cytokine secretion could be connected to the impact of volatile anesthetic on intracellular calcium concentrations, as Ca2+ is of vital importance in cytokine regulation. In contrast to isoflurane, halothane intensifies Ca2+ release mainly from the caffeine-releasable Ca2+ stores in vascular smooth muscle [30]. Both halothane and enflurane also restrict bradykinin- and adenosine- triphosphate-stimulated Ca2+ transients in endothelial cells [31]. The intracellular Ca2+ pools can be altered individually by volatile anesthetics. The metabolites generated by the vast hepatic metabolism of halothane, in comparison to isoflurane which is less metabolized, might also determine changes in cytokine activity. IFN-γ has potential immunoregulatory impact, being an inhibitor of viral reproduction. It initiates Th1 lymphocytes and consequent cell-mediated immunity.[25] The design of IFN-γ secretion in the subjects in this study in reaction to anesthesia and surgery was similar in the two groups.[26] The outcome is in agreement with that from former studies demonstrating the depressant impact of inhalational anesthetics on IFN-γ secretion. An in vitro study on biological response modifiers (BRM) released by T cells indicated reduced IFN-γ secretion after exposure to halothane.[27] An in vivo study examining BRM release accounted significantly lower postoperative IFN-γ secretion when using general anesthetic agents, but no effect when using epidural anesthesia. This immunomodulatory impact of anesthesia on cytokine secretion could have therapeutic potential for many patients requiring anesthesia, especially those with septic, neoplastic or immunocompromised diseases. Impaired IL-2 secretion has been noticed in various conditions, such as acquired immunodeficiency syndrome (AIDS), chronic infectious diseases and autoimmune diseases.[28] There are ongoing clinical research studies for treating human immunodeficiency virus (HIV) infection and others which are unresponsive to conventional antibiotic therapy, by means of IL-2 administration.[29] Interleukin-2 is another promising anticancer drug which triggers lymphokine-activated cells and tumor -infiltrating lymphocytes. Allograft rejection and suppression of auto-immune disease could be prevented by IL-2 and IL-2 receptor antibodies.[30] IL-1α has also proved to be beneficial for the prevention or treatment of thrombocytopenia generated by cancer chemotherapy.[31] Moreover, anti -IL-6, anti -IL-6 or anti -TNF-α receptor monoclonal antibodies have proved beneficial for treating septic shock. In the present study, both groups only differ in terms of the inhalational anesthetic type received and thus, the impact on cytokine secretion notes the potential impact of halothane and isoflurane.[32] Therefore, it might be more cautious to treat individuals with pre-existing immnosuppression with halothane. Isoflurane, which generates lower IL-2 secretion, could inhibit immunological reactions in subjects with marginal immunocompetence. Halothane and isoflurane are mostly given together with opioids which could also have immunomodulatory influence.[33-35] A better consideration of anesthesia -induced immune response adjustment should promote future reduced morbidity and mortality rates due to perioperative inflammation, tumor growth and immunosuppression. The use of another anesthetic method might be needed. Future studies are required in order to examine the impact of halothane or isoflurane -based anesthesia on transplant surgery and patients with pre-existing immunological disorders, such as allergy, autoimmune disease, inflammation, AIDS and malignant disorders.

References


