Surgery induced immunosuppression

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Review

Surgery induced immunosuppression

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Abstract

Surgery and anaesthesia result in a variety of metabolic and endocrine responses, which result in a generalised state of immunosuppression in the immediate post-operative period. Surgery induced immunosuppression has been implicated in the development of post-operative septic complications and tumour metastasis formation. In addition the effectiveness of many treatments in the adjuvant setting is dependent on a functioning immune system. By understanding the mechanisms contributing to surgery-induced immunosuppression, surgeons may undertake strategies to minimise its effect and reduce potential short-term and long-term consequences to patients.

Introduction

Surgical operations cause a variety of immunological disturbances. With a few exceptions the overall picture is one of a generalised state of immunosuppression in the post-operative period. It would appear that the degree to which this occurs and its duration are determined in part by the magnitude of the initial surgical insult. The clinical consequences to patients as a result of this suppression are unclear. There are reports in the literature suggesting that it results in an increased incidence of post-operative wound complications and tumour progression. This review examines the effects of surgery and anaesthesia on components of the immune system, the mechanisms by which these effects may be mediated and the clinical implications of such immune disturbance. In addition we discuss strategies and novel therapies that can be used to modulate the immune system during surgery.

Surgery induced immunosuppression

Surgery induced immunosuppression is caused by the effect on the cellular components of the immune system. Surgery and trauma cause an increase in the total number of white blood cells circulating in the body. However when critical individual leucocyte subpopulations are examined it seems that important groups are suppressed in both number and function. Circulating lymphocyte numbers fall peri-operatively and the extent and duration of this fall is related to the magnitude of the surgery. This reduction in lymphocyte numbers may be accounted for by a decrease in the lymphocyte proliferation rate or as a result of a redistribution of lymphocytes from the peripheral blood to the body compartments. When lymphocytes have been differentiated into T and B cells it appears that T lymphocytes are most affected,
Mechanisms of immunosuppression

Immune changes occurring peri-operatively are primarily as a result of surgical trauma and subsequent neuroendocrine responses. Activation of the hypothalamic–pituitary–adrenal axis (HPA) is the key response to stress and plays a central role in mediating the effect of surgery on the immune system.32,33 Peri-operative stresses both physical and psychological result in the increased production of adrenocorticotropic hormone (ACTH) from the pituitary gland, and subsequent release of glucocorticoids such as cortisol from the adrenal gland. This increase in ACTH and glucocorticoid production may persist for several days following surgery and is proportional to the severity of the surgical stress. Glucocorticoids are known to suppress cell mediated immunity.34,35 Cortisol prevents proliferation of T lymphocytes by rendering interleukin-2 producing T cells unresponsive to IL-1 and unable to produce T cell growth factor.36 Glucocorticoids not only reduce T cell proliferation but are also known to increase apoptosis of immature T cells leading to atrophy of the cortical area of the thymus gland.37 Glucocorticoid induced lymphopenia may also be partly due to a redistribution of lymphocytes out of the circulation into other body compartments.38 It is uncertain where the lymphocytes migrate to, with one report suggesting that they may be redistributed from the spleen and peripheral blood to the lymphatic tissues.39

More recent work suggests that the immunosuppressive effect of glucocorticoids as seen in the peri-operative period may be mediated through their effect on the expression of certain target genes in leucocytes. Glucocorticoids increase expression of a number of anti-inflammatory genes resulting in increased production of lipocortin and secretory leucocyte proteinase inhibitor.40 Lipocortin 1 inhibits production of phospholipase A2 and is a regulator of the production of pro-inflammatory prostaglandins and leukotrienes. Secretory leukocyte protease inhibitor is active against neutrophil elastase and cathepsin G, neutrophil proteases involved in inflammation and phagocytosis.41 Glucocorticoid inhibition of gene expression in leucocytes, results in decreased production of many pro-inflammatory cytokines including IL-1, IL-2, IL-6, IL-11, IL-13 and TNF-α.42–44 It is now known that cytokines IL-1 and IL-6 stimulate the HPAA resulting in increased production of glucocorticoids from the adrenal gland.45,46 This is believed to be mediated through the release of corticotrophin releasing hormone CRH from the hypothalamus and may represent an important negative feedback effect on the immunosuppressive actions of the HPA axis.

Activation of the sympathetic nervous system during surgery also has a profound effect on the immune system. The immune organs or lymphoid organs are innervated with sympathetic nerve fibres and can be directly stimulated by the sympathetic nervous system as part of the “fight or flight response.”48 The subsequent release of catecholamines; adrenaline and noradrenaline from the nerve terminals has predominantly immunosuppressive effects. These effects are mediated through the interaction of catecholamines with adrenergic receptors present on the surface of immune cells. These adrenergic binding sites have been identified on many immune cell subtypes and are predominately of the β2 subtype.49,50 Adrenaline released as a result of surgical stress activates β2 receptors on T lymphocytes. This inhibits T cell proliferation by decreasing IL-2 expression and secretion.51,52 In vitro studies suggest that exposure of NK cells to a β2 agonist such as adrenaline also reduces NK cell activity.53,54 Neutrophils are also inhibited by exposure to adrenaline. Neutrophil production of anti-microbial superoxide radicals is reduced50,55 as is their ability to adhere to vascular endothelium.56 In contrast however, other reports suggest that β2 stimulation results in increased cell motility and increased accumulation of neutrophils at sites of inflammation.49

Recently, along with immune suppression caused by surgical stress, numerous studies have shown that anaesthetic and analgesic agents used peri-operatively may have a direct toxic effect on components of the immune system. Propofol, a commonly used intra-venous anaesthetic agent,
inhibits neutrophil and macrophage chemotaxis and phagocytosis.\textsuperscript{26,27} However propofol has also been shown to have a less pronounced effect on circulating lymphocyte numbers than other anaesthetic agents such as sevoflurane.\textsuperscript{57} The mode of anaesthetic administration may also affect the degree of immunosuppression; for example, the use of spinal anaesthesia results in better preservation of T cell proliferation than general anaesthesia for prostate surgery.\textsuperscript{58} Opioids are commonly used analgesic agents in surgery and are known to have immunosuppressive effects. Morphine is known to suppress a variety of immune functions including NK cell activity,\textsuperscript{59} T lymphocyte proliferation\textsuperscript{60} as well as neutrophil and macrophage phagocytic activity.\textsuperscript{61} These immunosuppressive effects are mediated indirectly by opiate activation of the HPA axis\textsuperscript{62} and also through activation of the sympathetic nervous system.\textsuperscript{63} In addition opioid receptors are found on many subtypes of immune cells allowing for a direct effect of opiates on the immune system.\textsuperscript{64}

**Clinical consequences of surgery induced immunosuppression**

The clinical consequences of peri-operative immunosuppression were documented as far back as 1911 when Graham reported that ether induced a reduction in bacterial phagocytosis increasing the risk of post-operative septic complications.\textsuperscript{65} Gaylord in 1916 showed an increased frequency of metastases from mammary carcinoma in mice following anesthesia and blood loss.\textsuperscript{66} More recent studies also suggest that the immunological effects of surgery have both immediate and delayed consequences for patients. In the oncological setting the effect of surgery on NK cell number and activity has been linked to an increased risk of mortality and cancer recurrence in patients with colorectal,\textsuperscript{67} breast,\textsuperscript{68} head and neck,\textsuperscript{69} and lung cancers.\textsuperscript{70} Tartter showed that a low level of NK cytotoxicity in the immediate pre-operative period, was an independent predictor of recurrence in colorectal carcinoma.\textsuperscript{67} In the post-operative period reduced NK activity was an independent predictor of survival in patients with non-small cell lung carcinoma.\textsuperscript{68} In all forms of surgery, oncological and otherwise, peri-operative immunosuppression can result in more immediate consequences for patients including delayed wound healing and other septic events. Wakefield et al showed that a perioperative drop in HLA-DR expression of monocytes was associated with the occurrence of wound complications and respiratory infections post-operatively.\textsuperscript{71} Duignan showed that impairment of neutrophil chemotaxis as a result of surgery was also associated with the development of septic complications.\textsuperscript{72}

**Measures to reduce immunosuppressive effect of surgery**

An understanding of the mechanisms by which surgery induces immunosuppression allows for the implementation of certain measures to minimise negative consequences to patients. Efforts to reduce the immunosuppressive effects of surgery and anaesthesia must be initiated in the pre-operative period. These efforts should be focussed on minimising the neuroendocrine stress response associated with surgery. Effective emotional support and counselling as well as appropriate pre-medication use may help reduce pre-operative psychological stress. Physical stressors associated with surgery such as dehydration and hypothermia also contribute to activation of the HPA axis and thereby subsequent immunosuppression. Ensuring adequate tissue perfusion is essential as are measures to maintain core body temperature such as fluid warmers and external body warming devices. A key issue in minimising the immunosuppressive effect of surgery is adequate pain control throughout the surgical experience. Epidural analgesia can be considered in suitable individuals as a means of reducing stress-induced immunosuppression in patients undergoing major abdominal surgery.\textsuperscript{73} While opiates are known to have direct suppressive effects on immune cell activity, it has also been shown that analgesic doses of morphine significantly reduce the tumour promoting effects of surgery.\textsuperscript{74} The reason for this contradictory effect is not understood. Tramadol, a synthetic opioid, has less inhibitory effects on phagocytic cells than conventional opiates,\textsuperscript{75} while buprenorphine appears to exhibit a neutral effect on the immune system.\textsuperscript{76} Non-steroidal anti-inflammatory drugs (NSAIDs), while possessing anti-inflammatory properties are also effective analgesics and antipyretics. They also reduce prostaglandin E2 induced immunosuppression and their use is therefore considered appropriate in minimising the immunosuppressive effect of surgery.\textsuperscript{77} Other immunoprotective measures that may be employed include minimising the use of blood transfusion products\textsuperscript{78} and ensuring the nutritional integrity of the patients particularly in the post-operative setting.

The development of minimally invasive surgery has allowed major changes in surgical practice, especially because it limits surgical trauma. This results in better preservation of lymphocyte subpopulations, neutrophil function and cell mediated immunity than conventional open surgery.\textsuperscript{25,79,80} This preservation of the immune system may contribute to the reduced post-operative complication rate and shorter hospital stay experienced by patients undergoing laparoscopic procedures.\textsuperscript{81,82} Future development of minimal access surgery may be an important step in minimising surgery induced immunosuppression and its potential complications.

The role of immunomodulators in the surgical setting has attracted much attention in recent years. The majority of work has focussed on immunosuppressants, particularly in the organ transplant setting. However, there has also been considerable interest in the use of immunostimulants to minimise the immunosuppressing effect of surgery and reduce the risk of metastatic spread. In this context, numerous animal studies have shown anti-neoplastic effects of IL-12.\textsuperscript{83,84} This effect is thought to be mediated through increased production of IFN-$\gamma$\textsuperscript{85,86} and upregulation of cell mediated immunity specifically through T cells.\textsuperscript{87} Research to date has shown limited success in treating advanced or recurrent disease.\textsuperscript{88,89} However a recent study showed that the prophylactic use of IL-12 peri-operatively abolished the metastasis-promoting effects of surgery in a murine model. In this case an IL-12 dependent increase in NK cell numbers was thought to be responsible.\textsuperscript{90} However, toxicities associated with IL-12 administration have thus far limited its clinical use. Other
animal studies have shown that the peri-operative administration of immune promoting cytokines such as IFN-γ can also inhibit the development of post-operative metastasis and increase survival rates.91,92 In the clinical setting there is evidence that the administration of IL-2 pre-operatively stimulates cell mediated immunity and improves survival for patients with colorectal and pancreatic cancer.93–95 Active immunotherapy in the form of a vaccine was initially shown to improve survival following resection of disseminated melanoma.96 This vaccine was prepared from allogeneic melanoma cell lines grown in culture. However, subsequent phase III trials did not support these initial positive findings and use of the vaccine was discontinued. While results from the clinical use of active immunomodulators are limited and varied it would appear that that their potential role should be targeted in the peri-operative setting to counteract the immunosuppressive effects of surgery and minimise the risk of metastatic development from minimal residual disease following resection of the primary tumour bulk.

Conclusion

Surgery induced immunosuppression has considerable implications for patients. It is associated with impaired wound healing and delayed post-operative recovery. Its implications for cancer patients are more profound, being associated with an increased incidence of cancer recurrence and reduced survival. In addition the effectiveness of many adjuvant treatments is dependent on the preservation of immune integrity in patients during and following resection of the primary tumour. An understanding of the neuroendocrine mechanisms contributing to this process may allow for the implementation of strategies to minimise peri-operative immunosuppression and its consequences for patients.

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