

Understanding the Effects of Surgical Procedures on the Immune System

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Introduction

Surgical trauma induces a cascade of events in the human body which are a result of immunological, neuroendocrine and haematological factors acting in concert. Research has elucidated the pattern of response to surgical trauma. Initially the innate immune system gets activated releasing cytokines such as IL-1, TNF alpha, which in turn stimulate the release of other pro-inflammatory cytokines(IL-6, IL-10) which constitutes the Systemic Inflammatory Response[SIRS]. This hyperimmunity is then followed by the counter-inflammatory response syndrome.[1]

The outcome of post surgical patients depends on this delicate balance of molecular and biochemical events where the balance may be shifted adversely resulting in complications like post surgical infections and MODS(multi organ dysfunction syndrome).[2,3]

Effects on innate and adaptive immune response

The innate immune response is the first line of defence. This is a rapid, non-specific response with no dependence on memory. Phagocytic and endothelial cells release cytokines such as TNF α and IL-1. IL-1 and TNF induce the systemic acute phase response which involves release of neutrophils into the circulation, release of corticotropin and corticosteroids, release of IL6, IL8 and PDGF(platelet derived growth factor).[1]

Out of the cytokines triggered, IL6 appears to play a significant role. IL6 is known to increase the number of circulating neutrophils and acute phase proteins such as CRP, amyloid and complement C3 [1,4].IL6 has also been shown to decrease apoptosis of immunocytes resulting in prolonged hyperimmunity [5]

IL6 also suppresses cell mediated immunity and increases humoral immunity[1]. This is one mechanism which causes the TH1/TH2 shift. Adrenergic response and cortisol release also trigger this shift towards suppression of TH1 response[6] Surgical stress also leads to dysfunction of NK cells which lead to in an increased susceptibility to infections.[7]

Non surgical factors

Inhalational and intravenous anaesthetic agents and opioids have been shown to reduce the function of NK cells while nitrous oxide apparently inhibits the phagocytic properties of neutrophils. Regional anaesthesia was however shown to counteract the diminishing effect of surgery on cell mediated immunity. [8]

Anesthesia administration, surgery, and mechanical ventilation each independently impair phagocytosis and bacterial killing by alveolar macrophages.[9]

Pain propagates the immune suppression by triggering the nociceptive receptors which in turn increase the release of catecholamines and corticosteroids.[10][11].

Allogenic blood transfusions have been shown to cause transfusion associated immunomodulation(TRIM). This causes increased inflammation and immune suppression which



can lead to post-operative complications such as infections, cancer metastasis and recurrence. [12][13]. The immune suppression is due to a reduction in T-helper cell and NK cell count, and a reduction in cytokine production including IL-2 and IFN- γ [14]

Clinical Implications

Understanding the effects of surgery and related non surgical factors have on the immune system can help us possibly predict and minimize certain adverse outcomes. Surgical site infections are the leading cause of worldwide health-care associated infections: 5.6 per 100 surgical procedures[15]. Modifying the immunological changes due to surgery may help us to reduce this burden. Another area of interest is reducing tumour metastasis due to surgical stress.[16][17][18]

Antibiotic prophylaxis is a standard practice which is in place to reduce surgical infections[19]. This can be supplemented by minimizing surgical trauma; laparoscopic procedures have shown to have a lesser impact on immune functions due to this reason [20], optimizing immunity by immune modulating diets designed to replace arginine which gets depleted during immune hyperstimulation and beta adrenergic blockade during surgery[21].[22]

Pain, anaesthesia and analgesia, all have been shown to affect the immune system. As previously mentioned pain has an immunosuppressive effect. Anaesthesia and opioids conflictingly show a similar effect.[3,8,11] A recent study was done to compare the immunosuppressive effects of fentanyl, morphine and buprenorphine. It concluded that buprenorphine has the least immunosuppressive effects with morphine being slightly less effective at preventing immunosuppression and fentanyl having the poorest immunosuppressive prevention.[23]. Tramadol was found to have a beneficial effect by improving post operative immunosuppression[24] and reduction of tumour metastasis[25]

While the exact effects of regional anaesthesia is still being explored, some studies have concluded that at least in animal models spinal anaesthesia has a beneficial effect on immunity compared to general anaesthesia.[26.]. Another study that support this inference found that epidural analgesia in post operative patients showed less T cell suppression and inflammatory cytokine activity compared to intermittent administration of opioids[27.]

Non steroidal anti-inflammatory drugs were found to have potential beneficial effects on reducing proinflammatory cytokine responses and reducing cancer metastasis[28][8]. Cytokines can be used as markers to predict clinical outcomes or for treatment. IL6 is a significant pro inflammatory cytokine. IL6 can be used as a marker to predict adverse outcomes of SIRS[29]. Perioperative supplementation of interferon alpha may alleviate tumour metastasis in patients undergoing surgery[30]. Similarly lactoferrin treatment has also shown to confer a protective function postoperatively by boosting immune response. [31]. Perioperative administration of the influenza vaccine has been shown interestingly to decrease NK cell dysfunction due to surgery thus offsetting the risk of tumour metastasis[32]

Immunomodulation pre and perioperatively is particularly important in patients who are already immune compromised. Thymostimulin has been found to be effective in preventing postoperative infections in anergic patients.[33.] Non-pharmacological measures such as improved oxygenation and proper thermoregulation also improve immune function[9.]

Conclusion

Immune hyperstimulation and subsequent immune suppression caused by surgical trauma is a natural process which allows the maintenance of immune homeostasis. In routine uncomplicated surgeries these effects almost always go unobserved. However, exaggerated SIRS or increased



immunosuppression can cause surgical complications especially in immunologically challenged patients. Understanding the effects helps prevention and prediction of adverse outcomes as well as develop immune therapies to counteract them.

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