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Overview

Anaestethic technique and cytokine response

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Abbreviations:

SIRS	– inflammatory response syndrome
MODS	– multiple organ dysfunction syndrome
ARDS	– acute respiratory distress sindrom
CNS	– central nervous system
TNF	– tumour necrosis factor
MSOF	– multi-system organ failure
IL-1	– interleukin-1 (IL-a and IL-b)
IL-6	– interleukin-6
IL-8	– terleukin-8
IL-10	– interleukin-10
IL-13	– interleukin-13
TGF-b	– transforming growth factor-b
CRP	– C-reactive protein
PC	– Protein C
PS	– protein S
DIC	– disseminated intravascular coagulation
E2	– prostaglandin E2

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Abstract

Surgery elicits broad alterations in haemodynamic, endocrine-metabolic and immune responses. The inflammatory response is essential for structural and functional repair of injured tissue, as complement, granulocytes, macrophages and many other mediators are required for appropriate wound healing. Injury, surgical or traumatical is connected with the acute disorder of immunological system which is manifesting as increased inclination to infections. The inflammatory response is an important determinant of outcome after major surgery. Perioperative excessive stimulation of the inflammatory and haemostatic systems plays a role in the development of postoperative ileus, ischaemia-reperfusion syndromes (e.g. myocardial infarction), hypercoagulation syndromes (e.g. deep venous thrombosis) and pain; together, these represent a significant fraction of major postoperative disorders. Regional anaestehsia administered local anaesthetics prevent or modulate many of these processes.

In the center of interests there are the serum-levels of Th1 i Th2 cytokines before and after regional and general anaesthesia and in such a way would like to confirm through the immunological status that the spinal anaesthesia is significantly more favourable for the patient.

INTRODUCTION

Survival depends on the immune system's ability to defend the body against attack from invading pathogens and injury. However, the extent of such a response is of critical importance; deficient responses may result in secondary infections from immunosuppression and excessive responses can be more harmful than the original insult *(1, 2)*. Cytokine synthesis and release is an essential component of the innate immune system, but inappropriate, excessive production results in a generalized systemic inflammatory response which damages distant organs.

Cytokines

Cytokines are lowmolecular- weight proteins which after binding to specific receptors affect immune cell differentiation, proliferation, and activity. They are not stored, but are newly synthesized and released during activation of the inflammatory cascade. They are multi-functional but in essence direct the inflammatory response to sites of infection and injury and enhance wound healing. Pro-inflammatory cytokines include tumour necrosis factor-a (TNF-a), interleukin-1 (IL-1), IL-6, and IL-8. Anti-inflammatory cytokines include IL-1 receptor antagonist, IL-10, IL-13, and TNF-binding proteins 1 and 2. *(3, 4, 5, 6, 7)*. Tumour necrosis factor (TNF) is a primary and potent mediator of inflammation synthesized mainly by monocytes/macrophages and T

cells and has a half-life within the circulation of 20 min. TNF is also a potent inducer of other pro-inflammatory cytokines and activating mediators distally in the cytokine cascade. TNF-a elicits considerable metabolic and haemodynamic changes and is capable of causing end--organ dysfunction. Other functions include activation of coagulation, muscle catabolism, and cachexia *(3, 6–11, 49)*. There are two forms of IL-1 (IL-a and IL-b) which recognize the same cell surface receptors and therefore share various biological activities. IL-1 is synthesized by monocytes and leucocytes and other cell types and has a halflife of 6 min. Both IL-a and IL-b evoke metabolic and haemodynamic changes similar to those of TNF-a, activate production of other cytokines, and attenuate pain perception by promoting the release of b-endorphins *(3, 6, 7, 8)*.

Effects of pro-inflammatory cytokines is a sensitive balance between pro- and anti-inflammatory cytokines. Pro-inflammatory cytokines operate close to their site of release, but if the inflammatory response escapes local control, it elicits a generalized systemic response. TNF-a and IL-1 have short half-lives and system of membrane reservoirs hold the cytokines close to the site of release and the anti-inflammatory cytokines modify the host inflammatory response(7) (Table 1).

1. TNF-a can produce immediate and delayed negative inotropic effects on myocardial tissue and has been shown to cause left ventricular dysfunction. (9.10) TNF-a, IL-1b, and IL-6 have also been implicated in causing myocardial depression by direct actions on the myocytes *(4, 11)*.
2. Pro-inflammatory cytokines have significant effects on vascular tone, mainly mediated through the NO pathway, with resultant vasodilatation. TNF-a and IL-1b have both been observed to increase NO production, and failure to respond to vasoconstrictors after prolonged exposure to these cytokines has been reported *(4)*.
3. Inflammatory lung injury occurs when activated neutrophils and macrophages migrate from the pulmonary vasculature into the alveolar and interstitial spaces. Macrophages secrete TNF-a, IL-1, and IL-8 which in turn stimulate further cytokine production by lung epithelial and mesenchymal cells *(4, 12)*. IL-8 has been shown to have a pathogenic role in the establishment of acute respiratory.
4. In animal studies, TNF-a has been shown to induce glomerular injury in kidneys without pre-existing renal disease. In response to TNF-a and IL-1, glomerular cells produce oxygen free radicals, complement, arachidonic acid derivatives, and NO which further escalates local inflammation with resultant additional glomerular and tubular cell damage *(4)*.
5. Predominantly IL-6, but also TNF-a and IL-1b stimulate the liver to alter its synthetic function and increase the synthesis of acute phase proteins such as serum amyloid A, a2-macroglobulins, and C-reactive protein (CRP). The substrates for this increase in production are provided by cytokine-mediated skeletal muscle breakdown, hence the alternative name for TNF-a; cachectin *(4)*.
6. Cytokines are not directly involved in the coagulation pathways, but TNF-a and IL-1 have been shown to modulate the extrinsic pathway of coagulation and the protein C pathway. Evidence suggests important roles for these cytokines in disseminated intravascular coagulation (DIC) and thrombosis *(13–27)*. IL-1 has also been shown to inhibit fibrinolysis *(14)*.
7. The consequences of ageing on the immune system are thought to contribute considerably to morbidity and mortality in the elderly *(15)*. TNF-a and IL-6 concentrations are raised in the elderly and studies have shown that, in response to surgical trauma, the elderly have a magnified and late inflammatory cytokine response *(16)*.

TABLE 1

Effects of pro-inflammatory cytokines on organ systems.

Cardiac	Negative inotropic effect on myocardium Left ventricular dysfunction
Vascular	Vasodilatation
Respiratory	Acute lung injury Pathogenic role in ARDS
Renal	Glomerular injury Tubular cell damage
Hepatic	Increased synthesis of acute phase proteins
Coagulation	Modulation of extrinsic and Protein C pathways Inhibition of fibrinolysis Role in development of DIC and thrombosis

Conditions of cytokine excess

Inappropriate synthesis of cytokines occurs with excessive or persistent activation of macrophages and neutrophils. If this escapes local control, cytokines enter the systemic circulation resulting in widespread activation of inflammatory cascades and the systemic inflammatory response syndrome (SIRS). This evokes further release of inflammatory cytokines resulting in a downward spiral of organ dysfunction and ultimately multiple organ dysfunction syndrome (MODS). In patients with ARDS alone, mortality is around 50% and with each additional organ failing, this risk increases in a multiplicative fashion. TNF-a, IL-1b, IL-6, and IL-8 have been strongly implicated as mediators of sepsis and studies of sepsis have shown elevated circulating levels of these cytokines *(3, 4, 18, 19)*. Furthermore, raised levels of pro-inflammatory cytokines generally appear to correlate with severity of illness and outcome *(3, 4, 19, 20)* with IL-6 most closely associated with mortality *(11, 16)*. Increased plasma concentrations of proinflammatory cytokines have been demonstrated after major surgery *(7, 21, 22)* and the magnitude of the cytokine-mediated inflammatory response appears to be related to the extent of the surgical

insult *(68)*. High plasma concentrations of IL-6 in response to major surgery appear to be associated with postoperative mortality *(7)*. After severe trauma, serum levels of TNF-a, IL-6, and IL-8 are significantly elevated and there appears to be a close relationship between the extent of pro-inflammatory cytokine release and the severity of injury and hospital mortality *(23, 24, 25)*. Haemorrhage results in a markedly increased production of pro-inflammatory cytokines in the lungs and is associated with the onset of ARDS with TNF-a playing a central role in the pathogenesis of acute lung injury after haemorrhage, even after adequate resuscitation *(26–32)*.

Anti-inflammatory mechanisms

Anti-inflammatory cytokines such as IL-10, TNF--binding protein, IL-receptor antagonist (IL-1ra), and transforming growth factor-b (TGF-b), which are produced through a normal immune response, can inhibit the release of TNF-a and other pro-inflammatory cytokines *(33, 1–20, 76)*. TNF-binding protein interferes with the binding of TNF to its receptor and thus inhibiting its actions *(46)*. 'Stress' hormones such as glucocorticoids, epinephrine, norepinephrine, and a-melanocyte-stimulating hormone inhibit cytokine production. Conditions of cytokine excess are systemic inflamatory response sindrom (SIRS)can be classified as resulting from either infectious or non-infectious conditions, surgery, trauma, haemorhagic shock, pankreatitis, burns, ischaemia-reperfusion injury.

Neural regulation of the immune response

Cytokines and the immunomodulatory function of the vagus nerve been shown to up-regulate IL-10 production thereby enhancing the anti-inflammatory action *(34)*. Other local effectors such as prostaglandin E2, acute phase proteins, heat-shock proteins, spermine, and feutin all have additional roles in limiting the immune response. Impairment or loss of any of these endogenous anti-inflammatory pathways can turn a normally self--limiting response into an excessive and potentially damaging one 1.

Immune system also functions as a sensory organ. This information would then be relayed to the central nervous system (CNS) to bring about a favourable physiological response *(35)*. Recent research has revealed an autonomic neural pathway termed 'the inflammatory reflex', which has both immunosensing and immunosuppressing functions. Compared with the humoral anti-inflammatory mechanisms which are slow, diffuse, and dependent on concentration gradients, the inflammatory reflex pathway is fast, localized, and integrated *(1, 36)*.

Pharmacological agents

Despite recent advances in intensive care treatment, MODS resulting from excessive and prolonged pro-inflammatory cytokine release in conditions such as sepsis, ischaemia/_reperfusion, and haemorrhagic shock remains associated with a high mortality rate. Pro-inflammatory cytokines such as TNF-a and IL-1b have been identified as 'early' mediators of the inflammatory response and when neutralized using specific antibodies can prevent the development of septic shock in animal models(76, 84). The studies have shown that TNF-a antibodies are ineffective for critically ill patients *(4, 37)* if treatment is commenced after serum TNF-a has been cleared.

Excessive inflammatory stimulation may lead to host auto-injury inflammatory syndromes (e.g. SIRS and ARDS), sepsis, multi-system organ failure (MSOF) and eventually death. In a much greater proportion of the surgical patient population, postoperative pain and postoperative hypercoagulation represent significant morbidity due to excess activation of inflammatory responses. Since these responses are initiated during surgery, intraoperative interventions might decrease their frequency and severity.

Immunological system in human beings is adaptable system, able to recognize and eliminate manifold strange cells and molecules. The role of immunoreaction is defence against infections, defence against tumor and maintenance of gene and antigene homeostasis(1z).Injury, whether surgical or traumatic, is connected with acute disorder of immunological system which is manifested as increased inclination to infections. This phenomenon is primarily characterized by disorder of cell immunity and function of macrophages. In serious infections and big extensive injuries there is present reduced production of Th1 cytokine and increased production of Th2 cytokine, which is connected with immunosuppresion *(2)*

General anaesthesia

Applied medicines may also affect the immunological status *(3)*. General anaesthesia with opioides cause depression of immunological system. Influence of non--opioide anaesthetics on immunological system is not explained to such an extent *(4)*. Propofol has antiinflammatory properties, decreasing production of proinflammatory cytokines, thus inhibiting neutrofile function *(7, 8)*. Inhalation anaesthetics in mechanical ventilation stimulate inflammatory response on transcription level within 2 hours (Volatile anaesthetics augment expression of proinflammatory cytokines in rat alveolar macrophages during mechanical ventilation.

Regional anaesthesia

Administration of local anaesthetics was designed to provide intraoperative anaesthesia and postoperative analgesia. However, in recent years it has become clear that regional administered local anaesthetics have benefits far beyond anaesthesia and pain relief; indeed, the technique has significant impact on the outcome of major surgical procedures. A recently published meta-analysis concluded that neuraxial anaesthesia using local anaesthetics decreased overall mortality by approximately one third, reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression

by 59%. There were also reductions in myocardial infarction and renal failure *(26)*. In addition, epidural anaesthesia using local anaesthetics has been shown to attenuate the endocrine and metabolic response to upper abdominal surgery, to reduce postoperative ileus, and to shorten duration of intubation and intensive care stay in patients undergoing abdominal aortic operations.

Local anaesthetics modulate the inflammatory response *in vivo (27)*. They prevent or reduce inflammatory disorders, such as reperfusion injury in heart *(28, 29, 38)*. Beneficial effects of local anaesthetic treatment in inflammatory bowel diseases are well documented *(39, 40)*. In contrast to corticosteroids, which depress the inflammatory response and impact negatively on postoperative outcome, local anaesthetics selectively inhibit only overactive responses of the inflammatory and haemostatic systems without affecting normal function *(41, 42)*. Local anaesthetics decrease inflammation without increasing the susceptibility to infections, and prevent postoperative thrombotic events without increasing bleeding.

The study was demonstrated that intravenous lidocaine effectively prevents postoperative thrombotic events, without increasing bleeding *(3, 10, 47)*. Similar effects to those obtained after epidural administration of local anaesthetics, and can potentially be explained by an antiinflammatory effect of local anaesthetics. That the effects are likely due to systemic absorption, and not to neuraxial block, is suggested by findings that epidural anaesthesia using local anaesthetic (leading to neuraxial blockade plus significant plasma local anaesthetic concentrations) prevents surgery-induced hypercoagulation *(41)*, whereas spinal anaesthesia (leading to neuraxial blockade but no significant plasma local anaesthetic levels) does not affect coagulation.

Local anaesthetics reduce postoperative ileus and duration of hospital stay *(35)*.

Recent findings demonstrate a neuroprotective effect after intravenous administration of local anaesthetics, leading to significant reduction in cognitive dysfunction after surgery *(4)*.

Mechanisms of action of local anaesthetics

The cellular substrate for these actions is likely to reside, in part, in the fact that priming, but not activation, that neutrophils is inhibited by local anaesthetics *(44, 23)*. Priming refers to a process whereby the response of neutrophils to a subsequent activating stimulus is potentiated. Release of oxygen metabolites is markedly enhanced when neutrophils have previously been primed. The priming process has been shown to be a critical component of neutrophil-mediated tissue injury both in vitro and *in vivo (5),* and inhibition of this process by local anaesthetics would be expected to reduce such injury. The mechanisms underlying these actions of local anaesthetics on priming have not been elucidated in detail, but selective inhibition of Gq protein function by local anaesthetics has been demonstrated recently *(45)*. Since Gq protein is important for many inflammatory and haemostatic signalling pathways, the effects of local anaesthetics might be explained at least in part by functional inhibition of Gq protein. The antithrombotic actions of local anaesthetics might result in part from inhibition of Gq protein function in platelets. There is strong evidence for an inflammatory modulating action of local anaesthetic, and it is reasonable to hypothesise that this effect explains why continuous intravenous administration of these compounds in the perioperative period has several beneficial effects, similar to those obtained with epidural administration. However, the underlying molecular and cellular mechanisms of those actions are not applying them to manage the inflammatory response during surgery, could open possibilities for a new, effective therapeutic approach to prevention of postoperative disorders.

Regional anaesthesia-analgesia attenuates perioperative immunosuppression. The hypothesis that patients who receive combined propofol/paravertebral anaesthesia-analgesia (propofol /paravertebral) exhibited reduced levels of protumorigenic cytokines and matrix metalloproteinases (MMPs) and elevated levels of antitumorigenic cytokines compared with patients receiving sevoflurane anaesthesia with opioid analgesia (sevoflurane/opioid). Regional anaesthesia-analgesia for cancer surgery alters a minority of cytokines influential in regulating perioperative cancer immunity *(50)*.

However, any reduction of immunosupression is less expressed in regional – spinal anaesthesia. Local anaesthetics lidokain and bupivacain have influence on a release of IL-1 beta from human lymphocytes in vitro reducing chemotaxial and fagocite activity of neutrofiles and inhibits motogen-induced proliferation of lymphocytes *(51, 52, 53, 54, 55)*. However, the influence of levobupivacain that we shall apply to a spinal area, on T lymphocytes and production of cytokine has not yet been explored *(56, 57, 58)*.

CONCLUSION

General or regional anaesthesia alone, without operation, has periodical and minimum effects to immunological system. It is established that various anaesthesiological procedures in the same operation cause various trend of alteration of cytokine level in serum. Spinal anaesthesia results in less immunosupression, i.e. maintains the number of Th1 cells, thus stimulating the cell immunity. Serious disorder of immunological system may cause complications as there are disorders in wound healing, increased number of infections, non-adequate response to the stress, multiorganic suppression and increased incidency of metastases.

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