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Systemic cytokine response after major surgery

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The systemic cytokine response to major surgical trauma was studied in 20 patients undergoing elective aortic surgery and five patients after inguinal hernia repair. Tumour necrosis factor alpha and interferon gamma were not detected in these patients. An early and short-lived interleukin 1 beta (IL-1β) response to major surgery was detected only by intensive sampling in the perioperative period. The IL-1β peak preceded a more marked interleukin 6 (IL-6) response that peaked 4–48 h after surgery. IL-6 levels had fallen sharply by 48–72 h in all patients who had an uneventful postoperative course. The IL-6 peaks were significantly lower after hernia surgery than after major aortic operations ($P < 0.001$); IL-1β was not detected in any samples. Three patients undergoing aortic surgery developed unexpected major postoperative complications. IL-6 levels in this group were significantly higher than those of the other patients undergoing aortic surgery within 6–8 h of skin incision, and remained elevated for longer. These rises in plasma IL-6 levels preceded the clinical onset of major complications by 12–48 h. The systemic IL-1β and IL-6 response to surgical trauma increased with the severity of the surgical insult. An early, exaggerated IL-6 response was associated with the subsequent clinical development of major complications.

Surgery and trauma induce a generalized state of immunodepression[1] that correlates with sepsis[2] and late death[3]. Cytokines, which are polypeptides produced by cells of the immune system and a variety of other tissues, act as mediators of the immune and acute-phase responses. Each cytokine mediates a variety of frequently overlapping effects and their actions can be additive.

Tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) are major mediators of the acute-phase response in humans. TNF-α and IL-1β are considered to be primarily responsible for the non-hepatic manifestations of the response such as fever, elevated prostaglandin levels, tachycardia and accelerated catabolism[4]. IL-6 *in vitro* is primarily responsible for the hepatic component of the acute-phase response, resulting in the synthesis of acute-phase proteins[5,6]. IL-1β and TNF-α also induce synthesis of acute-phase proteins, in particular C-reactive protein (CRP)[7–9]. The transcription and production of IL-6 in fibroblasts, endothelial cells, keratinocytes and monocytes is enhanced *in vitro*[10–13] by IL-1β and TNF-α. There is evidence, therefore, that IL-1β and TNF-α may be partly responsible for the induction of IL-6. All of these cytokines may then mediate the acute-phase response.

These cytokines all have immunostimulatory capabilities; interferon gamma (IFN-γ) acts primarily on monocytes and macrophages to enhance cell-mediated cytotoxicity. The release of these cytokines may therefore represent an attempt by the body to counter the observed immunodeficiency associated with injury or sepsis. Immunotherapy in oncological and inflammatory conditions centres around the evaluation of the administration of cytokines and their inhibitors in various disease states.

The measurement of cytokines in the peripheral blood has proved difficult and most reports in humans have been of sporadic detections involving single or daily measurements. There have been few attempts to assay cytokines over a series of times during an acute illness or after severe trauma. TNF-α has seldom been detected except after endotoxin administration, which does not induce a detectable IL-1β response *in vivo*[14]. Shenkin *et al.*[15] recently detected a consistent rise in the serum concentration of IL-6 in elective surgical patients but were unable to detect such a rise in IL-1β or TNF-α; these patients had an uncomplicated clinical course and the difference between a pathological and a physiological IL-6 response remains unclear.

This study examined patients before, during and after major surgery, exploring the association between plasma cytokine levels, the clinical course and CRP response. The levels of IL-1β, IL-6, TNF-α and IFN-γ were assessed in patients undergoing elective aortic aneurysm surgery. This provided a relatively uniform population in terms of age and general health undergoing comparable surgical insult. The patients did not have malignant disease and were at relatively low risk of bacterial contamination and sepsis. The impact of major surgical trauma on cytokine levels was therefore evaluated without the conflicting influences of bacterial infection or malignancy on the immune system.

A smaller group of patients undergoing inguinal hernia repair was assessed to determine whether the cytokine response was related to the magnitude of surgical trauma.

Patients and methods

Subjects

Group 1 consisted of 20 patients (17 men and three women) aged between 59 and 83 years undergoing elective aortic aneurysm repair. Operative and postoperative details were recorded, including the duration of operation, aortic clamping and ventilation, the blood transfusion volume, postoperative temperature, leucocyte count and APACHE II scores. APACHE II scoring was performed on the initial and worst physiological parameters during the first 24 h after surgery.

Group 2 consisted of five patients (four men and one woman) aged between 55 and 78 years who underwent elective inguinal hernia repair. The studies were approved by the Central Oxford Research Ethical Committee.

Samples

Cold-spun plasma was prepared from venous blood collected in pyrogen-free tubes containing ethylenediamine tetra-acetic acid (0·34 mmol/l). Aliquots of plasma were stored at −70°C. A preliminary study showed that using tubes containing aprotinin conferred no advantage.

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