Changes in the Levels of Serum-Soluble Interleukin-2 Receptor After Surgical Stress

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Abstract

Purpose. Surgical stress induces alterations in numerous physiological functions, including the cell-mediated immune response. It is known that interleukin-2 receptor (IL-2R) is released from its specific affinity membrane receptor on activated T lymphocytes and then is detected as a form of the α-chain of the IL-2R in the bloodstream. The levels of serum-soluble IL-2R (sIL-2R) reflect the quantity of activated T lymphocytes. This study investigated the changes in the serum sIL-2R levels and the relationship of such changes with other cytokines and the number of lymphocytes after abdominal surgery.

Methods. Twenty-four patients who were scheduled to undergo abdominal operations were enrolled in this study. Blood samples of these cases were collected before surgery, and on postoperative days (POD) 1, 3, 7, and 14. The levels of serum sIL-2R were measured by an enzyme-linked immunosorbent assay.

Results. The levels of serum sIL-2R achieved the maximal values on POD 1, and gradually decreased until POD 14. The levels of serum sIL-2R on POD 1, 3, and 7 were significantly higher than the preoperative levels. There was a significant and positive correlation between the levels of serum sIL-2R and serum IL-6. There were significant and positive correlations between the levels of sIL-2R and the number of white blood cells and neutrophils. Conversely, there was a significantly negative correlation between the levels of serum sIL-2R and the number of lymphocytes.

Conclusions. As high levels of serum sIL-2R were recognized after abdominal operations, the proliferation of T lymphocytes might still be highly activated in a state of surgical stress, though it is popularly acceptable that surgical stress induces a suppression of cell-mediated immunity.

Key words Serum-soluble interleukin-2 receptor · Cytokine · Surgical stress

Introduction

Surgical intervention induces numerous physiological dysfunctions, including a depression of the cell-mediated immune response. It is generally known that it induces a profound but transient depletion of all types of circulating lymphocytes, which may contribute to postoperative immunosuppression. Cytokines (tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), etc.), which are polypeptides produced by cells of the immune system and a variety of other cells, act as mediators of the immune response after surgery. Recent studies have shown that surgical stress results in an imbalance of cell-mediated (Th1) and humoral (Th2) immune response. Naive T cells (Th0 cell) produce various mixtures of cytokines and it is difficult to identify Th1/Th2. As a result, Th0 cells are matured by IL-2 to Th1 cells and Th2 cells. Th1 cells produce interferon-γ, interleukin (IL)-2, transforming growth factor (TGF)-β, etc., and are also related to cell-mediated immunity. On the other hand, Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, which induce humoral immunity. According to recent studies, IL-2, a glycoprotein with a molecular weight of 15,500 Da, plays an integral function in the growth and activation of T lymphocytes. However, as the short circulation half-life of IL-2 is less than 10 min, it is generally difficult to detect IL-2 in the bloodstream of patients. On the other hand, interleukin-2 receptor (IL-2R) is released from its specific affinity membrane receptor on activated T lymphocytes and detected as a form of the α-chain of the
IL-2R in the bloodstream (Fig. 1). Therefore, the levels of serum-soluble IL-2R (sIL-2R) can reflect the activity of IL-2 that attaches its receptor and the status of T-lymphocyte proliferation. Serum sIL-2R is easily detectable in the bloodstream, as the half-life of IL-2R is relatively long. High concentrations of serum soluble IL-2R can be recognized in the patients not only with malignancy but also with inflammatory diseases. However, there have been few reports on the changes in the serum sIL-2R concentrations in patients after surgical stress. Therefore, this study investigated the changes in the serum-soluble IL-2R levels and the relationship of such changes with other cytokines to clarify the status of cell-mediated immunity after surgical stress. Furthermore, we also referred to the etiology of the decrease of lymphocytes in the bloodstream after surgical stress.

Materials and Methods

Patients

We selected 24 patients who were scheduled to undergo various gastrointestinal operations without any postoperative complications. One for esophageal cancer (subtotal esophagectomy), 11 for gastric cancer (total gastrectomy 5, distal gastrectomy 6), 7 for rectal cancer (low anterior resection 3, Miles’ operation 4), one for transverse colon cancer (right hemi-colectomy), and 4 for sigmoid colon cancer (sigmoidectomy) were enrolled in this study. Blood samples of these patients were collected before surgery, and on postoperative days (POD) 1, 3, 7, and 14. After centrifugation, the cell-free supernatants were stored at −80°C for later assays. Written informed consent for this study was obtained from all patients.

Methods

The levels of serum sIL-2R were measured by an enzyme-linked immunosorbent assay (ELISA) using CELLFREE interleukin-2 receptor kits (Yamanouchi, Tokyo, Japan), according to the manufacturer’s instructions. Briefly, the serum samples were reacted with a monoclonal antibody that recognized one epitope of human soluble IL-2R. After 2h of incubation and washing, horseradish peroxidase-conjugated monoclonal antibody directed to a second epitope was added. This bound to the IL-2R captured by the first monoclonal antibody. The color reaction was terminated by the addition of 2N H₂SO₄ and absorbance was measured at 490nm. According to the manufacturer’s instructions for CELLFREE interleukin-2 receptor kits, a normal range of serum-soluble IL-2R in a healthy control is 121–382 U/ml.

The levels of serum immunosuppressive acidic protein (IAP) were measured by a turbidimetry immunoassay, using human anti-IAP serum (purchased from Sanko, Tokyo, Japan). An IAP value of less than 500 mg/ml is considered to be normal.

The levels of serum IL-1β and IL-6 were measured by an ELISA kit (ImmuneTech, Marseille, France). The serum concentrations of IL-4 and IL-10 were measured by an enzyme amplified sensitivity immunoassay kit (Biosource, Nivelles, Belgium). The concentration of IL-8 was measured by an ELISA kit (TFB, Tokyo, Japan).

Statistics

The results are presented as the mean ± standard error of the mean. The data were analyzed with the analysis of variance (ANOVA) procedure and the linear correlation coefficient. A P value of less than 0.05 was considered to be statistically significant.

Results

The levels of serum sIL-2R achieved the maximal values on POD 1, and gradually decreased until POD 14. The levels of serum soluble IL-2R on POD 1, 3, and 7 were significantly higher than the preoperative levels (Fig. 2 and Table 1). A significant increase in the levels of serum IL-6 was observed on POD 1, compared with those on the preoperative day (Table 1). A slight increase in the levels of serum IL-8 was recognized on POD 1 and 3, and returned on POD 7 to the value of the preoperative day (Table 1). Serum IL-4 could be detected in one case on POD 1, in three cases on POD 3, and in one patient on POD 7, but the levels were too low to evaluate the trend of the postoperative changes.