

Changes in Serum Granulocyte Colony-Stimulating Factor Concentration after Gastrointestinal Surgery

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Granulocyte colony-stimulating factor (G-CSF; normal range < 30 pg/ml) is a cytokine that stimulates the proliferation and activation of neutrophils. In this study, we investigated changes in the plasma G-CSF level after gastrointestinal surgery. The subjects were 23 patients undergoing subtotal esophagectomy (Group E, n = 8), pancreaticoduodenectomy (Group P, n = 5), radical total gastrectomy (Group G, n = 5), or cholecystectomy (Group C, n = 5). In addition to G-CSF, duration of surgery, transfused fluid volume, C-reactive protein (CRP) concentration and neutrophil counts were recorded. G-CSF levels just after surgery were $3,301 \pm 2,130$ pg/ml (mean \pm SD), $1,442 \pm 180$ pg/ml, 941 ± 538 pg/ml, and 111 ± 73 pg/ml for patients in groups E, P, G and C, respectively. G-CSF levels were correlated with postoperative maximum CRP, the duration of surgery and the transfused fluid volume during the operation. The results show that extensive surgical procedures are associated with higher postoperative plasma G-CSF levels, suggesting that the increase in plasma G-CSF may be due to activation of the host defense in response to surgical stress.

Key words : gastrointestinal surgery
granulocyte colony-stimulating factor

Introduction

In recent years, the roles of cytokines in host defenses against invasion and in the ensuing acute-phase reactions have been elucidated gradually¹⁻³. Consequently, some cytokines, such as interleukin-6 (IL-6) has been regarded as an index of the magnitude of inflammation or surgical invasions^{4,5}.

Granulocyte colony-stimulating factor (G-CSF) is a cytokine produced by macrophages and interstitial cells at the site of surgical invasion in response to tissue damage and cell injury. G-CSF acts specifically both to increase the number of neutrophils and to activate them^{5,6}. The present study was carried out to determine whether G-CSF could serve as an index of surgical invasiveness in patients undergoing a variety of gastrointestinal surgical procedures.

Patients and Methods

The subjects in this study were 23 patients who were admitted to the intensive care unit or the post-anesthetic recovery room after gastrointestinal surgery at Oita Medical University Hospital during the period from December 1991 to May 1992. As shown in Table 1, the patients were divided into four groups according to the type of surgical procedure: group E, subtotal esophagectomy followed by reconstruction with the stomach (n = 8); group P, pancreaticoduodenectomy (n = 5); group G, radical total gastrectomy (n = 5); and group C, cholecystectomy (n = 5).

In a preliminary experiment, the time course of changes in the level of G-CSF was studied in 8 patients with esophageal cancer, from whom a blood sample was drawn before surgery (control), immediately after the operation, and on the 1st, 3rd, 5th, and 7th postoperative days (PODs) (Fig. 1). The plasma G-CSF reached its peak immediately after the operation. Based on these results, blood samples from other patients were drawn only once immediately after operation. A 5-ml aliquot of each blood sample was centrifuged at 3,000 rpm for 10 min. The plasma was separated, frozen immediately and stored at -20°C until analysis. We used the enzyme immunoassay (EIA) technique reported by Motozima et al.⁷ to measure the plasma G-CSF level. The limit of sensitivity of this assay method was 30 pg/ml.

The parameters of surgical invasiveness including the duration of surgery, blood loss, total volume of fluid infused during the operation, maximum postoperative neutrophil counts and maximum postoperative C-reactive protein (CRP) levels were also recorded for comparison with plasma G-CSF levels. The two patients who developed serious postoperative complications, such as leakage or sepsis, were excluded from the study.

The results are expressed as means \pm SD. The results of repeated measures and multiple groups were analyzed by one-way analysis of variance. Multiple pairwise comparisons between groups were assessed by Scheffe's test. Correlation coefficients between parameters were calculated by regression analysis. Differences and correlations

Table 1. Patient Characteristics

Group	Surgery	Age(yr)	Duration(min)	Blood loss(g)	Fluid(ml)
Group E n=8	Esophagectomy	69.3±2.3	674±63	871±148	5,072±993
Group P n=5	Pancreaticoduodenectomy	63.6±3.7	504±53 ^a	1,440±230 ^a	4,504±763
Group G n=5	Total gastrectomy	71.8±3.4	304±25 ^{a,b}	402±95 ^{a,b}	2179±1,123 ^{a,b}
Group C n=5	Cholecystectomy	58.6±6.4	100±14 ^{a,b,c}	38±5 ^{a,b}	1,510±403 ^{a,b}

^ap < 0.05 vs. Group E, ^bp < 0.05 vs. Group P, ^cp < 0.05 vs. Group G

Table 2. Maximum Absolute Neutrophil Counts (ANC) and C-Reactive Protein (CRP) before and after Surgery

Group	ANC/mm ³		CRP (mg/dl)	
	Before surgery	After surgery	Before surgery	After surgery
Group E n=8	3,010±680	6,920±640 ^a	0.5±0.1	25.2±7.1
Group P n=5	2,370±520	6,830±690 ^a	(-)	17.3±5.4
Group G n=5	2,360±790	8,440±3,280 ^a	(-)	9.0±3.2 ^b
Group C n=5	3,000±680	6,990±2,260 ^a	(-)	8.1±4.3 ^b

^ap < 0.05 vs. before Surgery, ^bp < 0.05 vs. Group E

were considered statistically significant when p was less than 0.05.

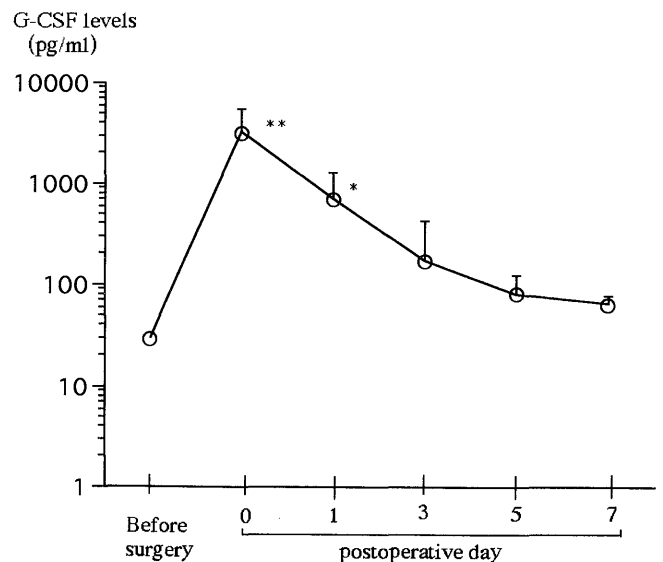
Results

In each group, the postoperative maximum absolute neutrophil counts (ANC) increased 2-3 times over that before operation (Table 1). However, there were no significant differences in postoperative maximum ANC among these groups. Postoperative maximum CRP, duration of surgery, blood loss, and total volume of fluid infusion during operation differed significantly among the groups. The maximum CRP level of Group E was significantly higher than that of Groups G and C. The duration of surgery was longest in Group E and shortest in Group C (Table 1). Blood loss was greatest in Group P and least in Group C. Transfused fluid volume during operation was greatest in Group E and least in Group C (Table 2).

Figure 1 shows the time course of G-CSF in patients undergoing esophageal operation. Although the plasma G-CSF before operation was below the limit of sensitivity in all patients, it is indicated as 30 pg/ml the detection limit in the figure. The plasma G-CSF reached a peak of $3,301 \pm 2130$ pg/ml, which was a dramatic increase from the control. On the 1st POD day, the plasma G-CSF decreased but remained at a significantly high level. Plasma G-CSF continued to decline until the 7th POD. Plasma G-CSF concentrations after the operations were: $1,442 \pm 180$ pg/ml in group P, 941 ± 538 pg/ml in group G, and 111 ± 73 pg/ml in group C (Fig. 2).

Figure 3 shows the correlation between G-CSF and CRP in the all patients studied. Plasma G-CSF was correlated

significantly with the postoperative maximum CRP level ($R = 0.78$). The plasma G-CSF level was also correlated significantly with the operative time and the total volume of fluid infused during the operation, with correlation coefficients of 0.71 and 0.64, respectively ($p < 0.01$). However the G-CSF level showed no correlation with the amount of intraoperative blood loss or maximum postoperative neutrophil count.



Mean ± SD; N=8 for each point. Plasma G-CSF levels reached a peak just after surgery. On the 1st, 3rd, 5th and 7th postoperative days, there was time-related decrease in the G-CSF levels.

*p < 0.05 vs. before surgery; **p < 0.01 vs before surgery.

Fig. 1 Plasma G-CSF levels after subtotal esophagectomy

Discussion

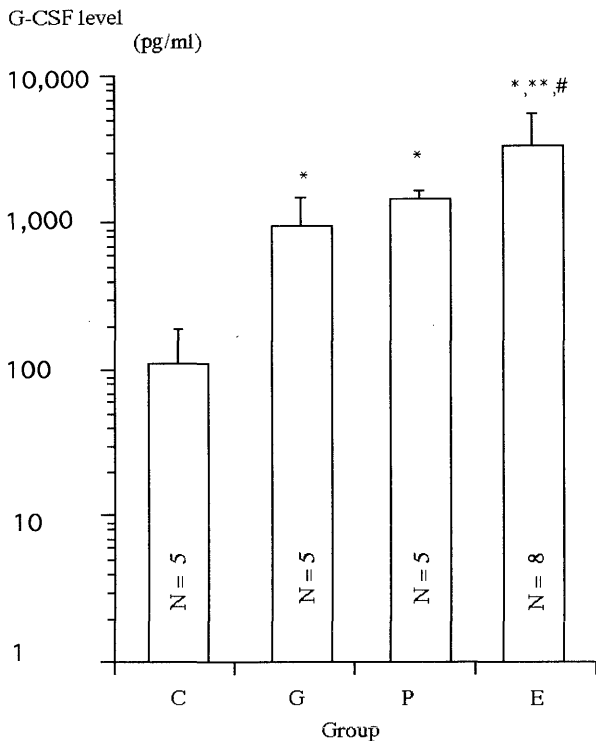
Surgical procedures trigger several host defense reactions, called as acute phase responses, which involve the immune, metabolic, and neuroendocrine systems. The extent of these reactions depends on the magnitude of the surgical stress. While interleukin-1 (IL-1) and tumor

necrosis factor (TNF) have attracted attention as mediators of acute phase response, they are difficult to detect in the blood. For this reason, reports of the potential of cytokines as indicators of the invasiveness of surgical procedures are currently limited to IL-6^{4,5}.

The present results show that G-CSF increases sharply in response to surgical invasion, and this cytokine is easily detected in blood, and suggest that, like other cytokines, G-CSF production follows various stresses including inflammation or surgery. The increase in the postoperative plasma concentration of G-CSF differs in each surgical procedure. The order of magnitude is as follows: cholecystectomy < radical total gastrectomy < pancreaticoduodenectomy < subtotal esophagectomy. These findings suggest that the more invasive procedures are associated with the higher plasma G-CSF levels. The time course of plasma G-CSF in the present study is similar to that of IL-6 reported previously⁵. Our results show that the plasma G-CSF concentrations were correlated closely with post operative maximum CRP levels. IL-6 production stimulated by IL-1 and TNF and was reported to induce CRP production in the liver and thus to be correlated with CRP. Also, G-CSF is considered to be stimulated by IL-1 or TNF and G-CSF was correlated with CRP in this study. Therefore, G-CSF is considered to be stimulated by IL-1 and TNF to the same degree as IL-6. The plasma G-CSF levels were also correlated with the duration of surgery and the total volume of fluid infused. The fluid volume infused is thought to represent surgical invasiveness, because it would depend on the thirdspace or the tissue edema caused by the surgical procedure. These results suggest that plasma G-CSF levels reflect the magnitude of surgical invasion similarly to IL-6.

G-CSF is produced by macrophages and interstitial cells at the site of tissue damage¹. Through the effects of G-CSF on bone marrow, it increases the peripheral blood neutrophil counts and activates them^{6,9,10}. Thus, G-CSF plays an important role in the host defense mechanism in the early stages of tissue damage.

In this study, we also measured neutrophil counts before and after operation with the expectation that they might reflect the severity of surgical invasiveness. Although the neutrophil counts were significantly higher after the operation compared with preoperative control values, there was no correlation with plasma G-CSF levels. Neutrophil counts and CRP levels respond to G-CSF and IL-6, respectively, and are considered to be indicators of the severity of inflammation. Our findings suggest two possible explanations for the absence of correlation between G-CSF and the neutrophil count. Firstly, in spite of the elevated G-CSF level, increased neutrophils might be exhausted or sequestered⁸. Secondly, although the G-CSF concentration increased in response to the surgical stress, the effect of G-CSF on neutrophils might have a ceiling effect.



*p < 0.05 vs group C, **p < 0.05 vs group G, *p < 0.05. vs group P

Fig. 2 Plasma G-CSF levels after gastrointestinal surgeries (mean±SD).

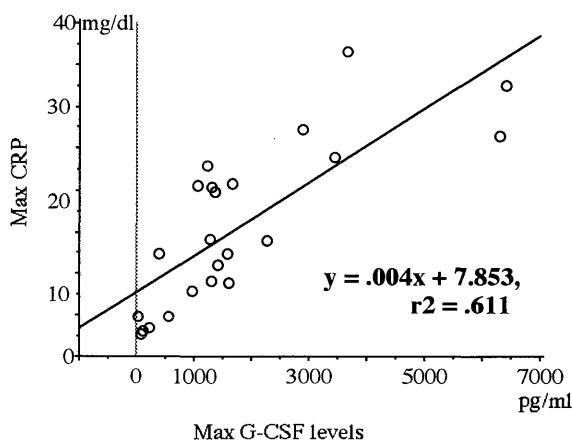


Fig. 3 The correlation between postoperative maximum plasma levels of CRP and G-CSF.

In conclusion, more extensive surgical procedures are associated with higher postoperative plasma G-CSF levels suggesting that plasma G-CSF may be a useful clinical index of the magnitude of the host-defense response to surgical stress.

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