Surg Today (2000) 30:403–409

SURGERY TODAY

Original Articles

Significant Changes in the Serum Levels of IL-6, h-HGF, and Type IV Collagen 7S During the Perioperative Period of a Hepatectomy: Relevance to SIRS

KOJI NAMEKATA, SHIGERU TAKAMORI, KUNIAKI KOJIMA, TOMOE BEPPU, and SHUNJI FUTAGAWA

Second Department of Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Abstract: We analyzed the changes in the serum levels of both interleukin-6 (IL-6), human hepatocyte growth factor (h-HGF), and type IV collagen 7S (7S) during the perioperative period of a hepatectomy and evaluated their relationship with systemic inflammatory response syndrome (SIRS). The study subjects consisted of 40 patients who underwent a hepatectomy. In 14 out of 40 patients, postoperative SIRS(+) was observed. Between the SIRS(+) and SIRS(−) cases, there were significant differences in the preoperative values of prothrombin time, hepaplastin test, cholinesterase, and indocyanine green retention at 15 min ($P < 0.01$). Compared with the SIRS(−) cases, the IL-6, h-HGF, and 7S of the SIRS(+) cases fluctuated in a higher range and remained significantly higher after postoperative day 1 ($P < 0.05$). Eight out of 14 SIRS(+) patients had postoperative complications. In the 8 SIRS(+) patients with postoperative complications and in the 4 patients in which the SIRS(+) state lasted 3 days or longer, the 7S levels were significantly higher during the perioperative period ($P < 0.05$). In the SIRS(+) cases, the postoperative levels of IL-6 and h-HGF, as well as pre- and postoperative levels of 7S, were elevated. We therefore consider these levels to be risk factors for complications during the perioperative period of a hepatectomy.

Key Words: interleukin-6, human hepatocyte growth factor, type IV collagen 7S, systemic inflammatory response syndrome

Introduction

In recent years, the concept of systemic inflammatory response syndrome (SIRS)[1] has been commonly applied to specific clinical symptoms, including fever, tachycardia, and leukocytosis, caused by various invasive maneuvers. In the field of gastrointestinal surgery, most of the cases with SIRS symptoms immediately after surgery and a number of humoral factors, especially proinflammatory cytokines, have been considered to be of great importance. Proinflammatory cytokines are known to play an important role in the progression from SIRS and a septic condition to multiple organ dysfunction syndrome (MODS).[2,3] The most common underlying complications in hepatectomy cases include liver dysfunction due to the basal disease of chronic hepatitis and liver cirrhosis. Such conditions may readily lead to postoperative liver failure and MODS. However, the exact pathophysiological mechanism involved in the onset of multiple organ failure after a hepatectomy has yet to be elucidated. In response to such cytokines, the liver produces both acute phase proteins and various cytokines.[4] In several reports, interleukin-6 (IL-6) and human hepatocyte growth factor (h-HGF) have been measured during the perioperative period of a hepatectomy and found to be significant indicators of surgical stress.[5,6] In addition, the level of type IV collagen 7S, which is a marker for liver fibrosis, has been known to have significant predictive value for postoperative complications in hepatectomy cases with underlying liver dysfunction.[7] We measured the serum levels of IL-6, h-HGF, and 7S over the postoperative course, and studied their relationship to the liver function tests and SIRS. Consequently, we attempted to determine whether or not the IL-6, h-HGF, and 7S levels measured during the perioperative period are significant predictive factors for complications.

Materials and Methods

The study subjects included 40 patients, who underwent a hepatectomy from 1994 to 1997 (average age of 58.1 and a male to female ratio of 7 : 1) at the Second Department of Surgery, Juntendo University Hospital, and

Reprint requests to: K. Namekata
(Received for publication on Dec. 14, 1998; accepted on Nov. 11, 1999)

preoperatively did not demonstrate SIRS. Among these 40 patients, 26 had hepatocellular carcinoma, 9 metastatic liver tumor, 2 cholangiocellular carcinoma, and 1 each of combined hepatocellular and cholangiocarcinoma, bile duct cystadenocarcinoma, and liver hemangioma. In 22 patients (55%) there was histological evidence of liver cirrhosis as a background factor. The mean operating time was 276 min, the mean blood loss was 1201 ml, and the mean weight of the resected liver was 308 g. Ten patients underwent a partial resection, 10 a subsegmental resection, 11 a unisegmental resection, and 9 a bisegmental resection. The SIRS(+) cases were defined as those in which the SIRS diagnostic criteria (Table 1) were fulfilled on the second day after the operation.[1] Sepsis was defined as a SIRS accompanying infection.[1] Postoperative complications were included only when medical or interventional treatment was given.

The serum levels of IL-6, h-HGF, and 7S were measured during the perioperative period of a hepatectomy, and were analyzed separately in the SIRS(+) and SIRS(−) groups. In addition, the relationship between the changes in the liver function tests before and after a hepatectomy was comparatively analyzed.

For each case, peripheral venous blood samples were obtained before the operation, immediately after the operation (0), and on postoperative days (POD) 1, 3, 5, and 7. The separated serum was preserved at −80°C for measurement of IL-6, h-HGF, and 7S. The IL-6 was measured by CLEIA (Fuji-Revio, Tokyo, Japan), the h-HGF by the ELISA kit (Ohtsuka-Assay Laboratories, Tokushima, Japan) and the 7S by the RIA kit (Japan DPC, Tokyo, Japan).

Statistical Analyses

Statistical analyses of the results were made using the Mann-Whitney *U*-test. Differences in proportions were compared using a χ^2 test or Fisher's Exact test. Simple regression analyses were performed to assess the correlations of the serum levels of IL-6, h-HGF, and 7S, and the correlations of these cytokine levels and liver function tests were also determined. The results are presented as the mean ± standard error. A *P* value of less than 0.05 was considered to be statistically significant.

Table 1. Criteria for SIRS

SIRS to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:	
1. Temperature	>38°C or <36°C
2. Heart rate	>90 beats/min
3. Respiratory rate	>20 breaths/min or $PaCO_2$ < 32 torr (4.3 k Pa)
4. WBC count	>12 000 cells/mm^3, <4 000 cells/mm^3 or >10% immature (bands) forms

SIRS, systemic inflammatory response syndrome; WBC, white blood cell

Results

SIRS and Changes in the Serum IL-6, h-HGF, and 7S Levels

The changes in the serum levels of IL-6, h-HGF, and 7S of the SIRS(+) group were compared with those of the SIRS(−) group. The mean IL-6 level in the SIRS(+) group was 4.5 ± 0.6 pg/ml before the operation, 136 ± 23 pg/ml on POD 0, 145 ± 41 pg/ml on POD 1, 70 ± 15 pg/ml on POD 3, 30 ± 5 pg/ml on POD 5, and 36 ± 7 pg/ml on POD 7. The IL-6 level peaked on POD 1. The postoperative values were significantly higher than the corresponding values for the IL-6 levels in the SIRS(−) group ($P < 0.05$). Furthermore, in the SIRS(−) group, the IL-6 levels peaked on POD 0, and gradually decreased thereafter. The h-HGF levels in the SIRS(+) group were 0.34 ± 0.03 ng/ml before the operation, 0.45 ± 0.05 ng/ml on POD 0, 0.59 ± 0.08 ng/ml on POD 1, 0.55 ± 0.06 ng/ml on POD 3, 0.47 ± 0.06 ng/ml on POD 5, and 0.46 ± 0.04 ng/ml on POD 7. The h-HGF level peaked on POD 1. The h-HGF levels were significantly higher on POD 1, 3, and 7 in the SIRS(+) than in the SIRS(−) group ($P < 0.05$). In the SIRS(−) group, the levels peaked on POD 1, and gradually decreased thereafter. The 7S level in the SIRS(+) group was 6.6 ± 0.4 ng/ml before the operation, 6.4 ± 0.5 ng/ml on POD 0, 8.9 ± 0.6 ng/ml on POD 1, 8.9 ± 0.4 ng/ml on POD 3, 7.4 ± 0.7 ng/ml on POD 5, and 7.2 ± 0.6 ng/ml on POD 7. The levels peaked on POD 1 and 3. The 7S levels on POD 1, 3, and 7 were significantly higher in the SIRS(+) than those in the SIRS(−) group ($P < 0.05$). In addition, in the SIRS(−) group, the levels peaked on POD 3, and then gradually decreased thereafter (Fig. 1).

Relationship Between SIRS and the Maximum IL-6, h-HGF, and 7S Levels

The maximum postoperative levels of IL-6, h-HGF, and 7S in the SIRS(+) group were compared with those in the SIRS(−) group. The maximum IL-6 level was 223 ± 32 pg/ml in the SIRS(+) group, which was significantly higher than the level of 95 ± 10 pg/ml observed in the SIRS(−) group ($P < 0.01$). The maximum levels of h-HGF and 7S in the SIRS(+) group were 0.7 ± 0.08 ng/ml and 9.7 ± 0.6 ng/ml, respectively, which were also significantly higher than those in the SIRS(−) group ($P < 0.05$) (Fig. 2).

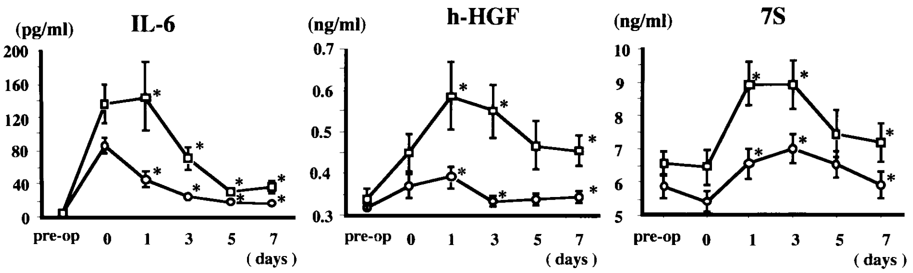

Fig. 1. Changes in the serum interleukin-6 (*IL-6*), human hepatocyte growth factor (*h-HGF*), and type IV collagen 7S (*7S*) levels after a hepatectomy with and without systemic inflammatory response syndrome (*SIRS*). Compared with the SIRS(−) cases (*circles*, $n = 26$), the IL-6, h-HGF, and 7S levels of the SIRS(+) cases (*squares*, $n = 14$) showed a greater range of fluctuation and a significantly higher than after POD 1 ($*P < 0.05$)

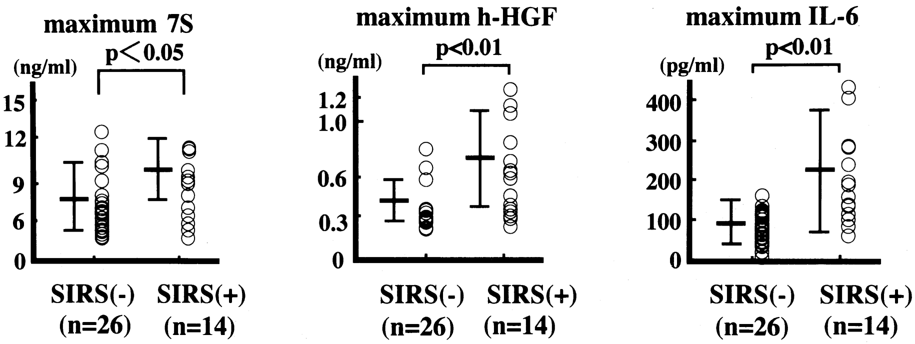

Fig. 2. Maximum serum IL-6, h-HGF, and 7S levels after a hepatectomy with and without SIRS. The postoperative maximum serum IL-6, h-HGF, and 7S levels of SIRS(+) cases were significantly higher than those of SIRS(−) cases

Table 2. Correlations between the maximum postoperative serum IL-6, h-HGF, and 7S levels and liver function tests (PT, HPT, ChE)

	PT (%)	HPT (%)	ChE (IU/l)
IL-6	$r = -0.55$ $P < 0.01$	$r = -0.4$ $P < 0.05$	$r = -0.38$ $P < 0.05$
h-HGF	$r = -0.42$ $P < 0.01$	$r = -0.41$ $P < 0.01$	$r = -0.41$ $P < 0.01$
7S	$r = -0.58$ $P < 0.01$	$r = -0.64$ $P < 0.01$	$r = -0.45$ $P < 0.01$

IL-6, interleukin-6; h-HGF, human hepatocyte growth factor; 7S, type IV collagen 7S; PT, activated prothrombin time; HPT, activated hepaplastin test; ChE, cholinesterase

Analyses of the Postoperative Maximum Levels of IL-6, h-HGF, and 7S and Liver Function Tests

The maximum postoperative IL-6 level negatively correlated with the serum level at activated prothrombin time (PT) ($r = -0.55$, $P < 0.01$) and the serum level in the activated hepaplastin test (HPT) ($r = -0.4$, $P < 0.05$). The maximum levels of h-HGF and 7S also showed a negative correlation with the serum levels of PT, HPT, and cholinesterase (ChE) (Table 2).

Preoperative and Intraoperative Parameters in SIRS Cases

Postoperatively, 14 patients developed SIRS(+) and 26 continued to demonstrate SIRS(−). The preoperative and intraoperative background data for the two groups are shown in Table 3. There were no significant differences between the two groups in terms of age, sex ratio, intraoperative blood loss, operating time, and the weight of resected liver. The preoperative liver function tests, and serum levels of PT, HPT, and ChE, were significantly lower in the SIRS(+) group than in the SIRS(−) group ($P < 0.01$). The value of indocyanine green dye retention rate at 15 min after the injection of 0.5 mg/kg (ICG-R_{15}) was significantly higher in the SIRS(+) group than in the SIRS(−) group ($P < 0.01$) (Table 3).

Preoperative IL-6, h-HGF, and 7S Levels and Postoperative Complications

The preoperative levels of IL-6, h-HGF, and 7S were estimated for their predictive relevance to postoperative complications. In the 8 SIRS(+) patients who developed postoperative complications, the preoperative levels of IL-6 and h-HGF did not significantly differ

Table 3. Background data for cases with and wihout SIRS

		SIRS (+) (n = 14)	SIRS (−) (n = 26)	P value
	Age	58 ± 2	58 ± 2	0.94
	Gender (M/F)	6:1	8:1	0.81
Operative findings	Blood loss (g)	1211 ± 198	1196 ± 134	0.95
	Operating time (min)	234 ± 18	285 ± 16	0.08
	Resected liver weight (g)	227 ± 50	358 ± 64	0.16
Preoperative liver function tests	PT (%)	81 ± 3	93 ± 2	<0.01
	HPT (%)	72 ± 5	86 ± 3	<0.01
	ChE (IU/l)	857 ± 64	1074 ± 51	<0.01
	T-Bil (mg/dl)	0.93 ± 0.1	0.83 ± 0.1	0.32
	ICG-R_{15} (%)	18.3 ± 3.4	9.8 ± 1.0	<0.01

Values are expressed as mean ± SE
T-Bil, total bilirubin; ICG-R_{15}, the value of indocyanine green dye retention rate at 15 min after the injection of 0.5 mg/kg

Table 4. Postoperative complications and the preoperative serum IL-6, h-HGF, and 7S levels

	(a) (n = 8)	(b) (n = 32)	P value	(c) (n = 4)	(d) (n = 36)	P value
IL-6 (pg/ml)	5.1 ± 1.0	4.0 ± 0.2	0.23	6.1 ± 1.8	4.0 ± 0.2	0.11
h-HGF (ng/ml)	0.34 ± 0.04	0.32 ± 0.01	0.94	0.39 ± 0.1	0.32 ± 0.01	0.57
7S (ng/ml)	7.2 ± 0.5	5.9 ± 0.2	P < 0.05	8.1 ± 0.7	5.9 ± 0.3	P < 0.05

Values are expressed as mean ± SE
(a) SIRS (+) and complications (+); (b) all cases other than (a); (c) SIRS (+) for 3 days or longer; (d) all cases other than (c)

from the control group. The preoperative 7S level, however, was 7.2 ± 0.5 ng/ml, which was significantly higher than the level of 5.9 ± 0.2 ng/ml measured in the SIRS(−) group and the cases without postoperative complications ($P < 0.05$). In the 4 patients that demonstrated SIRS(+) for 3 days or longer, no significant difference was found in the preoperative levels of IL-6 and h-HGF. However, the preoperative 7S level was 8.1 ± 0.7 ng/ml, which was significantly higher than the level of 5.9 ± 0.3 ng/ml measured in other cases ($P < 0.05$) (Table 4).

Postoperative SIRS(+) Period and Complications

The relationship between the duration of postoperative SIRS(+) and the development of complications was investigated. Complications were observed in 8 patients (20%) and consisted of: renal dysfunction (n = 5); intraperitoneal infection (n = 4); pneumonia (n = 2); and pleural effusion (n = 1). Six of the 14 patients (43%) with SIRS(+) showed the presence of sepsis. One SIRS(+) patient with sepsis developed MODS. In 14 SIRS(+) patients, the mean duration of the SIRS state was 2.3 days, and the period lasted for a day in 5 cases, 2 days in 5 cases, and 3 days or longer in 4 cases. Two out of 5 patients with SIRS(+) for a day (40%), 2 out of 5 patients with it for 2 days (40%), and 4 out of 4 patients with it for 3 days or longer (100%) developed postoperative complications (Table 5).

Discussion

Various factors have been investigated and analyzed in association with the development of complications after surgery. In addition, such factors as age, gender, operating time, volume of blood loss, the need for transfusion, and imbalance among the biological defense systems including the nervous system, endocrine system, and immune system have all been considered as causes. In the 1980s, various cytokines were discovered, and as their functions have been elucidated, increasing attention has been focused on those which act as mediators, thus inducing systemic inflammatory responses after trauma, burn injury, and infection. The concept of SIRS[1] has become well accepted in recent years, and the

Table 5. Relationship between postoperative complications and SIRS

Duration of SIRS	Frequency rate of complications	Complications
1 day (n = 5)	40%	Intraperitoneal infection (1 case), renal dysfunction (1 case)
2 days (n = 5)	40%	Intraperitoneal infection (1 case), intraperitoneal infection and renal dysfunction (1 case)
3 days or longer (n = 4)	100%	Intraperitoneal infection (1 case), renal dysfunction and pleural effusion (1 case), renal dysfunction and pneumonia (2 cases)

Renal dysfunction: serum creatinine level ≧ 1.0 mg/dl

state involving proinflammatory cytokines is now recognized as a step prior to the disease progression from postoperative complications or sepsis to MODS.[2,3] Several reports have indicated the importance of proinflammatory cytokines in the serum to the pathophysiology of surgical stress, rejection in organ transplantation, SIRS, and MODS.[2,8–11]

IL-6 is mainly produced by Kupffer and Ito cells in the hepatic sinusoids, by vascular endothelial cells, and by fibroblasts.[4,12,13] Serum IL-6 is a useful marker for the early prediction and diagnosis of SIRS and postoperative complications during the perioperative period,[14,15] since it promptly reflects the changes in biological response of the individual.[14–16] h-HGF is produced in the liver, kidney, and lung. Similarly to IL-6, h-HGF is produced by endothelial cells, and by Kupffer and Ito cells of the hepatic sinusoids.[17] The serum h-HGF level increased in association with hepatocellular dysfunction, hepatic necrosis, and systemic inflammation.[6,18,19] An elevated serum h-HGF level after a hepatectomy usually represents an unfavorable environment for the restoration of the liver function, and if such a condition persists, it may be necessary to prepare for progression to hepatic failure.[6] Type IV collagen, localized in the Disse space of the liver, is mainly produced by Ito cells of the hepatic sinusoids, endothelial cells, and hepatocytes during the early stage of liver dysfunction, and accumulates as fibrosis and liver impairment progress.[20] The 7S is a fragment located in the N-terminal domain of type IV collagen[21,22] and its measurement in cases complicated by various liver diseases has been reported to be extremely useful in predicting postoperative complications.[7,23]

In this study, we selected IL-6 and h-HGF as parameters, since they are relatively easy and reliable to measure as compared to the other serum cytokines. We also chose 7S because it is considered to be a useful preoperative predictor for postoperative complications. We next analyzed the correlations among these parameters, and evaluated their predictive worth for complications after a hepatectomy.

The serum levels of PT, HPT, and ChE, which are conventional indices of liver parenchymal cell injury after a hepatectomy, are still considered to be important and reliable laboratory data. After a hepatectomy, the serum IL-6, h-HGF, and 7S levels showed negative correlations with the serum levels of PT, HPT, and ChE (Table 2), thus suggesting a close association between the postoperative liver parenchymal cell injury and the nonparenchymal cell destruction. As a result, the serum IL-6, h-HGF, and 7S levels may be considered to be useful markers for estimating the degree of nonparenchymal cell injury after hepatectomy and evaluating the hepatic sinusoidal function.

Ever since the concept of SIRS has been proposed,[1] the systemic inflammatory response to infectious diseases, trauma, burns, and pancreatitis has been collectively discussed. All the clinical signs listed in the criteria for diagnosis of SIRS can be explained by cytokines, and SIRS is thus considered to be a state of hypercytokinemia.[9]

Although cytokine measurements are important in diagnosing SIRS, they play a more important role in determining whether or not SIRS develops during the recovery from the surgical stress or is induced by various complications.[15] However, it remains to be elucidated as to exactly when a diagnosis of SIRS in postoperative cases should be made. In the present study, we regarded the cases in which the diagnostic criteria were fulfilled on the second day after surgery to be SIRS(+), since the circulatory dynamics such as instabilities in blood pressure and pulse are generally stabilized by POD 2.

There were no significant differences of the serum IL-6, h-HGF, and 7S levels, measured before and immediately after surgery, between the SIRS(+) and the SIRS(−) groups. However, the serum IL-6, h-HGF, and 7S levels were significantly higher on POD 1 in the

SIRS(+) group than in the SIRS(−) group (Fig. 1). Therefore, SIRS(+) cases can be predicted by measuring the serum IL-6, h-HGF, and 7S levels on POD 1, and may thus allow for the early determination of cases likely to develop postoperative complications and MODS. In addition, considering the fact that progression to SIRS(+) is frequent in cases of liver dysfunction before operation (Table 3), SIRS(+) cases can be predicted by measuring the preoperative serum levels of PT, HPT, ChE, and ICG-R_{15}.

The frequency of postoperative complications is considered to depend on the duration of SIRS, rather than the number of SIRS-related signs.[24] In this study, all 4 patients in whom the SIRS(+) lasted for 3 days or longer developed postoperative complications. Renal dysfunction (serum creatinine level ≧1.0 mg/dl) is also considered to be associated with an increased incidence of SIRS and postoperative complications, since the cytokine clearance is reduced.[24] In this study, in 5 out of 8 SIRS(+) patients with postoperative complications the serum creatinine level was elevated to 1.0 mg/dl or higher, thus suggesting that the decrease in cytokine clearance is related to SIRS. In one patient the SIRS(+) lasted for 2 days, and was complicated by renal dysfunction (serum creatinine level of 1.67 mg/dl) and sepsis induced by intraperitoneal methicillin-resistant *Staphylococcus aureus* infection. A second elevation of the serum levels of IL-6, h-HGF, and 7S was observed on POD 3 and the liver dysfunction persisted, thus resulting in MODS. The outcome in this case suggested that the decrease in cytokine clearance was also related to the severity of SIRS.

Utilizing SIRS as one of the warning signs for determining serious cases is thus considered to be effective[9,15,25] since it may require strict and intensive management in order to avoid progression to MODS. After a hepatectomy, the serum peak levels of IL-6, h-HGF, and 7S were significantly higher in the SIRS(+) cases (Fig. 2), and were thus found to be a useful marker for predicting postoperative SIRS(+).

In 8 SIRS(+) patients with postoperative complications and 4 patients with SIRS(+) lasting for 3 days or longer, no significant elevation was found in the preoperative serum IL-6 and h-HGF levels. However, the preoperative serum 7S levels in these cases were significantly higher than in other cases ($P < 0.05$) (Table 4).

In summary, we demonstrated that the measurements of serum IL-6, h-HGF, and 7S levels before and immediately after surgery may be important indices for predicting the occurrence of SIRS and postoperative complications after a hepatectomy. Especially, patients with liver dysfunction before the operation with an elevated serum 7S level of about 7 ng/ml or higher before the operation, and with higher postoperative maximum serum levels of IL-6, h-HGF, and 7S were regarded to be SIRS(+). In such patients, intensive management directed against postoperative complications, septic SIRS, and MODS is therefore required.

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