Effects of Preoperative Steroid Administration on Surgical Stress in Hepatic Resection

Prospective Randomized Trial

Yo-ichi Yamashita, MD; Mitsuo Shimada, MD; Takayuki Hamatsu, MD; Tatsuya Rikimaru, MD; Shinji Tanaka, MD; Ken Shirabe, MD; Keizo Sugimachi, MD

Hypothesis: Preoperative administration of methylprednisolone sodium succinate can control surgical stress in patients undergoing hepatic resection.

Design: A prospective randomized trial.

Setting: A university hospital department of surgery.

Patients: Thirty-three patients who underwent hepatic resection were classified into 2 groups: a control group (n=16) and a steroid group (n=17) in which patients were intravenously administered 500 mg of methylprednisolone 2 hours before surgery.

Main Outcome Measures: Perioperative levels of interleukin (IL)-6 and IL-10 (serum and peritoneal), immunosuppressive acidic protein, *Candida* antigen, and other laboratory and clinical variables were measured.

Results: Postoperative levels of serum and peritoneal IL-6 and levels of C-reactive protein were significantly lower in the steroid group than in controls. Furthermore, serum and peritoneal IL-10 levels were significantly higher in the steroid group. The total bilirubin value on postoperative day 1 was significantly lower in the steroid group than in controls. Postoperative immunosuppressive acidic protein levels were also significantly lower in the steroid group, as was the positive rate of serum *Candida* antigen. No differences were found in the incidence of postoperative complications.

Conclusions: Preoperative steroid administration significantly elevated anti-inflammatory cytokine IL-10 levels, suppressed the levels of inflammatory cytokines IL-6 and C-reactive protein, and prevented postoperative elevation of total bilirubin values. Furthermore, postoperative elevation of immunosuppressive acidic protein levels and the positive rate of *Candida* antigen were suppressed, indicating that the immune response was maintained by preoperative steroid administration.

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THE LIVER is one of the organs most closely involved in vital reactions against surgical stress; in the liver, these reactions are characterized by production of acute-phase proteins, such as C-reactive protein (CRP), and alteration of glucose and protein metabolism. Moreover, we have long advocated hepatectomy as a suitable model by which to analyze the mechanism of such reactions against surgical stress, and Shimada et al[1-4] previously reported on the role and regulation of these reactions, including those involving prostaglandins and coagulant and fibrinolytic systems during and after hepatectomy.

Elevated plasma interleukin (IL) 6 levels have been reported to correlate with postoperative morbidity and mortality.[5,6] Elevated plasma levels of the anti-inflammatory cytokine IL-10 also have been reported during and after surgery.[7] Gastrointestinal surgery has been associated with elevated peritoneal cytokine (tumor necrosis factor α, IL-1, IL-6, and IL-10) levels in the first 72 hours after surgery, suggesting that the cytokine response by abdominal surgery largely originates from the abdominal cavity.[8-10] In patients with cirrhosis of the liver, IL-6 and tumor necrosis factor α levels have been reported to be higher in infected than in sterile ascites and peritoneal IL-6 to be an independent predictor for the development of renal impairment.[11] Furthermore, Shimada et al[12] previously reported that a perioperative short-term steroid pulse using methylprednisolone reduced surgical stress as measured by plasma IL-6 and CRP levels.

Immunosuppressive acidic protein (IAP) is an acid glycoprotein that activates tumor growth and shows strong immunosuppressive activity in lymphoblastic reactions.[13] Takenoshita et al[14] found a significant correlation between serum IAP levels and the variables of surgical stress after abdominal surgery.

From the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

PATIENTS AND METHODS

PATIENTS

Thirty-six patients with American Society of Anesthesiologists physical status I and II undergoing hepatic resection in the Second Department of Surgery at Kyushu University Hospital, Fukuoka, Japan, were entered in this trial. Patients were randomly assigned by sealed envelope to a steroid group (n=18) or a control group (n=18). Patients in the steroid group intravenously received 500 mg of methylprednisolone 2 hours before surgery. It was decided beforehand that any patient with an unexpected event that affected surgical stress would be excluded. All patients gave informed consent before enrollment in the trial.

ANESTHESIA AND HEPATIC RESECTION

All patients received 0.5 mg of atropine sulfate and 50 mg of hydroxyzine hydrochloride intramuscularly 45 minutes before the induction of anesthesia. After placement of a thoracic continuous epidural catheter at the T8-T9 intraspaces and confirmation of upper sensory block up to the T4 level, all patients received thiopental sodium, 10 mg/kg, followed by intravenous vecuronium bromide, 0.1 mg/kg. Patients then received general endotracheal anesthesia with 0.5% to 1% sevoflurane and 50% nitrous oxide. Combined epidural anesthesia was also performed with continuous administration of 1.5% lidocaine at a rate of 6 to 10 mL/h. Intraoperative muscle relaxation was facilitated by administration of vecuronium. An intraoperative nafamostat mesylate drip infusion (200 mg/d) was used in all patients.

Laparotomy was performed through a right subcostal incision and a midline incision. The Pringle maneuver or the hemihepatic vascular occlusion method with total vascular exclusion[15] was performed in almost all cases of hepatic resection. A closed suction drain was placed in the peritoneal cavity in all patients.

Unless clinically contraindicated, a systemic antibiotic (second-generation cephalosporin) was routinely applied after surgery, ending on the fourth or fifth postoperative day.

SAMPLING

Peritoneal fluid and serum samples were obtained during the first 7 postoperative days (at 0, 6, and 12 hours and on days 1, 3, and 7). Peritoneal fluid samples were obtained through a flat drain (7.0 × 20 mm) (Davol Inc, Cranston, RI). Serum samples were obtained through a peripheral vein. To avoid collecting the peritoneal fluid with degradated cytokines at room temperature, the fluid in the collection chamber was excluded 1 hour before the collection period. For cytokine analysis, samples were centrifuged at 3000 rpm for 15 minutes at 4°C and stored at –80°C until analysis.

ASSAYS FOR IL-6 AND IL-10

Human IL-6 (Fujirebio, Tokyo, Japan) was measured by chemiluminescent enzyme immunoassay and human IL-10 (Biosource Europe SA, Nivelles, Belgium) was measured by enzyme-amplified sensitivity immunoassay according to the instructions of the respective manufacturers. The detection limit of the assays was 0.2 pg/mL for IL-6 and 1 pg/mL for IL-10.

CANDIDA ANTIGEN TITERS

Candida antigen determinations were made using a latex agglutination test (CAND-TEC; Ramco Laboratories, Houston, Tex). An elevated *Candida* antigen titer was defined as one of 1:2 or greater.

OTHER CLINICAL VARIABLES

Serum levels of CRP, total bilirubin (T-bil), asparaginic acid aminotransferase (AST), and alanine aminotransferase (ALT), as well as prothrombin time, hepaplastin test, and indocyanine green retention rate at 15 minutes, were measured and compared during the 7-day postoperative period (at 6 hours and on days 1, 3, and 7). In addition, IAP levels during the 14-day postoperative period (on days 1, 3, 7, and 14) were quantified by the immunologic calorimetric method.

STATISTICS

Continuous variables were compared using the *t* test and are expressed as mean ± SE. Categorical variables were compared using χ^2 or Fisher exact tests, as appropriate. IL-6 and IL-10 (serum and peritoneal), IAP, CRP, and T-bil values were compared between the control and steroid groups using repeated-measures analysis of variance. All analyses were performed using statistical software (Statview 5.0; Abacus Concepts, Berkeley, Calif). Differences were considered statistically significant at $P < .05$.

Thus, the aim of the present prospective randomized trial was to investigate the effects of preoperative steroid administration on surgical stress and postoperative immune function in patients undergoing hepatic resection.

RESULTS

THE TRIAL PROFILE

Between August 1999 and February 2000, 36 patients undergoing hepatic resection in the Second Department of Surgery at Kyushu University Hospital were registered to enter the trial. Eighteen patients were randomly entered into the control group and 18 into the steroid group by sealed envelope (**Figure 1**). Three patients were excluded from this trial because they underwent procedures that might have affected surgical stress, ie, unexpected colorectal resection (n=2) and thoracotomy (n=1). The final cohort included 33 patients, 17 in the steroid group and 16 in the control group.

IL-6 AND IL-10 IN PERITONEAL AND VENOUS SAMPLES

Serum IL-6 levels in both groups reached a peak 6 hours after surgery and gradually declined thereafter. Peritoneal IL-6 levels in both groups reached a peak on day 1 and immediately declined thereafter. Serum and peritoneal IL-6 values 6 and 12 hours after surgery and on postoperative days 1 and 3 were also significantly lower in the steroid group than in the control group ($P<.01$ for all) (**Figure 2**). Furthermore, serum IL-10 levels also reached a peak 6 hours after surgery and immediately declined thereafter. Peritoneal IL-10 levels in both groups reached a peak on day 1 and then immediately declined. Serum IL-10 values 6 hours after surgery ($P<.01$) and peritoneal IL-10 values 12 hours after surgery ($P=.03$) and on postoperative day 1 ($P=.02$) were also significantly higher in the steroid group than in the control group) (**Figure 3**).

CLINICAL VARIABLES OF PATIENTS

Perioperative clinical variables of the steroid and control groups are listed in the **Table**. Regarding preoperative and intraoperative clinical variables, including patient characteristics and operative factors, no differences were found between the 2 groups.

The concentration of CRP on postoperative day 3 in the steroid group was significantly lower than that in the control group (6.8±0.8 vs 11.3±0.8 mg/dL; $P<.01$). The CRP levels of both groups reached a peak on day 3 and then gradually declined. The CRP values on days 1, 3, and 7 were significantly lower in the steroid group than in the control group ($P<.01$ for all) (**Figure 4**).

The postoperative T-bil value in the control group reached a peak on day 1 and that of the steroid group peaked slightly later, on day 3. The T-bil value on postoperative day 1 was also significantly lower in the steroid group than in the control group (21±2 vs 29±3 μmol/L [1.2±0.1 vs 1.7±0.2 mg/dL]; $P=.02$) (**Figure 5**).

In other liver function tests, such as AST, ALT, prothrombin time index, and hepaplastin tests, no differences were found between the 2 groups (Table).

Postoperative IAP levels in both groups reached a peak on day 7 and then gradually declined. The level of IAP on day 7 in the steroid group was significantly lower than that in the control group (409±29 vs 712±38 μg/mL; $P<.01$). Furthermore, IAP values on days 3, 7, and 14 in the steroid administration group were significantly lower than those in the control group ($P<.01$ for all) (**Figure 6**).

The positive rate of serum *Candida* antigen on day 3 in the steroid group was significantly lower than that in the control group (12% vs 50%; $P=.02$).

There was no significant difference in the duration of postoperative hospital stay or the incidence of postoperative complications between the 2 groups (Table). In addition, no adverse effects attributable to steroid administration were observed.

COMMENT

We confirm that the peak point of serum IL-6 and IL-10 occurred 6 hours after surgery and that the peak point of peritoneal IL-6 and IL-10 occurred on postoperative day 1. Peritoneal samples were diluted by intraoperative irrigation, so the peak point was considered to be delayed. In the present prospective randomized trial, preoperative steroid administration significantly increased the level of anti-inflammatory cytokine IL-10. In recent studies,[16,17] IL-10 was found to suppress hepatic ischemia-reperfusion injury. In this trial, however, the postoperative elevation of AST and ALT were not suppressed in the steroid group. Shimada et al[12] previously reported that preoperative steroid administration in hepatic resection significantly suppressed IL-6 release and subsequently

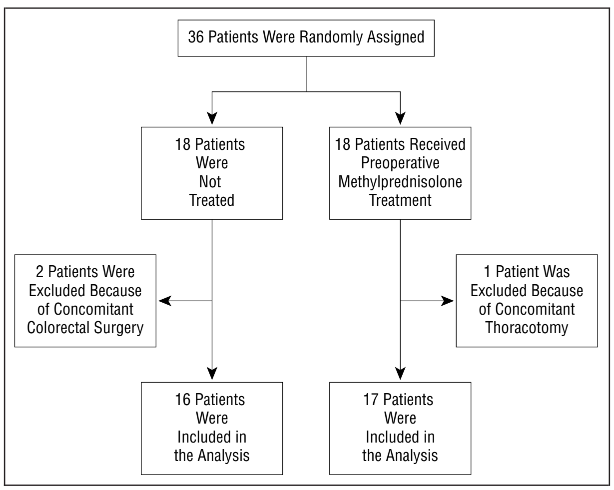

Figure 1. *The trial profile.*

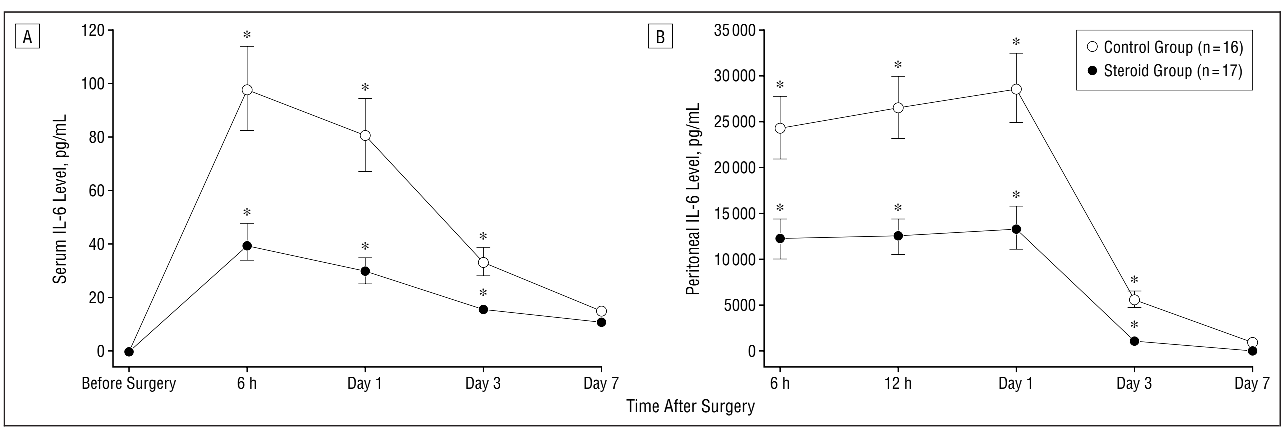

Figure 2. *Comparison of serum (A) and peritoneal (B) interleukin 6 (IL-6) levels between the control and steroid groups. Data are expressed as mean±SE. Asterisk indicates* P<.05.

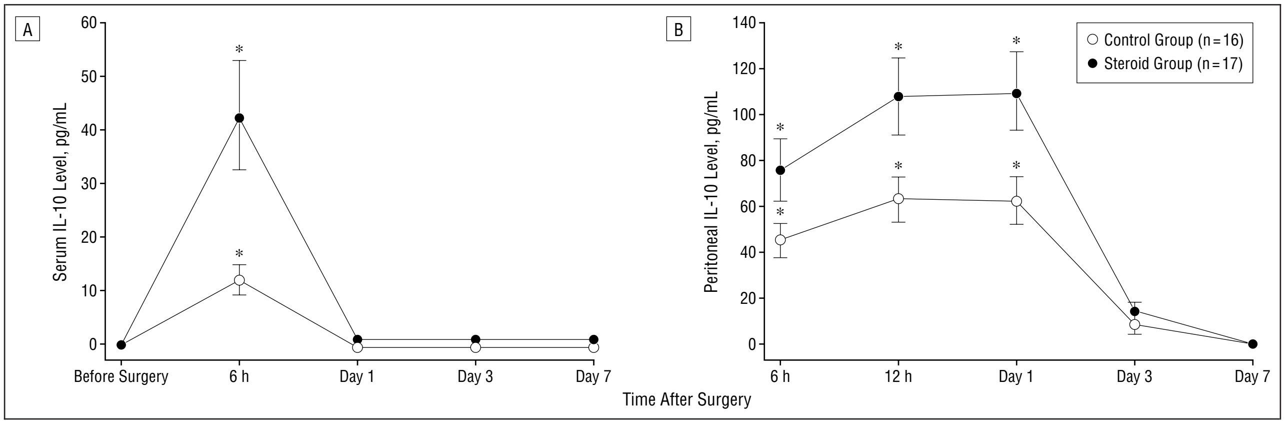

Figure 3. *Comparison of serum (A) and peritoneal (B) interleukin 10 (IL-10) levels between the control and steroid groups. Data are expressed as mean±SE. Asterisk indicates* $P<.05$.

Comparison of Clinical Variables Between the Control and the Steroid Groups*

	Control Group (n = 16)	Steroid Group (n = 17)	*P*
Preoperative variables			
Age, y	56.8 ± 3.9	60.3 ± 1.8	.40
Sex, M/F, No.	11/5	13/4	.62
Diagnosis, No.			
Hepatocellular carcinoma	8	13	
Metastatic liver tumor	3	0	.43
Cholangiocellular carcinoma	1	0	
Donor of living related liver transplant	4	4	
Albumin, g/L	41 ± 1	39 ± 1	.25
Bilirubin, μmol/L (mg/dL)	14 ± 2 (0.8 ± 0.1)	12 ± 2 (0.7 ± 0.1)	.82
Prothrombin time, %	91.9 ± 2.9	89.4 ± 3.1	.56
Hepaplastin test, %	83.6 ± 4.2	77.9 ± 3.5	.30
Asparaginic acid aminotransferase, U/L	38 ± 7	45 ± 6	.50
Alanine aminotransferase, U/L	35 ± 6	46 ± 5	.20
Indocyanine green retention rate at 15 min, %	15.4 ± 4.0	17.1 ± 2.2	.70
Intraoperative variables			
Operative procedure, No.			
Lobectomy or more	6	5	
Segmentectomy	1	2	.70
Subsegmentectomy or less	9	10	
Operative time, min	352 ± 14	338 ± 21	.57
Blood loss, mL	822 ± 55	892 ± 106	.56
Resected liver volume, g	187 ± 33	239 ± 50	.40
Postoperative variables			
Bilirubin on POD 1, μmol/L (mg/dL)	29 ± 3 (1.7 ± 0.2)	21 ± 2 (1.2 ± 0.1)	.02
Asparaginic acid aminotransferase on POD 1, U/L	282 ± 44	375 ± 50	.18
Alanine aminotransferase on POD 1, U/L	263 ± 39	403 ± 70	.09
Prothrombin time on POD 1, %	64.1 ± 3.5	67.5 ± 3.4	.49
Hepaplastin test on POD 1, %	64.1 ± 3.5	67.5 ± 3.4	.53
C-reactive protein on POD 3, mg/dL	11.3 ± 0.8	6.8 ± 0.8	<.01
Candida antigen on POD 3, No. (%)	8 (50)	2 (12)	.04
Immunosuppressive acidic protein on POD 7, μg/mL	712 ± 38	409 ± 29	<.01
Postoperative complications			
Postoperative hospital stay, d	17.8 ± 1.6	19.2 ± 1.8	.57
Intra-abdominal sepsis, No.	1	1	
Bile leakage, No.	0	0	
Ascites, No.	0	1	.78
Liver failure, No.	0	0	
Wound infection, No.	1	0	

**Data are given as mean ± SE except where indicated otherwise. POD indicates postoperative day.*

suppressed the elevation of CRP levels; the production of hepatocytes is known to be enhanced by IL-6.[18] Ohzato et al[19] suggested that monitoring IL-6 levels, the elevation of which is triggered by surgical procedures, might be more helpful than monitoring CRP levels for estimating the extent of surgical stress. This effect of suppression of surgical stress monitored by IL-6 by preoperative steroid administration was confirmed by findings in

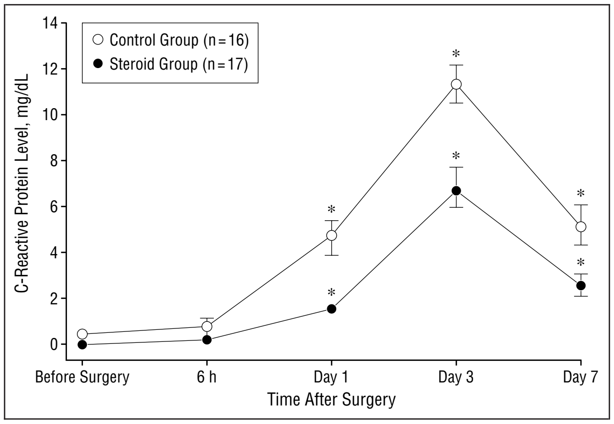

Figure 4. *Comparison of C-reactive protein levels between the control and steroid groups. Data are expressed as mean ± SE. Asterisk indicates* P<.05.

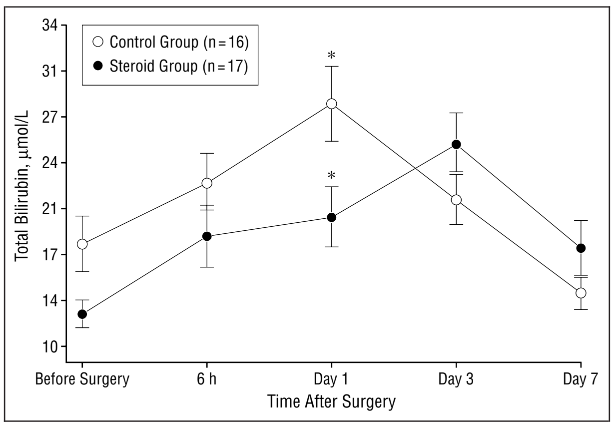

Figure 5. *Comparison of postoperative total bilirubin levels between the control and steroid groups. Data are expressed as mean ± SE. To convert bilirubin from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 17.1. Asterisk indicates* P<.05.

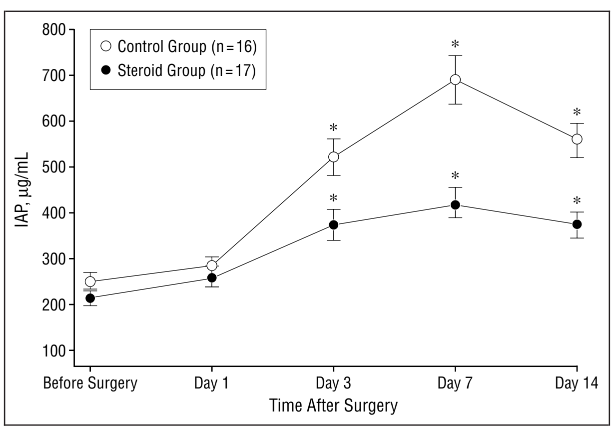

Figure 6. *Comparison of immunosuppressive acidic protein (IAP) levels between the control and steroid groups. Data are expressed as mean ± SE. Asterisk indicates* P<.05.

this prospective randomized study. In recent studies,[20] however, IL-6 −/− mice showed an impairment of liver regeneration characterized by liver necrosis and failure after partial hepatectomy. In this study, on the other hand, no adverse effects on liver function after hepatectomy (AST, ALT, prothrombin time, hepaplastin test, etc) were found in the steroid group. Furthermore, it is of clinical interest that significant suppression of the postoperative elevation of T-bil concentration on postoperative day 1 was found in the steroid group.

The steroid administration regimen used in this study was based on the following considerations. First, the mechanism by which steroids inhibit cytokine production is known to inhibit the induction of messenger RNA,[21] although steroids have no effect on cytokines, which have already been released from the cells. Second, cytokine production of monocytes and macrophages has been reported to be suppressed by methylprednisolone.[22,23] Moreover, this suppressive effect was dose dependently strengthened in the range of 0.1 to 100 µg/mL. Intravenous administration of 500 mg of methylprednisolone has been confirmed to result in a methylprednisolone level of more than 1 µg/mL in blood or more than 10 µg/mL in liver tissue. Third, it has been reported that the best time to administer methylprednisolone in the rat model to suppress cytokine release is 2 to 3 hours before the experiment.[24]

In an investigation on the control of surgical stress, Sayama et al[25] found that a preoperative single administration of methylprednisolone (250 mg) reduced postoperative production of IL-6 and granulocyte colony-stimulating factor in patients undergoing surgery for esophageal cancer. However, this regimen, including the dose of steroid, is considered to be insufficient, and further investigation is needed to determine the most appropriate regimen of steroids to control surgical stress.

Serum IAP values have been reported to show a marked increase beginning 1 week after surgery and to be significantly higher in patients who underwent complicated surgery.[26] In our study, preoperative steroid administration significantly suppressed IAP elevation during postoperative day 14. Furthermore, the postoperative positive rate of serum *Candida* antigen was significantly suppressed by preoperative steroid administration. Shirabe et al[27] previously observed an impairment of systemic immunity and frequent infection in patients with *Candida* antigen after hepatectomy. This suppression of postoperative IAP levels induced by steroid administration might be one of the main reasons for the reduction of the positive rate of *Candida* antigen, and it can be said that preoperative steroid administration decreases the postoperative immune suppression. Further detailed study is needed to confirm this postulated mechanism.

Neither the duration of postoperative hospital stay nor the rate of postoperative complications was altered by steroid administration in this study, probably because of the overall low rate of surgical complications in modern hepatic resection. Adverse effects of steroid use, such as abnormality in glucose tolerance, infection, and delay in wound healing, did not occur in any of our patients.

This prospective randomized trial confirmed the effect of suppression of surgical stress by preoperative steroid administration in patients undergoing hepatic resection. Preoperative steroid administration significantly elevated the level of anti-inflammatory cytokine IL-10 and suppressed the level of inflammatory cytokine IL-6. In addition, the elevation of IAP concentration was suppressed by steroid administration, and the positive rate of *Candida* antigen was also suppressed, which indicates the reduction of postoperative immune suppression by preoperative steroid administration.

Corresponding author and reprints: Yo-ichi Yamashita, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (e-mail: yamashi@surg2.med.kyushu-u.ac.jp).

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