

Postoperative Coagulation Changes in Patients with esophageal carcinoma

Hideo IWASAKA, Takaaki KITANO, Shinichi MATSUMOTO
Hiroshi MIYAKAWA, Takayuki NOGUCHI
Kazuo TANIGUCHI and Natsuo HONDA

*Department of Anesthesiology, Medical College of Oita,
1-1, Idaigaoka, Hazama-cho, Oita-gun, Oita 879-56 JAPAN*

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SUMMARY: Postoperative coagulation changes were studied in 50 patients with esophageal carcinomas for 7 days following operation. Of these, 12 patients were examined further for changes in platelet aggregation rate as an index of platelet function. Just after operation, both platelet count and aggregation rate decreased, but at day 2 when the platelet count reached its lowest point, platelet aggregation returned to the preoperative level. Although platelet aggregation decreased again, it recovered to the preoperative level earlier than did the platelet count. Changes in prothrombin time, activated partial thromboplastin time and fibrinogen and FDP-E levels may suggest pre-DIC state.

INTRODUCTION

There have been numerous reports on changes in the coagulation and fibrinolytic system in patients before and after operation. However, little has been reported regarding changes in platelet function, coagulation, and the fibrinolytic system after massive blood transfusions for major surgeries such as surgery for esophageal carcinoma. Therefore, we investigated changes of these factors in preoperative and postoperative days.

SUBJECTS AND METHODS

The subjects for this study were 50 patients who underwent esophagectomy and or esophageal reconstruction for esophageal carcinoma, and had not received anticoagulants. Of these, 12 patients were assessed for changes in the maximum platelet aggregation rate. During operation a crystalloid solution was administered

as transfusion fluid at the rate of 10ml. kg/hr, and preserved whole blood was transfused to supplement blood loss by bleeding. Furthermore, fresh frozen plasma was transfused to maintain circulating blood volume. Platelet transfusions were not performed during or after operation. Postoperatively, the patients were transfused with fresh frozen plasma for up to 7 days to maintain serum albumine and coagulation factors. Within 3 hours after blood samples were obtained, the maximum platelet aggregation rate was determined in the presence of ADP at a final concentration of $3\mu\text{M}$ or in the presence of collagen at $2\mu\text{g/ml}$, using a HEMA TRACER PAC-8S (Niko Bioscience Co., Ltd.). The platelet count was determined with an automatic blood counting cytometer MEK 7108 (Nihon Koden Co., Ltd.). The prothrombin time (PT), the activated partial thromboplastin time (APTT), and the fibrinogen level were all measured with a coagostat Auto II (International Reagent Co., Ltd.). FDP-E was measured with a diayatron LPIA system. Measure-

ments were performed before operation (control values) and for postoperative 7 days. The data were statistically analyzed using an unpaired t-test, and statistical differences were considered significant for $p < 0.05$. All values were expressed as means \pm SE.

RESULTS

1) Changes in platelet count (Fig. 1)

Mean blood loss was 1,150g during operation. After operation, platelet count decreased significantly from $24.1 \pm 1.4 \times 10^4/\text{mm}^3$ (control) to $10.6 \pm 0.7 \times 10^4/\text{mm}^3$ at day 2 after operation. Thereafter, the platelet count increased gradually, recovering to the preoperative level by day 7.

2) Changes in the maximum platelet aggregation rate in the presence of ADP.

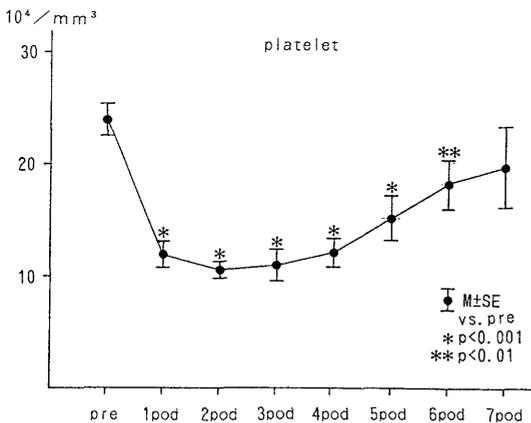


Fig. 1. Changes in platelet count after surgery. Each point represents mean \pm SE.

The maximum platelet aggregation rate began to decline after operation, and reached $67.0 \pm 4.0\%$ at day 1. This represented a significant decrease from the preoperative value of $91.4 \pm 2.6\%$. At

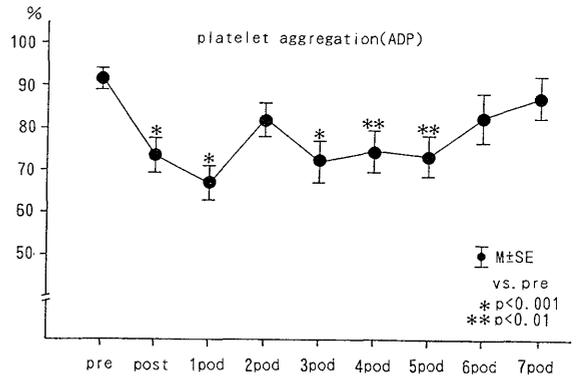


Fig. 2. Changes in the maximum platelet aggregation rate in the presence of ADP. Each point represents mean \pm SE.

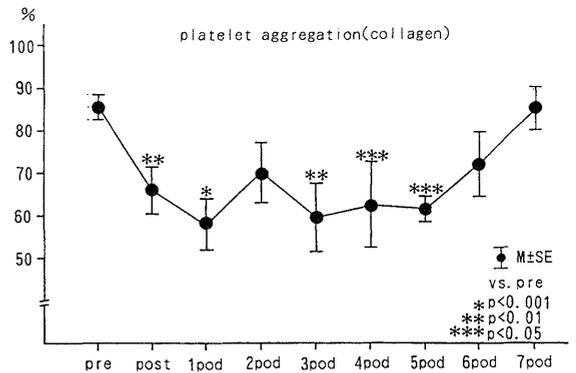


Fig. 3. Changes in the maximum platelet aggregation rate in the presence of collagen. Each point represents mean \pm SE.

Table 1. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen and FDP changes after operation.

	Pre	1POD	2POD	3POD	4POD	5POD	6POD	7POD
PT (%)	100.9 \pm 2.4	83.2 \pm 2.4 *	99.2 \pm 7.4	118.8 \pm 12.3	104.4 \pm 9.5	88.8 \pm 10.3	96.3 \pm 21.6	92.5 \pm 10.8
APTT (%)	109.0 \pm 2.1	80.0 \pm 1.9 *	74.1 \pm 3.9 *	78.9 \pm 4.6 *	79.0 \pm 3.2 *	82.4 \pm 4.3 **	86.8 \pm 3.6 ***	92.1 \pm 1.6 **
Fibrinogen (mg/dl)	415.0 \pm 20.0	468.2 \pm 12.3	545.4 \pm 26.9 *	586.2 \pm 32.1 **	550.1 \pm 24.6 *	584.5 \pm 81.1 **	564.4 \pm 65.9 **	648.7 \pm 35.1 *
FDP (ng/ml)	48.5 \pm 8.4	409.8 \pm 47.3	237.5 \pm 39.1	409.3 \pm 110.2	491.0 \pm 62.3 *	738.2 \pm 75.0 *	658.4 \pm 110.4 *	617.3 \pm 87.5 *

VS. pre *P<0.001 **P<0.01 ***P<0.05 All data are presented as mean \pm SE.

day 2, when the platelet count reached minimum level, the aggregation rate temporarily rose to $82.4 \pm 4.4\%$, but fell again to $71.9 \pm 4.8\%$ at day 3. Thereafter, this rate rose to $82.7 \pm 6.1\%$, equivalent to control level at day 6, which is earlier than recovery of the platelet count.

3) Changes in the maximum platelet aggregation rate in the presence of collagen (**Fig. 3**).

An aggregating agent, ADP, mainly indicates changes in primary platelet aggregation, whereas collagen detects secondary platelet aggregation in response to intrinsic ADP release. Changes in the collagen induced maximum platelet aggregation rate show similar tendency to those induced by ADP. Namely, the aggregation rate decreased significantly from $85.1 \pm 2.9\%$ (control level) to $57.9 \pm 6.0\%$ at day 1. At day 2, when the platelet count fell to minimum level, the aggregation rate rose temporarily to the preoperative level, and fell again. As with ADP, it recovered to the control level by day 6.

4) Changes in prothrombin time (**Table 1**).

After operation, prothrombin time decreased significantly from $100.9 \pm 2.4\%$ (control) to $83.2 \pm 2.4\%$ at day 1 and returned to the preoperative value at day 2.

5) Changes in the partial thromboplastin time (**Table 1**).

After operation, partial thromboplastin time (PTT) decreased significantly from $109.0 \pm 2.1\%$ (control) to $74.1 \pm 3.9\%$ at day 2. Although this PTT increased gradually thereafter, it remained significantly lower than the preoperative level even at day 7.

6) Changes in fibrinogen level (**Table 1**).

Fibrinogen level was already high ($415.6 \pm 20.0\text{mg/dl}$) before operation because of the malignant disease. After operation, fibrinogen level rose further to $545.4 \pm 26.9\text{mg/dl}$ at day 2, significant difference from the preoperative level. This elevation persisted up to day 7.

7) Changes in the FDP-E level (**Table 1**).

After operation, FDP-E level was significantly elevated from $48.5 \pm 8.4\text{ng/ml}$ (control) to $409.9 \pm 47.3\text{ng/ml}$ at day 2. This elevation persisted up

to day 7.

DISCUSSION

Major surgeries, such as curative surgery for esophageal carcinoma, involve extensive areas of invasion and massive bleeding, and require large blood transfusions. This is believed to produce a preliminary DIC state, such as decrease in coagulation factors and activation of the coagulation and fibrinolytic system by release of tissue thromboplastin⁶. This study was designed to clarify the changes in platelet count, aggregation, and the coagulation and fibrinolytic system of patients with surgically treated esophageal carcinomas during the first week after surgery.

Postoperatively platelet count decreased significantly to about 40% of the preoperative level at day 2. This was due to blood dilution resulting from massive bleeding and blood transfusions during surgery. Thereafter, platelet count increased gradually, recovering to the preoperative level by day 7.

Reactive thrombocytosis is usually known to develop after operation. It is due to increased platelet production resulting from stimulation of bone marrow by bleeding and blood transfusion. However, this phenomenon was not observed in our patients throughout the 7 days observed period, probably because platelet consumption increased during and after operation due to extensive surgical invasion and massive bleeding. Reactive thrombocytosis is likely to occur about two weeks after operation. Although the data were not statistically analyzed, there were some cases with increased platelet counts around that time in our study. Platelets play various roles in coagulation and the fibrinolytic system, including establishment of hemostasis by forming a thrombus, activation of coagulation factors, supporting the capillary endothelium, and storing carrying materials^{11, 12}. For those reasons, besides platelet count, platelet aggregation, reflecting the platelet function, was also determined to evaluate various pathological states such as myocardial infarction, cerebrovascular impairment, and diseases requiring hemodialysis¹. And the effects of anesthetics on platelet function were also studied^{2, 4, 7, 9}.

In this study, we assessed changes in platelet aggregation rate concurrent with changes in platelet count for up to 7 days following operation. After operation, platelet aggregation rate decreased significantly, as did platelet count. However, at day 2, when platelet count was depressed to low level, aggregation rate temporarily rose to preoperative level as if to compensate for the depression of platelet counts. Although it again decreased, aggregation rate returned to the preoperative level at day 6, one day earlier than recovery of the platelet count. From the result at day 2, it is suggested that in spite of decreased platelet count, the tendency to bleed was inhibited by temporary restoration of platelet function. However, DIC is a unique pathological state in which activation of the intravascular coagulation and platelet systems produces multiple thrombosis, thereby depleting coagulation factors and platelets. These results in a tendency to bleed. Therefore, paradoxically speaking, it is possible that activation of the platelet function at day 2 contributed to the acceleration of DIC. Our study clearly indicates that recovery of platelet aggregation rate is faster than recovery of platelet count, though only by one day. According to a study that measured the speed of recovery of platelets and coagulation factors reduced by DIC, recovery of factor VIII and fibrinogen was faster than recovery of platelets. However, we believe that restoration of platelet function precedes recovery of the platelet count, as seen in our study. Therefore, we must be careful in deciding platelet transfusion based solely on a decrease in platelet count¹⁰⁾. In fact, it has been reported that administration of desmopressin acetate helped restore platelet function reduced by extracorporeal circulation during cardiac surgery, thereby reducing bleeding⁸⁾. Therefore, if recovery of sufficient platelet count is not observed within two days following surgery in spite of a lack of bleeding, it is necessary to measure platelet function and take caution in the development of DIC. A blood vessel ruptured by surgical invasion causes blood to come into contact with the rough surface. This activates factor XII, which leads to activation of the intrinsic coagulation mechanism. Surgical invasion also causes intravascular influx of

tissue thromboplastin and thromboplastin-like substances, triggering activation of the extrinsic coagulation mechanism. After operation, both PT and APTT decreased significantly in our patients. PT recovered at day 2, whereas APTT remained low level even at day 7. Normal level of PT and prolonged low level of APTT suggest deficiency or absence of factors XII, XI, IX, and VIII. Since our patients were transfused with sufficient amounts of fresh frozen plasma to supplement serum albumin, deficiencies of these factors are unlikely. Decreases in the half-lives of these factors, the presence of catheter in the blood vessel, or depletion of platelet factor III due to decreased platelet function may explain the prolonged low APTT levels in our patients¹¹⁾. In anyway, further study is necessary to clarify this question. It appears that the decreases in coagulation factors in our patients were not great enough to induce bleeding³⁾. After surgery, both fibrinogen and FDP-E levels were significantly elevated and remained high even at day 7. Fibrinogen is one of proteins produced by acute reactions, and its elevation in our patients seems to have been caused by surgical invasion. FDP-E, a degradation product of fibrinogen, was probably elevated for the same reason. Therefore, elevation of fibrinogen levels is common after surgery. We must be aware that even if fibrinogen is not decreased, the possibility of DIC cannot be ruled out.

We have discussed changes in coagulation, fibrinolysis, and platelet systems of patients with esophageal carcinoma after surgery. Although there are many methods for determining coagulability^{5, 11)}, we believe that evaluation of platelet function is important, because it plays a major role in postoperative bleeding.

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