Intraoperative Changes in Blood Coagulation and the Effectiveness of Ulinastatin during Liver Resection

Motoichi OKIDA, Ohishi MASAKO, Hirotaka MARUYA, Tatsuo HIGASHI and Hirofumi YUKAYA*

The blood coagulation status of 16 patients undergoing liver resection was monitored by thrombelastograph (TEG). Coagulation test by TEG was performed at three different times: before and one hour after induction of anesthesia and after liver resection. The four variables such as r (reaction time), k (coagulation velocity), ma (maximum amplitude) and me (maximum elasticity) were measured. In 8 patients, Ulinastatin was not administered during the operation and FFP was transfused after the second measurement of TEG (group I). The other 8 patients were administered totally 300,000 units of Ulinastatin after induction until the second measurement of TEG, thereafter FFP was transfused (group II). The TEG showed poor preoperative coagulation state in both groups. In group I, TEG variables showed coagulopathy was exacerbated significantly during liver resection. In group II TEG variables showed no significant changes during operation. Between the two groups there were statistical differences in the TEG variables during the operation. The TEG was useful for monitoring coagulation function during liver resection. It was impossible to improve TEG data by only replacement of FFP. Ulinastatin was useful in normalizing the coagulation function and in preventing the changes in TEG measurements during liver resection. (Key words: liver resection, TEG, Ulinastatin)

(Okida M, Masako O, Maruya H, et al.: Intraoperative changes in blood coagulation and the effectiveness of Ulinastatin during liver resection. J Anesth 5: 43–47, 1991)

At our hospital liver resection was conducted on about 200 cases of hepatoma during the last five years[1–3], and it is now recognized as a major means of therapy for patients with hepatocellular carcinoma. The management of blood loss and coagulation state during liver resection is still a major concern[4]. The liver produces most of the blood coagulation factors, so we encounter the lowered value of coagulation factors and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) in most of the patients receiving hepatectomy. We have frequently seen thrombocytopenia due to splenomegaly[5]. In addition numerous collateral channels and capillary fragility make surgical hemostasis very difficult[4].

In addition, there was the difficulty in monitoring the coagulation system and determining the appropriate treatment during liver resection. However, recently the use of thrombelastograph (TEG) is suggested, and the efficacy of thrombelastographic monitoring of blood coagulation during liver transplantation has been reported[4,6].

The purpose of our study is to investigate the changes in blood coagulation function

Department of Anesthesiology, Hiroshima Red Cross & Atomic-bomb Survivors Hospital, Hiroshima, Japan

**Department of Surgery, Hiroshima Red Cross & Atomic-bomb Survivors Hospital, Hiroshima, Japan*

Address reprint requests to Dr. Okida: Department of Anesthesiology, Hiroshima Red Cross & Atomic-bomb Survivors Hospital 1-6-9, Senda-Machi, Naka-ku, Hiroshima, 733 Japan

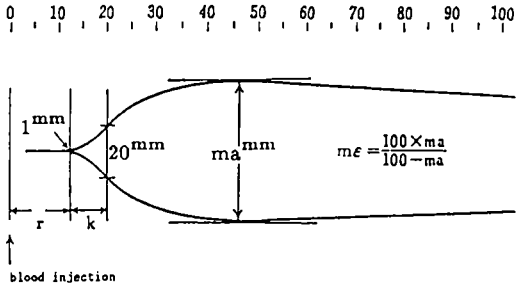

Fig. 1. Variables and normal values measured by thrombelastography.

Abbreviations: r-reaction time, 9–14 min; k-coagulation velocity, 5–7.5 min; ma-maximum apmlitude, 50–70 mm; me-maximum elasticity, 85–120%.

by TEG during liver resection and the role of Ulinastastin, which is a human urinary trypsin inhibitor and has inhibitory activity on various enzymes[7–10], during liver resection by TEG.

Methods

I Sampling method and laboratory techniques

Patients undergoing liver resection between January 1989 and July 1989 were observed for this study. All patients had two indwelling 8.5 French catheters inserted for volume infusion, one in an antecubital vein and another in an internal or an external jugular vein, and an indwelling catheter was placed in a radial artery to monitor the direct blood pressure. Blood samples (10 ml each) were obtained at about one hour intervals. Coagulation test by TEG was performed at three different times: before and one hour after induction of anesthesia and after liver resection. At the same time white blood cell count, red blood cell count, Hb, Ht, platelet count and blood gas analysis were performed. Whole blood (1.0 ml) was injected in the Thrombelastograph D (Hellinge Company, Freiburg, Germany). The real time from sampling of the blood to starting of the record was measured. TEG is shown schematically in figure 1. The following variables were measured. (fig. 1): r (reaction time, min); k (coagulation velocity, min); ma (maximum amplitude, mm); me (maximum elasticity, %) me = (100 × ma)/(100 − ma)

II Patients and method (table 1)

During 1989, subsegmental and segmental resections of liver were carried out in 13 patients with hepatocellular carcinoma (HCC) and liver cirrhosis; two other patients underwent distal splenorenal shunt operations and another one patient had a hepatic artery cannulation. The diagnosis of hepatocellular carcinoma (HCC) and liver cirrhosis was made histologically in all cases. In 8 patients, Ulinastafin was not injected during the operation and FFP was transfused after the

Table 1.

		group I	group II
cases		8 male 8	8 male 7 female 1
age		54.8 ± 11.5 (38–74)	52.3 ± 10.7 (31–66)
operation	subsegmental	3	
	segmental	5	segmental 5 shunt ope 2 cannulation 1
operation time(h)		2.2 ± 0.6	3.3 ± 1.2
anesthesia time(h)		3.8 ± 0.6	4.5 ± 1.3
fluid ($ml \cdot kg^{-1} \cdot hr^{-1}$)		6.5 ± 0.8	6.9 ± 2.6
blood loss (ml)		537.5 ± 351.4 (130–1100)	610 ± 425.0 (180–1450)
blood transfusion (ml)		502.5 ± 301.9	591.2 ± 149.1
FFP/blood loss (%)		97.9 ± 57.8	119.9 ± 86.9
urine volume ($ml \cdot kg^{-1} \cdot hr^{-1}$)		1.3 ± 0.3	1.4 ± 1.1

Table 2.

		before induction	one hour after induction	after liver resection
r	(group I)	15.6 ± 0.6 min	60.4 ± 59.9 min	26.6 ± 10.9 min*
		NS	NS	++
	(group II)	14.9 ± 7.4 min	17.7 ± 9.0 min	13.4 ± 4.9 min
k	(group I)	13.2 ± 11.4 min	94.5 ± 75.6 min**	35.6 ± 23.9 min*
		NS	++	NS
	(group II)	14.2 ± 11.2 min	18.3 ± 12.9 min	15.2 ± 17.9 min
ma	(group I)	37.2 ± 6.3 mm	21.5 ± 9.6 mm**	27.8 ± 8.1 mm*
		NS	++	+
	(group II)	36.3 ± 6.0 mm	35.0 ± 6.1 mm	39.2 ± 8.6 mm
me	(group I)	60.8 ± 16.6%	32.8 ± 16.0%**	40.3 ± 16.4%*
		NS	++	++
	(group II)	58.3 ± 14.7%	55.4 ± 14.5%	67.0 ± 19.7%

values are mean ± SD.
significantly different from the corresponding preoperative value
**($P < 0.01$), *($P < 0.05$).
significantly different between two groups
++($P < 0.01$), +($P < 0.05$).
NS no significant difference.

second measurement of TEG (group I). The other group of 8 patients were administered 200,000 units of Ulinastatin after induction of anesthesia and 100,000 units of Ulinastatin which was continuously infused until the second measurement of TEG, thereafter FFP was transfused (group II).

Anesthesia was induced with bupurenorphine hydrochloride (5–6 mg·kg^{-1}), thiopental (5 mg·kg^{-1}) and succinylcholine chloride (1 mg·kg^{-1}). Anesthesia was maintained with GO enflurane supplemented pancuronium bromide. Acetated Ringer's solution containing 5% glucose was infused intravenously during the operation. Blood transfusion was performed with packed red cell blood and fresh frozen plasma (FFP).

The details of patients, anesthesia, fluids and blood administrations are shown in table 1. There was no statistically significant difference between each of the items of the two groups.

Statistical analysis was made with unpaired Student's t test, and a P value of less than 0.05 was considered to be statistically significant.

Results

The intraoperative changes in TEG variables are shown in table 2. Before induction of anesthesia r and k were longer than the normal values in both groups. Ma and me were lower than the normal values in both groups. In group I, k at one hour after induction were significantly prolonged compared with the value of k before induction ($P < 0.01$). Moreover, ma and me at one hour after induction decreased significantly compared with the value of ma and me before induction ($P < 0.01$). R and k after liver resection tended to improve, but there was no statistical difference between one hour after induction and after liver resection. In spite of improvement, r and k after liver resection were significantly prolonged compared with the value of r and k before induction ($P < 0.05$). Ma and me also tended to improve and increase, but there was no statistical difference between one hour after induction and after liver resection. But ma and me after liver resection decreased significantly compared with the value of ma

and me before induction ($P < 0.05$). In group II there was no statistical difference through the operation in the each value of r, k, ma or me. When we compared group I with group II, there was no statistical difference in r, k, ma or me before induction between the two groups. However, at one hour after induction k was significantly shortened and ma and me increased significantly in group II compared with group I ($P < 0.01$). After liver resection in group II r was significantly shortened ($P < 0.01$) and ma increased significantly ($P < 0.05$), and me also increased significantly ($P < 0.01$) compared with group I.

Discussion

Our results demonstrated the poor preoperative coagulation status: prolonged r and k and decreased ma and me, which reflect the decreased function of coagulation factors, including fibrinogen and platelet. These findings may result from pathophysiologic changes in liver cirrhosis, because hepatocellular carcinoma (HCC) complicates liver cirrhosis in nearly all cases which disrupts the synthesis of the blood coagulation factors. After starting the operation the coagulation function was significantly aggravated. This was clearly demonstrated by the TEG measurements: the significantly prolonged r and k and the decreased ma and me. These findings, which are in agreement with reports by Groth et al.[11] may result from release of tissue thromboplastin into the circulating blood by surgical stress, which induced hypercoagulation and aggravated consumption of coagulation factors. Groth et al.[11] suggested that loss and decrease of hepatic clearance function of activated coagulaltion factors due to the malfunction of RES in liver played a major role in localized or disseminated intravascular coagulation. The changes in the TEG at one hour after starting the operation suggested the possibility of a provocative state which triggers the disseminated intravascular coagulation or consumption coagulopathy.

After liver resection, all of the mean values of r, k, ma and me improved, but was not significant compared with the value at one hour after induction. These results indicate that, although the coagulopathy is slightly improved by FFP, replacement therapy by only FFP could not completely improve the coagulopathy after starting the operation. During liver resection nearly 30–40% of blood loss is usually replaced by FFP in our hospital, but it is in question now how much replacement by FFP is appropriate. In this study we replaced nearly the same volume of blood lost with FFP, but we have found that it is difficult to improve TEG measurements by replacement of only FFP.

Our results clearly demonstrated that aggravation of TEG measurements during liver resection, shown as prolonged r and k and decreased ma and me, was significantly improved by Ulinastatin. Therefore Ulinastatin was found to be quite useful in normalizing the coagulation function and in preventing changes in the TEG measurements during liver resection.

Inaba[12] reported Ulinastatin significantly improved the TEG measurements in endotoxin-induced DIC in rabbits. He suggested that Ulinastatin might prevent DIC in vivo and in vitro through the inhibition of Factor XII activity and through the prevention of thromboplastin release caused by endotoxin. During liver resection Ulinastatin also might inhibit the consumption of coagulation factors by preventing the tissue thromboplastin release[10].

(Received Jan. 16, 1990, accepted for publication Jul. 20, 1990)

References

1. Nagasue N, Yukaya H, Ogawa Y, Sasaki Y, Akamizu H, Hamada T: Hepatic resection in the treatment of hepatocellular carcinoma; report of 60 cases. Br J Surg 72:292–295, 1985
2. Nagasue N, Yukaya H, Suehiro S, Ogawa Y: Torelance of the cirrhotic liver normothermic ischemia: A clinical study of 15 patients. Am J Surg 147:772–775, 1984
3. Nagasue N, Yukaya H, Ogawa Y, Hirose S, Okida M: Segmental and subsegmental resections of the cirrhotic liver under hepatic inflow and outflow occlusion. Br J Surg 72:565–568, 1985

4. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr, Starzel TE, Winter PM: Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 64:888–896, 1985
5. Toghill PJ, Green S, Ferguson R: Platelet dynamics in chronic liver disease with special reference to the role of spleen. J Clin Pathol 30:367–371, 1977
6. Kaulla KN, Kaye H, Kaulla E, Marchioro TL, Starzl TE: Changes in blood coagulation before and after hepatectomy or transplantation in dogs and man. Arch Surg 92:71–79, 1966
7. Sumi H, Takada Y, Takada A: Studies on human urinary trypsin inhibitor. 1. Its modification on treatment of urine with acid. Thromb Res 77:747–754, 1977
8. Muramatsu M, Mori S, Matsuzawa Y, Horiguchi Y, Nakanishi Y, Tanaka M: Purification and characterization of urinary trypsin inhibitor, UTI, from normal human urine, and its clearage by human uropepsin. J Biochem 88:1317–1329, 1980
9. Mayehiro A: Studies of trypsin inhibitor in urine. Report III. The trypsin inhibitor in urine and serum of rabbits during anaphylactic reactions. Yokohama Med Bull 11:125–138, 1960
10. Faarvang HJ: The excretion of trypsin inhibitor in urine in normal pregnacy. Acta Endocrinol 31:117–122, 1959
11. Groth CG: Changes in coagulation. Existence in hepatic transplantation. Philadelphia: WB Saunders, 159–175, 1969
12. Inaba H, Kato K, Ohzawa N, Nakayama K: Effect of ulinastatin on disseminated intravascular coagulation. Folia Pharmacol Japon 88:239–244, 1986