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IMPACT OF THE INTRAOPERATIVE USE OF FIBRINOGEN CONCENTRATE FOR HYPOFIBRINOGENEMIA DURING THORACIC AORTIC SURGERY

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ABSTRACT

Thoracic aortic surgery often causes massive bleeding due to coagulopathy. Hypofibrinogenemia is one of the major causative factors, but the utility of the intraoperative administration of fibrinogen concentrate has not yet been proven. The aim of this study was to estimate incidence of hypofibrinogenemia and to evaluate efficacy of using fibrinogen concentrate intraoperatively. The perioperative serum fibrinogen levels (SFL) had routinely been measured in consecutive 216 thoracic aortic surgeries performed from 2010 to 2012. Fibrinogen concentrate was principally used for hypofibrinogenemia (< 150 mg/dl of SFL) at cardiopulmonary bypass (CPB) termination. The patients who received fibrinogen concentrate (FIB group) were compared with the patients who did not received (non Fib group). There were 147 patients (68%) in FIB group at a dose of 5.5±3.5 g. The SFL were dramatically decreased with values of 164±71 mg/dl at CPB termination, compared to the preoperative SFL of 352±131 mg/dl. In the FIB group, the intraoperative and postoperative SFLs were 139±53 and 262±75 (mg/dl), respectively. Thus the SFL was recovered quickly by the administration. 110 cases (51%) showed hypofibrinogenemia at the termination of CPB. The predictors of hypofibrinogenemia were preoperative SFL < 250 mg/dl, emergency surgery and thracoabdominal aortic surgery. Hypofibrinogenemia frequently was observed at the termination of CPB during thoracic aortic surgery. Administering intraoperative fibrinogen concentrate appears to be a useful option to treat coagulopathy.

Key Words: fibrinogen concentrate, coagulopathy, thoracic aortic surgery

INTRODUCTION

The management of massive bleeding due to intraoperative coagulopathy is a major concern during thoracic aortic surgery. The bleeding tendency is associated with numerous factors; however, the consumption of coagulation factors and platelets is one of the main factors. In particular, hypofibrinogenemia is an important factor associated with coagulopathy during thoracic

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Tel: +81 52 744 2375, Fax: +81 52 744 2383, E-mail: yaraki@med.nagoya-u.ac.jpIntroduction

aortic surgery. Fibrinogen concentrate is a useful blood product that can help to improve hypofibrinogenemia when intraoperative coagulopathy occurs. However, it is not yet approved for the treatment of intraoperative hypofibrinogenemia in Japan. The use of fibrinogen concentrate has been limited to only cases of congenital hypofibrinogenemia or other congenital coagulopathy disorders. These clinical limitations of fibrinogen concentrate in Japan are probably the same as in Western countries. Therefore, the use of fibrinogen concentrate to manage intraoperative coagulopathy has not been approved, even during thoracic aortic surgery. In the literature,[1,2] the transfusion of fibrinogen concentrate during cardiac surgery reduced the amount of intraoperative blood transfusion required. The advantage of the administration of fibrinogen products is that they can raise the serum fibrinogen levels (SFL) quickly without volume loading, unlike fresh frozen plasma (FFP) products.

At our institute, fibrinogen concentrate was approved to treat intraoperative coagulopathy due to hypofibrinogenemia by our institutional ethics committee, not only for thoracic aortic surgery, but also all other highly invasive surgeries. We have routinely measured the SFL during cardiac and thoracic aortic surgery and have aggressively used fibrinogen concentrate intraoperatively when patients showed hypofibrinogenemia. There are no definite guidelines regarding when to administer fibrinogen concentrate during thoracic aortic surgery at our institute, however, fibrinogen concentrates are principally used for patients who show the SFL under 150 mg/dl and/or patients who show a massive bleeding tendency, regardless of the values of SFL.

In this study, we measured the changes in the SFL during thoracic aortic surgery and clarified the incidence and predictors of hypofibrinogenemia. We also evaluated the clinical efficacy of fibrinogen concentrate for the management of hypofibrinogenemia during thoracic aortic surgery.

PATIENTS AND METHODS

This retrospective survey was performed on consecutive patients surgically treated for diseases of the thoracic aorta at our institution from 2010 to 2012. Excluding stent grafting therapy (TEVAR; Thoracic Endovascular Aortic Repair), hybrid therapy without cardiopulmonary bypass and wrapping of the ascending aorta, there were 216 thoracic aortic surgeries performed between January 2010 and December 2012. The patient characteristics are shown in Table 1. The mean age of the patients was 64.0±12.7 years. There were 25 patients who underwent emergency surgery and 33 patients who underwent urgent operations. The details of the surgical procedures were as follows: 23 patients underwent root reconstruction, 59 ascending aortic replacement, 92 arch replacement, 22 descending aortic replacement and 19 patients underwent thoracoabdominal surgery. The other surgeries included descending aorta tailoring in one case, anti-anatomical arch reconstruction in one and descending aorta formation in one case.

Hypothermia, which may be related to coagulopathy,[3,4] has been applied for brain protection. Selective cerebral perfusion is mainly used for total aortic arch replacement under moderate hypothermia around 25°C. Retrograde cerebral perfusion is routinely used for hemiarch replacement in patients with acute aortic dissection under deep hypothermia around 20°C. When aortic cross-clamping could be applied, the root surgery or proximal ascending aorta replacement required no intentional hypothermia. Descending and/or thoracoabdominal replacement was mainly performed with partial bypass under mild hypothermia.

Informed consent for the intraoperative use of fibrinogen concentrate was obtained from all patients undergoing thoracic aortic surgery before the operation. The retrospective review of the medical records for this study was also approved by the institutional ethics committee. The administration of fibrinogen concentrate was decided by discussions between surgeons and

Table 1 The Patient Characteristics

Patient number	216
Age (years)	64 ±12.7
Male gender	146 (67.6%)
DM	26 (12.0%)
Hypertension	156 (72.2%)
Hyperlipidemia	64 (29.6%)
CKD	22 (10.1%)
HD	7 (3.2%)
COPD	8 (3.7%)
Current smoking	131 (60.6%)
Surgery	
Elective	158
Urgent	33
Emergency	25
Surgical extent	
Root	23
(Root + Asc + Arch)	(5)
(Root + Asc)	(4)
Asc	59
(Asc + Arch)	(4)
Arch	92
Desc	22
Desc + Thoracoabdominal	6
Thoracoabdominal	13
Hypothermia	163
No BTF	14
Fibrinogen concentrate	147 (68.1%)
Platelet products	168 (77.8%)
Intraoperative RBC (U)	14.2±12.7
Intraoperative FFP (U)	20.5±17.0
Intraoperative PC (U)	25.4±12.4

Asc Ascending Aorta, Desc Descending Aorta, BTF Blood Transfusion
Values are expressed as *n* (%), mean ±SD

anesthetists, based on the SFL and/or aspects of the bleeding tendency. Fibrinogen concentrates are principally administrated for patients who show hypofibrinogenemia (< 150 mg/dl) or patients who show a serious bleeding tendency, regardless of the values of the SFL. There were 147 patients (68%) who received fibrinogen concentrates, with an average dose of 5.6±3.5 g (FIB group), and the other 69 patients underwent surgery without fibrinogen products (non-FIB group).

The average usage of the red blood cells (RBC), FFP and platelet concentrate (PC) were 18±13, 25±18 and 25±14 (U) in the FIB group, which were significantly higher than those of 6±7, 10±8 and 8±10 (U), respectively, in the non-FIB group.

A quick blood test was routinely performed about 20 minutes before the termination of cardiopulmonary bypass. It included the hemoglobin (Hb) level, platelet (PLT) counts, prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen levels. Furthermore, additional measurements were performed during the operation according to the visual aspect of surgical bleeding or the formation of clots, and were routinely done upon the admission to the intensive care unit.

The SFL was measured by the Clauss method[5] at our institute. The results of the quick blood test were promptly reported within 30 minutes. The administration of blood products, including fibrinogen concentrate, was considered before reversing the heparin with protamine sulfate.

In this study, the incidence and predictors of hypofibrinogenemia were also studied. For this purpose, the patients were divided into three groups according to their SFLs at the termination of CPB as follows: patients with SFLs < 100 mg/dl were defined as group 100, those with levels of 101–150 mg/dl were group 150 and those with levels of 151–200 was group 200. The intraoperative use of blood products was also compared among the groups.

All data were expressed as the means ± standard deviation. Differences between two groups were analyzed by means of a t-test. Comparisons between groups were done using the Chi square test or Fisher's exact test. Correlations among data were analyzed by determining Pearson's coefficients. A factor analysis was done by performing a univariate logistic regression analysis. A p value < 0.05 was considered to be statistically significant. These statistical analyses were performed with the SPSS version 22 software program.

RESULTS

1. Serum fibrinogen levels (SFL)

The serum fibrinogen levels (SFL) were dramatically decreased to half of the preoperative value (352±131 mg/dl to 164±71 mg/dl) at the termination of CPB, and recovered gradually up to 265±68 mg/dl at ICU admission. More than half (110 cases, 51%) of the patients showed hypofibrinogenemia (< 150 mg/dl) at the termination of CPB, including 28 cases (13%) who showed values < 100 mg/dl, and the lowest value noted was 25 mg/dl.

The SFL dropped more dramatically at CPB termination and had recovered almost fully by ICU admission in the FIB group (333±121, 139±53 and 262±75 mg/dl), while the non-FIB group showed a decrease by nearly half at CPB termination, but slight recovery at ICU admission (402±120, 228±81 and 286±98 mg/dl) (Fig. 1). The SFL at the termination of CPB were significantly lower in the FIB group ($p>0.05$) than those in the non-FIB group, while there were no significant differences between the preoperative values and values at ICU admission between the groups. Two-thirds (69%) of the FIB group showed hypofibrinogenemia under 150 mg/dl at the termination of CPB, whereas the majority of the non-FIB group (81.4%) showed the SFL over 150 mg/dl.

The SFL at the termination of CPB showed a strong correlation with the preoperative values ($r=0.64$); however, they showed a moderate negative correlation with the CPB time ($r=–0.25$) and no correlation with the lowest nasopharyngeal temperature ($r=0.09$). Preoperative values under 250 mg/dl resulted in hypofibrinogenemia under 150 mg/dl at the termination of CPB in 40 of the 42 cases (95%), however, 18 of the 26 cases (69%) with perfusion lasting more than six hours, and 41 of 68 cases (69%) with hypothermia less than 24°C showed hypofibrinogenemia

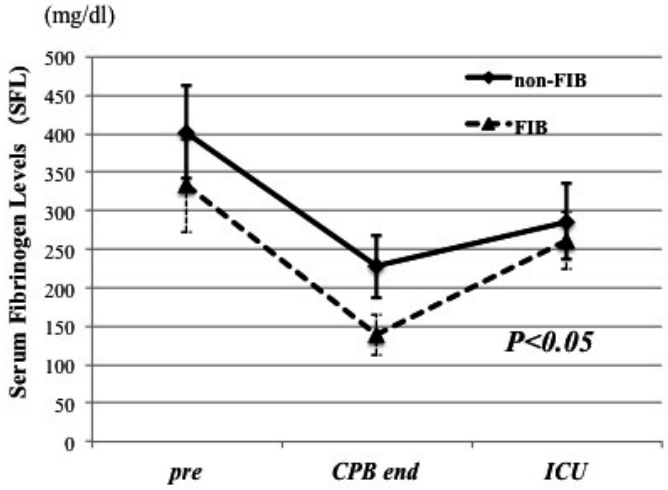

Fig. 1 The perioperative serum fibrinogen levels in the FIB group and non-FIB group

under 150 mg/dl at CPB termination. The predictors of hypofibrinogenemia under 150 mg/dl at the termination of CPB were preoperative SFL less than 250 mg/dl, emergency surgery and thoracoabdominal aortic replacement, as identified by a univariate logistic regression analysis, while acute aortic dissection or aortic rupture were not significant predictors.

2. Usage of blood products

Based on the SFL at the termination of CPB, there were 28 cases in group 100, 71 cases in group 150 and 32 cases in group 200 in the FIB group. The average SFL at CPB termination of group 100, group 150 and group 200 were 72±22, 127±15 and 173±15 mg/dl, respectively.

Fibrinogen concentrate was administered to recover the SFL with a dose of 9.5±4.5 g in group 100, 4.8±2.5 g in group 150 and 4.4±2.5 g in group 200. However, the SFL recovered to 226±79, 258±67 and 271±66 mg/dl, respectively, in these groups. Group 100 showed lower SFL at ICU admission despite the use of more fibrinogen concentrate (Fig. 2).

The intraoperative use of RBC, FFP and PC were 28±16, 36±24 and 33±16 U in group 100, 16±12, 22±16 and 25±14 U in group 150 and 14±9, 22±12 and 21±11 U in group 200, respectively. Group 100 required significantly larger amount of blood products, however, there were no significant differences between group 150 and group 200 in terms of the amount of blood products administered (Fig. 3).

There were no cases categorized as belonging to group 100, 11 cases in group 150 and 22 cases in group 200 in the non-FIB group. The SFL in group 150 and group 200 were 131±15 and 179±12 mg/dl at CPB termination, and recovered to 177±34 and 254±71 mg/dl at ICU admission, respectively.

The intraoperative use of RBC, FFP and PC were 6±8, 10±10 and 7±8 U in group 150 and 5±6, 10±8 and 9±11 U in group 200, respectively. There were no significant differences between the two groups in terms of the amount of blood products used (Fig. 3).

3. Surgical results and clinical safety

Among the 25 emergency surgeries, the fibrinogen concentrate was used in 18 cases (72%). In thoracoabdominal aortic surgeries, fibrinogen concentrate was used in but one case (17 patients,

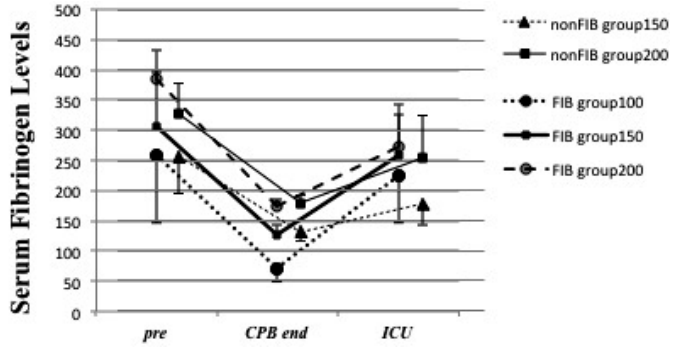

Fig. 2 The perioperative changes in the serum fibrinogen levels between the FIB group and the non-FIB group. The FIB group included three subgroups divided by the minimum fibrinogen values after CPB termination, and the non FIB group included two subgroups.

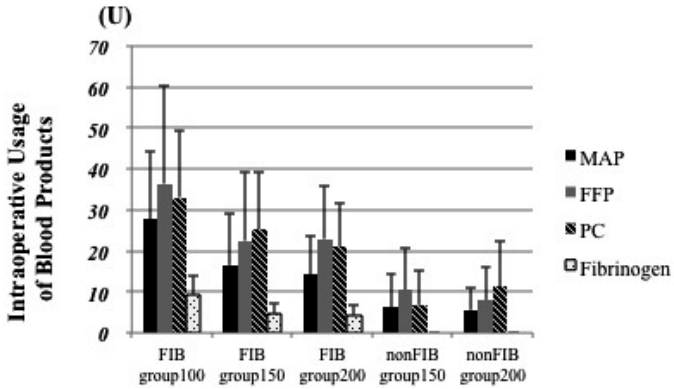

Fig. 3 The intraoperative use of blood products in the FIB group and the non-FIB group. The patients in Group 100 of the FIB group required a large amount of blood products. RBC: Red Blood Cells, FFP: Fresh Frozen Products, PC: Platelet Concentrate.

94%). The rate of fibrinogen concentrate use was higher in patients who required a long CPB time (> 6 hours; 92.0%) and patients who were exposed to hypothermia less than 24□ (75.3%). Fibrinogen concentrate was generally used in complex and long surgeries.

There were 14 cases (10%) that required re-exploration for bleeding in the FIB group and two such cases (3%) in the non-FIB group. Stroke was a complicating condition in 12 cases (8%) in the FIB group and seven cases (10%) in the non-FIB group. Hemodialysis was required in nine cases (6%) in the FIB group and one case (1%) in the non-FIB group. Postoperative atrial fibrillation was observed in 40 cases (27%) in the FIB group and 12 cases (17%) in the non-FIB group. There were no significant differences between the groups in each of these factors.

There were five cases of 30-day mortality (2.3%). There were four deaths (2.7%) in the FIB group and one death (1.4%) in the non-FIB group. There were also no significant differences between the groups in terms of the 30-day mortality rate. The causes of death were sepsis in three patients, ischemic colitis due to malperfusion in one and MRSA pneumonia in one. There were no deaths related to massive bleeding. There were also no serious allergic complications associated with fibrinogen concentrate.

DISCUSSION

The management of coagulation disorders has still been a major concern in thoracic aortic surgery. Most thoracic aortic surgeries, such as aortic arch surgery, require hypothermia for brain protection, which is associated with a long CPB time and may cause dysfunction of the platelets and coagulation system. Surgery for the thoracoabdominal aorta is performed via a large spiral incision, which makes a large and invasive surgical field, and creates a large foreign body surface for blood. The long cardiopulmonary bypass, hypothermia and large invasive surgical fields are all associated with the consumption of coagulation factors and dysfunction of the coagulation system, and may lead to intraoperative coagulopathy. Therefore, maintaining coagulation is mandatory to ensure that a safe surgery can be performed and to reduce the amount of blood transfusion required during thoracic aortic surgery.

The causes of coagulopathy during thoracic aortic surgery are numerous ; [6] however, hypofibrinogenemia is one of the major factors leading to coagulopathy. The present study demonstrated that more than half of the enrolled cases showed hypofibrinogenemia (< 150 mg/dl SFL) at CPB termination. Of note, 13% of all cases showed severe hypofibrinogenemia under 100 mg/dl, which generally causes critical coagulopathy.

Many studies have reported the perioperative fibrinogen levels during cardiac surgery[7-9] and have indicated that lower postoperative fibrinogen levels were associated with more extensive intraoperative blood loss. However, there have been few studies that have reported the intraoperative fibrinogen levels during surgery, especially during aortic surgery.[10,11] In these points, the present study contributes new information.

The administration of fibrinogen concentrate appears to be an optimal way to treat hypofibrinogenemia; however, the intraoperative use of fibrinogen concentrate for hypofibrinogenemia has not yet been approved in most countries. Therefore, FFP is a realistic alternative for fibrinogen products. To improve the coagulation under hypofibrinogenemia, however, a large volume of FFP transfusion would be necessary; furthermore, it takes a longer time for a full recovery of the SFL to be reached after the administration of FFP. Therefore, fibrinogen concentrate is the best way to increase the SFL promptly, and without volume loading. A quick recovery of the coagulation system should result in better surgical hemostasis and reduce the total amount of blood transfusion required. It may thus result in a reduction of the total medical expenses.

The criteria for when to administer fibrinogen products for intraoperative coagulopathy have not been determined. Based on the guidelines for blood transfusion proposed by the Ministry of Health, Labour and Welfare of Japan, the use of FFP is recommended for hypofibrinogenemia less than 100 mg/dl due to DIC or after a large amount of blood transfusion. In the present study, patients who showed hypofibrinogenemia with a value < 100 mg/dl required a significantly larger amount of fibrinogen products and blood transfusion than did the patients with higher levels. Hypofibrinogenemia under 100 mg/dl must be considered a critical coagulopathy, and should be treated with fibrinogen concentrate to achieve surgical hemostasis.

However, there are still no criteria for the administration of fibrinogen concentrate even at our institution. In fact, surgeons and anesthesiologists discussed the use of fibrinogen products not only based on the serum fibrinogen level, but also the blood clot formation in the surgical field. We generally administer fibrinogen concentrate for hypofibrinogenemia less than 150 mg/dl at the termination of CPB as a temporary criterion. Because the SFL at the termination of CPB are not the lowest value and they generally decreased during surgical hemostasis, it may be necessary to identify different cut-off values or to measure the levels at another time point. There were no significant differences in the total amount of blood products used between patients who showed fibrinogen values of 101–150 mg/dl and 151–200 mg/dl. This may indicate that

fibrinogen concentrate achieved sufficient hemostasis and reduced the use of blood products even in patients with SFL of 101–150 mg/dl. Hypofibrinogenemia less than 150 mg/dl may be a useful value as a cut-off criterion for when to administer fibrinogen concentrate.

The next concern is how much fibrinogen concentrate is required to achieve sufficient surgical hemostasis. The average SFL at ICU admission were 250 mg/dl, which may be the optimal target value for sufficient surgical hemostasis, because a sufficient SFL is necessary upon the neutralization of heparin. When the SFL are restored effectively and promptly at this point, the subsequent coagulation failure could be avoided. However, in cases without sufficient hemostasis, the surgical bleeding is prolonged, and the consumption of coagulation factors continues. This leads to a gradual decrease in the SFL, and leads to a vicious cycle of coagulopathy. Therefore, sufficient SFLs are mandatory before protamine injection, especially after complex and difficult surgeries. A dose of one gram of fibrinogen concentrate theoretically will increase the SFL by 20 mg/dl in a 65 kg patient with 5L of intravascular blood volume. When patients show a SFL of 150 mg/dl at CPB termination, 5 g of fibrinogen concentrate is therefore theoretically required to achieve the target SFL of 250 mg/dl.

The guidelines for blood transfusion also recommend that blood examinations, including fibrinogen, PT and APTT, are mandatory before the use of FFP. We have a quick measurement system to examine the coagulation in our laboratory, and can obtain a prompt response within 30 minutes even at night. We propose that such a quick measurement of the coagulation is mandatory for deciding whether to administer fibrinogen concentrate. The information obtained by this quick measurement of the coagulation is important for the surgical team to understand the patients' coagulation condition. A lack of factors such as fibrinogen or platelets should be noted and remedied before the neutralization of heparin and during surgical hemostasis. When the bleeding tendency is predicted to continue in the surgical field, additional measurements should be performed. Surgeons must understand the mechanisms underlying coagulopathy in order to achieve sufficient surgical hemostasis.

As noted above, fibrinogen concentrate has not been approved for hypofibrinogenemia during surgery in Japan. This situation is similar in many Western countries. Fibrinogen concentrate will be approved in the near future for intraoperative coagulopathy. Prior to this, the safety of the intraoperative use of fibrinogen concentrate should be confirmed. The present study was a retrospective observational study; however, there were observed no complications related to the fibrinogen concentrate. In addition, there is no evidence that fibrinogen concentrate increased the risk of major complications or mortality.

In conclusion, hypofibrinogenemia frequently was observed at the termination of CPB during thoracic aortic surgery. Hypofibrinogenemia is one of the major factors associated with intraoperative coagulopathy. Quick measurement of the coagulation status is mandatory for deciding whether to administer fibrinogen concentrate, and should provide important information to understand the patients' coagulation condition as well. Hypofibrinogenemia of < 150 mg/dl SFL may be a useful criterion to decide whether to administer fibrinogen concentrate. The intraoperative administration of fibrinogen concentrate appears to be an optimal strategy to increase the SFLs effectively and promptly. It can treat coagulopathy and reduce the need for a large blood transfusion, and can help to avoid massive bleeding during thoracic aortic surgery.

DISCLOSURE

All the authors have declared no competing interest.

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