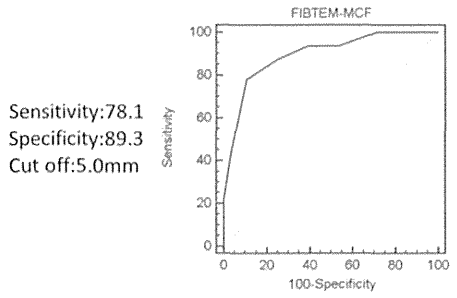
図２:FIBTEM-MCFのROC解析



D.考察

術中大量出血・大量輸血によって生じる希釈性凝固障害を適切に治療するためには、術中の凝固検査が必須である。しかしながら、その完全実施は難しい。その一番の理由は、検査用検体が採取されてから手術室に検査結果が報告されるまでの所用時間が長すぎることである。そのため、平成24年度の研究では多くの病院の検査室に設置されている血液凝固自動分析装置を用いた迅速凝固検査の方法を確立した。また、最近、一部の施設でPOCT機器であるROTEMが用いられるようになってきた。しかしながら、日本人の血液検体を用いて、凝固検査自動分析装置による凝固機能検査結果とROTEMによる結果を大量出血患者を対象として比較した成績は存在しない。

本研究では、20単位以上の赤血球輸血を要した患者を対象に、同一検体を凝固検査自動分析装置とROTEMで測定し、そのパラメーターを比較した。内因系凝固機能、外因系凝固機能は自動分析器ではAPPT、PTを測定し、ROTEMではINTEM、EXTEMという測定系を用いてそこから各種パラメーターを算出している。またフィブリノゲン濃度に関しては。自動分析器ではFbgを測定、ROTEMではFIBTEMを用いてパラメーターを求めている。

今回の検討では、APTTとINTEMパラメーター、PTとEXTEMパラメーター間には相関が認められなかった。またAPTTとINTEM-CT、PTとEXTEM-CTの基準値からの逸脱割合にも大きな差を認めた。測定法の違いによるデータの解釈には注意が必要であろう。

FbgとFIBTEM-MCFの間には、正の有意な相関を認めた。また、FIBTEM-MCFの分解能解析では、MCF5mm以上で得られた結果では信頼性があることが確認でき、ROC解析では、Fbg150mg/dLがFIBTEM-MCF　5mmに相等することが確認できた。Fbgが100mg/dLを切ると、明らかに止血は困難になるため、大量出血時の凝固検査にROTEMを用いる際には、FIBTEM-MCF 5mmがフィブリノゲン補充のトリガーとなる可能性が示された。

今後、共同研究者の藤井は周術期の大量出血患者でのフィブリノゲンの希釈性低下が引き起こす病態を詳細に解析するため電気泳動法とウエスタンブロットを用いて検討し結果を報告する準備中である。

E.結論

術中大量出血患者の血液検体を用いて、通常用いられる血液凝固自動分析装置の検査結果と、POCT機器であるROTEMの分析結果を比較検討した。

APTTとINTEMパラメーター、PTとEXTEMパラメーター間には相関が認められなかった。また、APTTとINTEM-CT、PTとEXTEM-CTの基準値からの逸脱割合にも大きな差を認めた。

Fbg と FIBTEM-MCF の間には、正の有意な相関が認められた。また、FIBTEM-MCF の分解能解析では、MCF5mm 以上で得られた結果の信頼性が上がることが確認でき、ROC 解析では、Fbg 150mg/dL が FIBTEM-MCF　5mm にだいたい相当することが確認できた。

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H．知的財産権の出願・登録状況

該当なし

III.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yamamoto K, Usui A, Takamatsu J.	Fibrinogen concentrate administration attributes tosignificant reductions of blood loss and transfusion requirements in thoracic aneurysm repair.	J Cardiothorac Surg.	9	90	2014
Araki Y, Usui A, Oshima H et al.	Impact of the intraoperative use of fibrinogen concentrate for hypofibrinogenemia during thoracic aortic surgery.	Nagoya J.Med.Sci.	77	265-273	2015
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紀野修一、諏訪部章	司会のことば：危機的出血に対する臨床部門の対応に関するアンケート調査結果.	臨床病理	62(12)	1268-1274	2014
紀野修一	夜勤担当臨床検査技師に必要な緊急輸血・大量輸血の対応.	臨床検査	59(3)	258-263	2015

前田平生、阿南昌弘、田中朝志、牧野茂義、紀野修一.	本邦における大量輸血症例の検討−平成25 年血液製剤使用実態詳細調査（300 床以上）より−	日本輸血細胞治療学会誌	印刷中		2015

IV.　研究成果の刊行物・別冊

JCTS JOURNAL OF CARDIOTHORACIC SURGERY

RESEARCH ARTICLE Open Access

Fibrinogen concentrate administration attributes to significant reductions of blood loss and transfusion requirements in thoracic aortic repair

Koji Yamamoto[1*], Akihiko Usui[2] and Junki Takamatsu[3]

Abstract

Background: Repair of thoracic aortic aneurysm (TAA) is often associated with massive hemorrhage aggravated by dilutional coagulopathy with severe hypofibrinogenemia. Although only fresh frozen plasma (FFP) is available for acquired hypofibrinogenemia in Japan, the hemostatic effect of FFP has not been enough for dilutional coagulopathy in TAA surgery. There are increasing reports suggesting that fibrinogen concentrate may be effective in controlling perioperative bleeding and reducing transfusion requirements.

Methods: We retrospectively analyzed the hemostatic effect of fibrinogen concentrate compared with FFP in total 49 cases of elective TAA surgery. In 25 patients, fibrinogen concentrate was administered when the fibrinogen level was below 150 mg/dL at the cardiopulmonary bypass (CPB) termination. The recovery of fibrinogen level, blood loss, and transfused units during surgery were compared between cases of this agent and FFP (n = 24).

Results: We observed rapid increases in plasma fibrinogen level and subsequent improvement in hemostasis by administration of fibrinogen concentrate after CPB termination. The average volume of total blood loss decreased by 64% and the average number of transfused units was reduced by 58% in cases of fibrinogen concentrate given, in comparison with cases of only FFP transfused for fibrinogen supplementation.

Conclusions: In patients showing severe hypofibrinogenemia during TAA surgery, timely administration of fibrinogen concentrate just after removal from CPB is effective for hemostasis, and therefore in reducing blood loss and transfused volumes.

Keywords: Massive hemorrhage, Thoracic aortic aneurysm, Cardiopulmonary bypass, Dilutional coagulopathy, Hypofibrinogenemia

Background

Aortic repair surgery for patients with thoracic aortic aneurysm (TAA) using cardiopulmonary bypass (CPB) is frequently complicated by massive hemorrhage, most commonly aggravated by dilutional coagulopathy with severe hypofibrinogenaemia. Patients with aortic aneurysms often show silent disseminated intravascular coagulation preoperatively [1]. Impairment of coagulation may be caused by CPB and be further aggravated by hypothermic circulatory arrest [2]. For example, the baseline plasma fibrinogen levels have been reported to decrease by 34% to 58% during CPB [3,4]. In general, failure to manage the coagulopathy and to control microvascular bleeding in cardiac surgery could lead to the increased risk of subsequent morbidity and mortality [5].

Severe hypofibrinogenemia in dilutional coagulopathy during cardiothoracic surgery causes uncontrollable oozing at multiple sites in the surgical field. This bleeding could be stopped only by quick and enough supply of coagulation factors, especially fibrinogen. As the final substrate of coagulation and the ligand of the platelet GPIIb/IIIa receptors, fibrinogen plays a key role in clot formation. Because fibrinogen is the first to fall below a critical value during massive bleeding and hemodilution [6], it would be the critical protein to be supplied first among coagulation factors. Although there are increasing reports describing

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the limitation of fresh frozen plasma (FFP) effect against ongoing severe hypofibrinogenemia in cardiac surgery [7,8], only FFP is currently available for acquired hypofibrinogenemia in Japan. Indeed, cryoprecipitate is not generally supplied from Japanese Red Cross and a purified fibrinogen concentrate derived from pooled human plasma (Fibrinogen HT; Japan Blood Products Organization, Tokyo, Japan) is available only for congenital fibrinogen deficiency in Japan. Fibrinogen concentrate shows a critical effect on fibrinogen recovery and subsequent hemostasis in both hereditary [9] and acquired [10,11] hypofibrinogenemic states, especially in obstetric hemorrhage [12,13], in trauma-induced coagulopathy [14,15], and in cardiovascular surgery [16,17].

The aim of this study is to examine the efficacy of fibrinogen concentrate for reduction in blood loss and transfused volume in TAA surgery. We measured the plasma level of fibrinogen at several time points in patients with TAA surgery and found that severe hypofibrinogenemia progressed during CPB. Because we hypothesized that the quick recovery from severe hypofibrinogenemia would be the most critical for hemostasis in TAA surgery, the hemostatic effect of fibrinogen concentrate was evaluated in comparison with FFP.

Methods

In this single-center retrospective study, we analyzed the plasma fibrinogen level, total amounts of blood loss, and total transfused units of allogenic blood products in 49 patients undergoing elective surgery of thoracic aortic repair involving CPB. Any type of aortic repair surgery with root/ascending aorta, aortic arch, and descending aorta was eligible in this analysis. We administered fibrinogen concentrate when the fibrinogen level in plasma was below 150 mg/dL at removal from CPB in 25 patients. The aim of fibrinogen concentrate administration was to maintain fibrinogen levels above 200 mg/dL. The initial fibrinogen dose was 3 to 5 gram (i.e., 50–60 mg of fibrinogen/kg), but additional fibrinogen concentrate was administered repeatedly when the first administration of fibrinogen concentrate could not elevate the fibrinogen level over 200 mg/dL or achieve complete hemostasis. Meanwhile, age-matched 24 cases in the past 2 years were enrolled as the FFP group, in which only FFP was transfused for correction of hypofibrinogenemia (e.g., < 150 mg/dL) or to stop oozing after CPB termination. Red blood cells (RBCs) were administered according to institutional guidelines, e.g., for hemoglobin levels below 8.0 g/dL in active hemorrhage. Five-unit FFP was administered when the prothrombin time (PT) INR was larger than 2.0, or the patient was actively bleeding. Ten to fifteen units of PC was administered when the platelet count was below $50 \times 10^3/\mu l$. One unit of RBC contains 130 ml of red blood cells derived from 200 ml of whole blood. Five units of FFP contain 400 ml of whole plasma, while 10 units of platelet concentrate (PC) contain $2–3 \times 10^{11}$ of platelets, both of which were obtained by apheresis. The off-label fibrinogen concentrate substitution therapy was approved by the Institutional Review Board of Nagoya University Hospital and complies with the Declaration of Helsinki. The average volume of total blood loss and the average number of transfusion units were compared between the FFP group and the group of fibrinogen concentrate. The significant difference was evaluated by unpaired *t*-test. Pre- and intra-operative levels of hemoglobin and hemostatic markers (e.g., platelet count, PT, activated partial thromboplastin time (APTT), and plasma fibrinogen level) in each group are shown in Table 1.

Results

The hemoglobin level and some hemostatic markers before surgery in patients showed no significant differences between the FFP group and the group of fibrinogen concentrates (Table 1). All patients analyzed in this study progressed hypofibrinogenemia during CPB and their fibrinogen levels frequently fell below 150 mg/dL at the end of CPB. Platelet counts during CPB showed lower than $50 \times 10^3/\mu l$ in most cases we analyzed, in which platelet transfusion was required. We show the representative case as Figure 1, in which only FFP was transfused for supplementation of fibrinogen. The fibrinogen level was gradually elevated by three times of transfusion with 5 units of FFP. In spite of large volume of FFP transfusion, we observed little improvement of hemostasis and continuing oozing at the surgical field, resulting in the additional massive transfusion with FFP, RBC, and PC in this case.

On the other hand, we demonstrate representative cases in which fibrinogen concentrate was administered at the end of CPB as Figures 2, 3 and 4. In the case of

Table 1 Parameters before TAA surgery (baseline) in each group analysed (mean ± SD)

	Only FFP (n = 24)	Fibrinogen concentrate (n = 25)
Hb (g/dL)	13.7 ± 2.7	14.2 ± 2.9
Platelet (× 1000/μL)	178 ± 57	153 ± 38
PT (sec.)	11.2 ± 1.3	11.4 ± 1.0
APTT (sec.)	33.7 ± 2.6	34.1 ± 2.8
Fibrinogen (mg/dL)		
Baseline	275 ± 66	268 ± 57
End of CPB	116 ± 33	108 ± 39
End of operation	141 ± 36	252 ± 46*

The fibrinogen levels at the end of CPB and of surgery in each group are also indicated.
TAA: thoracic aortic aneurysm; *CPB*: cardiopulmonary bypass; *Hb*: hemoglobin; *PT*: prothrombin time; *APTT*: activated partial thromboplastin time; *$P < 0.02$.

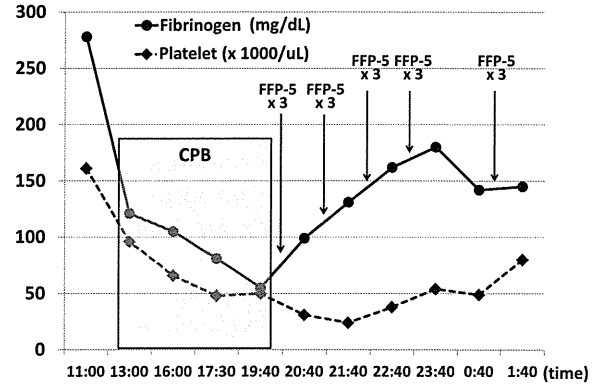

Figure 1 Time course of the fibrinogen level and transfusion with fresh frozen plasma in a patient receiving TAA surgery. The plasma fibrinogen level (mg/dL) and the platelet count are shown in a case of 71-year-old woman with dissecting aneurysm at aortic arch. The time points of administration of fresh frozen plasma (FFP) after cardiopulmonary bypass (CPB) are also indicated. The duration of CPB is shown as a gray box. FFP-5, 5 units of FFP.

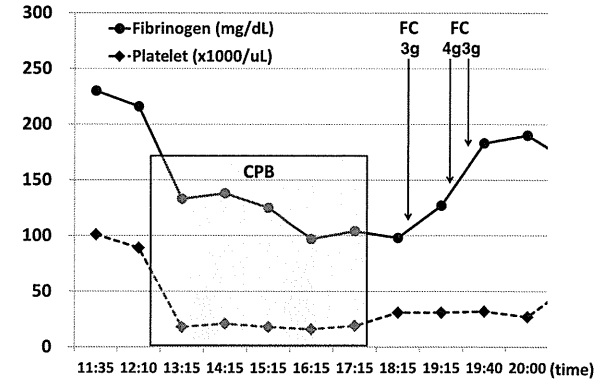

Figure 3 Time course of the fibrinogen level and administration with fibrinogen concentrate in a patient receiving TAA surgery. The plasma fibrinogen level (mg/dL) and the platelet count are shown in a case of 45-year-old man with replacement of aortic root. The time points of administration of fibrinogen concentrate (FC) after cardiopulmonary bypass (CPB) are also indicated. The duration of CPB is shown as a gray box.

Figure 2, a single administration with 4 gram of fibrinogen concentrate elevated the plasma fibrinogen level by 130 mg/dL, leading to complete hemostasis in a short time. Even though severe hypofibrinogenemia around 100 mg/dL progressed during CPB in the case of Figure 3, a rapid increase in the plasma fibrinogen level and subsequent hemostasis were achieved by enough supplementation with fibrinogen concentrate. Although the fibrinogen level did not reach over 200 mg/dL in this case, no more fibrinogen concentrate was necessary because complete hemostasis was achieved after the third administration of fibrinogen concentrate. Also in the case of Figure 4, a dramatic elevation of the fibrinogen level and subsequent complete hemostasis was observed after administration with 5 gram of fibrinogen concentrate two times although critical hypofibrinogenemia below 100 mg/dL progressed during CPB. The median dose of fibrinogen administered in the group of fibrinogen concentrate was 8.2 ± 4.8 gram. In general, the fibrinogen level at the end of surgery was greater than 200 to 250 mg/dL in the group of fibrinogen concentrate administered, which was significantly higher in comparison with the FFP group (Table 1). There was no observed safety concern with using fibrinogen concentrate during and after TAA surgery.

We compared total blood loss and transfusion volume in TAA surgery between the FFP group and the group of fibrinogen concentrates (Figure 5). Dramatic decreases in the bleeding volume and transfusion units of allogenic

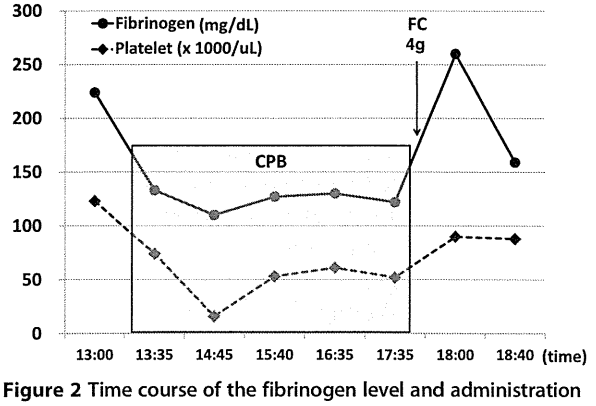

Figure 2 Time course of the fibrinogen level and administration with fibrinogen concentrate in a patient receiving TAA surgery. The plasma fibrinogen level (mg/dL) and the platelet count are shown in a case of 63-year-old man with replacement of ascending thoracic aorta. The time points of administration of fibrinogen concentrate (FC) after cardiopulmonary bypass (CPB) are also indicated. The duration of CPB is shown as a gray box.

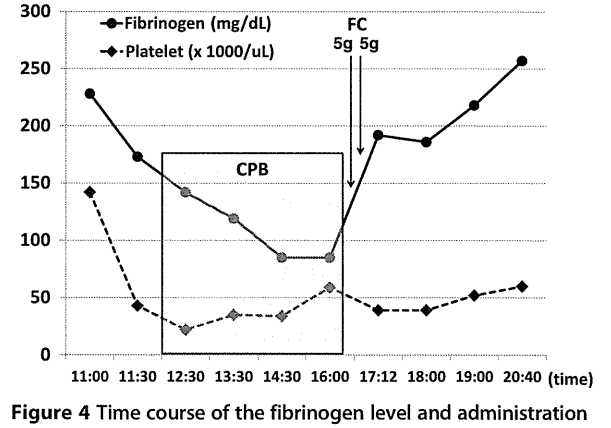

Figure 4 Time course of the fibrinogen level and administration with fibrinogen concentrate in a patient receiving TAA surgery. The plasma fibrinogen level (mg/dL) and the platelet count are shown in a case of 59-year-old man with dissecting aneurysm of descending thoracic aorta. The time points of administration of fibrinogen concentrate (FC) after cardiopulmonary bypass (CPB) are also indicated. The duration of CPB is shown as a gray box.

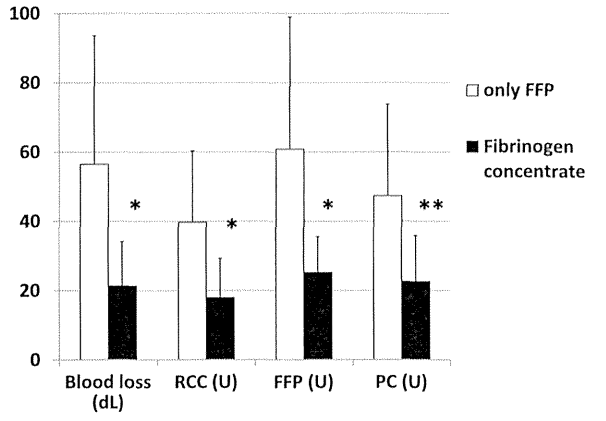

Figure 5 Volume of blood loss and number of transfusion units during TAA surgery. Open bars: cases treated with only FFP (n = 24); Closed bars: cases treated with fibrinogen concentrate as well as conventional transfusion (n = 25). RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate. One unit (U) of RBC contains 130 ml of red blood cells derived from 200 ml of whole blood. Five units of FFP contain 400 ml of whole plasma, while 10 units of PC contain $2–3 \times 10^{11}$ of platelets. The data are presented as the mean ± SD. $*p < 0.05$; $**p < 0.01$ (by unpaired *t*-test).

blood components were observed in the group of fibrinogen concentrate. In cases of fibrinogen concentrate given, the average volume of intraoperative blood loss decreased by 64% (5,640 ml in the FFP group vs. 2,140 ml in the group of fibrinogen concentrate) and the average number of transfusion units was reduced by 56% in RBC (39.7 units in the FFP group vs. 18.0 units in the group of fibrinogen concentrate), 61% in FFP (60.8 units vs. 25.3 units), and 55% in PC (47.3 units vs. 22.6 units), in comparison with cases in which only FFP was administered. Thus, significant reductions in total blood loss and transfused volume during surgery were achieved by timely administration of fibrinogen concentrate after CPB in repair of thoracic aortic aneurysms.

Discussion

We have frequently experienced massive hemorrhage over 5,000 ml, which is characterized by microvascular bleeding due to coagulopathy [18], in surgery of thoracic aortic repair. Cardiovascular surgery using CPB decreases the plasma concentration of coagulation factors primarily by hemodilution with CPB priming and intravenous fluids [4]. We chased the plasma fibrinogen level in patients with TAA surgery and found that the fibrinogen concentration frequently fell below 150 mg/dL during CPB (Figures 1, 2, 3 and 4). In several cases, the plasma fibrinogen level reached less than 100 mg/dL at the end of CPB, as representatively shown in Figure 1 and Figure 4. The CPB-associated reduction of fibrinogen depends, in part, upon the consumptive coagulopathy deteriorated by CPB through activation of coagulation pathway primarily caused by retransfusion of blood aspirated from the surgical field [19,20]. Fibrin clots made under low plasma fibrinogen levels may be feasible and easily lyzed by fibrinolytic system, which frequently activated by CPB [21]. Thus, severe hypofibrinogenemia at the removal from CPB leads to uncontrollable microvascular bleeding, e.g., oozing at multiple sites in the surgical field, after completion of surgical hemostasis, resulting in massive hemorrhage.

Accumulating new data including this study suggest that fibrinogen plays a critical role in achieving and maintaining hemostasis, particularly in patients suffering from severe hypofibrinogenaemia during massive bleeding [22]. Because fibrinogen seems to be the coagulation factor first reaching a critically low level (100 mg/dL) even before thrombocytopenia develops during massive hemorrhage, the hemostatic therapy in this setting should be focused upon quick and enough supplementation of fibrinogen. Although, the target plasma concentration for fibrinogen replacement was predicted by *in vitro* study to be higher than 200 mg/dL as only these concentrations optimized the rate of clot formation [23], high plasma fibrinogen levels over 300 mg/dL may even compensate for low platelet counts [24]. We have conventionally used FFP for the purpose of fibrinogen replacement in intraoperative massive hemorrhage because neither cryoprecipitate nor fibrinogen concentrate has been available for decades in Japan. However, FFP has a low and variable concentration of fibrinogen and cannot be used when targeting a high plasma fibrinogen level. Furthermore, the hemostatic efficacy of FFP has been questioned [8,25]. In fact, the fibrinogen concentration was elevated by only less than 50 mg/dL after 15 units (i.e., 25 ml/kg) of FFP transfusion in TAA surgery (Figure 1), suggesting that it is difficult to reach the fibrinogen concentration over 200 mg/dL by FFP without volume overload.

Several studies and systematic reviews have suggested that fibrinogen concentrate therapy may be effective in controlling perioperative bleeding and in reducing transfusion requirements as well as blood loss in cardiovascular surgery [25-27]. The remarkable observation in our retrospective study is that administration of fibrinogen concentrate after the CPB termination sufficiently elevated the plasma fibrinogen concentration for hemostasis in TAA surgery, while only FFP transfusion did not (Figures 1, 2, 3 and 4). The plasma fibrinogen concentration reached 200 to 250 mg/dL at the end of TAA surgery in patients who received fibrinogen concentrate (Table 1). Also, it appears that enough and repeated supplementation with fibrinogen concentrate in addition to conventional transfusion therapy was strongly associated with decreased blood loss and reduced requirements of RBC, FFP, and PC (Figure 5). The difference in the volume of total blood loss between two groups may be largely attributed to the blood loss

after CPB because most of blood leaking to surgical field is sucked and re-circulated during CPB. Although four products of fibrinogen concentrate, i.e., Haemocomplettan (CSL Behring, Marburg, Germany), Fibrinogene T1 and Clottagen (LFB, Les Ulis, France), Fibrinogen HT, and FibroRaas (Shangai RAAS, Shangai, China), are currently available in the world, the most widely used agent is Haemocomplettan P, commercialized as Ria-STAP in the U.S.A.. A randomized, placebo-controlled trial to investigate the efficacy and safety of Haemocomplettan P in managing severe perioperative bleeding in aortic repair surgery reported that the transfusion of allogenic blood products was significantly reduced in the fibrinogen concentrate group [28,29]. The use of Fibrinogen HT, available in Japan, in the clinical study may limit the possibility of comparison with similar trials. In any case, timely administration of fibrinogen concentrate at the fibrinogen level below 150 mg/dL after CPB termination may be the indispensable hemostatic therapy in aortic repair surgery, even if fibrinogen concentrate is not yet a standard component of many transfusion protocols. If confirmed in larger prospective randomized studies, fibrinogen concentrate would provide a concrete means of reducing transfusions and contribute to better prognosis of patients receiving thoracic aortic repair.

Conclusions

The results of this retrospective analysis strongly support that timely administration of fibrinogen concentrate at the fibrinogen level below 150 mg/dL after CPB termination is effective for hemostasis, and therefore contributes to reduction of blood loss and transfused volumes in patients with TAA surgery.

Abbreviations

TAA: Thoracic aortic aneurysm; CPB: Cardiopulmonary bypass; FFP: Fresh frozen plasma; RBC: Red blood cell; PC: Platelet concentrate; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KY substantially contributed to research design, analyzed data, and drafted the manuscript. AU conceived of studies and shared the overall responsibility with KY. JT revised the manuscript critically. All authors approved the submitted and final version of the manuscript.

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ORIGINAL PAPER

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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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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

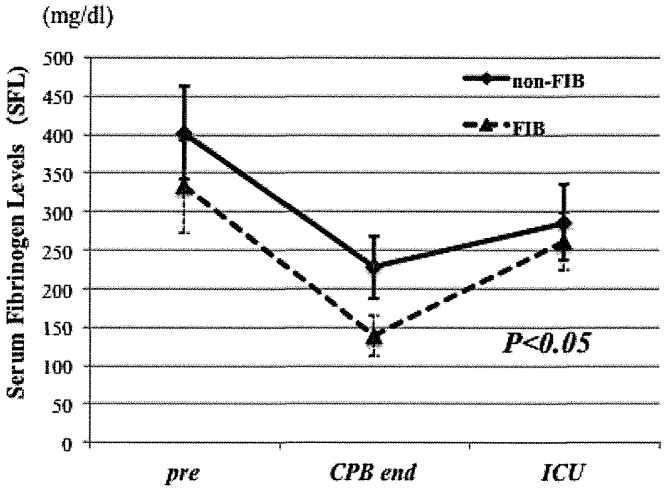

Fig. 1 The perioperative serum fibrinogen levels in the FIB group and non-FIB group

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,

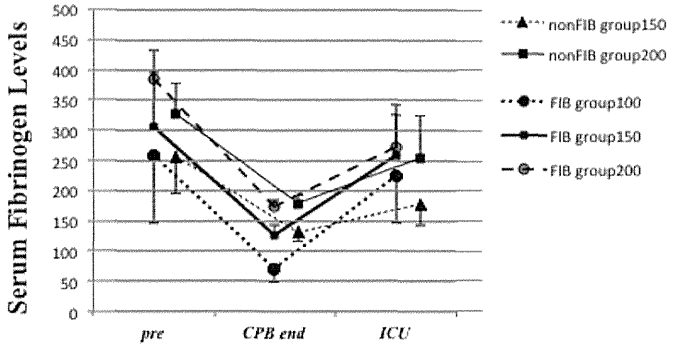

Fig. 2 The perioperative changes in the serum fibrinogen levels between the FIB group and the non-FIB group. The FIB group included three subgroups divided by the minimum fibrinogen values after CPB termination, and the non FIB group included two subgroups.

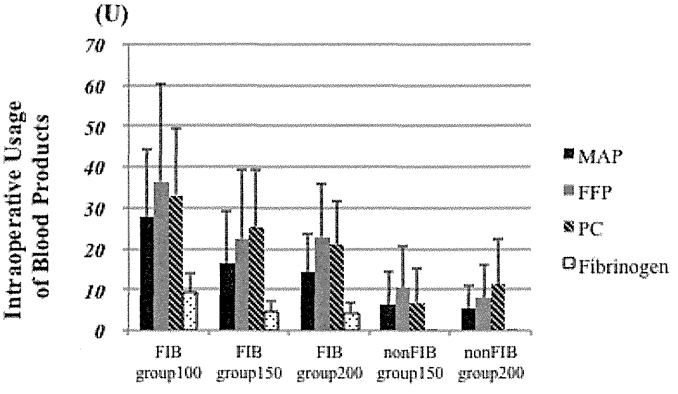

Fig. 3 The intraoperative use of blood products in the FIB group and the non-FIB group. The patients in Group 100 of the FIB group required a large amount of blood products. RBC: Red Blood Cells, FFP: Fresh Frozen Products, PC: Platelet Concentrate.

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