Introduction of thromboelastometry-guided administration of fresh-frozen plasma is associated with decreased allogeneic blood transfusions and post-operative blood loss in cardiopulmonary-bypass surgery

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Background. Cardiac surgery is frequently associated with excessive blood loss requiring multiple blood transfusions which are, in turn, associated with increased morbidity and mortality. We evaluated the effectiveness of rotational thromboelastometry (ROTEM®)-guided administration of fresh-frozen plasma (FFP) with regards to blood loss, transfusion requirements, and major post-operative complications.

Materials and methods. Coagulation management in 68 prospective patients undergoing cardiac surgery with cardiopulmonary bypass was based on a treatment algorithm guided by ROTEM® measurements. The primary end-point was blood loss at 24 hours after surgery. Secondary end-points were: (i) need for allogeneic blood products after cardiopulmonary bypass and 24 hours post-operatively, and (ii) post-operative complications until discharge. The results were compared with those of a retrospective, control group of 69 patients who received empirical coagulation management before implementation of the ROTEM®-guided algorithm.

Results. Although patients with significantly lower haemoglobin levels received less packed red blood cells (PRBC) (840 *vs* 1,120 mL; p=0.031) and FFP (480 *vs* 720 mL; p=0.007) after introduction of the ROTEM® algorithm, the intra-operative blood loss and post-operative haemoglobin levels were similar in the ROTEM® and the retrospective control groups. In addition to significantly reduced blood loss and decreased requirements for PRBC (30.8 *vs* 62.3%; p<0.001) and FFP (25.0 *vs* 56.5%; p<0.001), the amounts of PRBC (315 *vs* 840 mL; p<0.001) and FFP (480 *vs* 840 mL; p=0.001) received during the first 24 hours after surgery were significantly reduced in the ROTEM® group, as was the duration of post-operative hospitalisation.

Discussion. Compared with empirical treatment, timely ROTEM®-guided FFP administration during cardiac surgery can reduce not only overall blood product use and blood loss but also the duration of hospitalisation.

Keywords: blood coagulation, rotational thromboelastometry, cardiopulmonary bypass, fresh-frozen plasma, transfusion.

Introduction

Potential risks of blood product use include transmission of infections, immunosuppression, transfusion-related acute lung injury, and transfusion-associated circulatory overload[1-3]. Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk of excessive blood loss requiring blood transfusion due to dilutional and consumptive coagulopathies, increased fibrinolysis, issues related to heparin-protamine management, and CPB-associated platelet dysfunction[4,5]. The use of supplementary point-of-care (POC) testing has, therefore, been recommended[6-10] to avoid excessive blood loss while optimising blood product management during cardiac surgery with CPB.

Rotational thromboelastometry (ROTEM®) is a method that allows rapid viscoelastic evaluation of clot formation in whole blood. ROTEM® utilises a variety of activators and inhibitors to assess formation of a clot, which consists of an interaction between polymerising fibrin and platelets, thrombin generation, and potential fibrinolysis. The assessment of clot formation enables haemostatic disorders to be identified in a short time. It has been reported that ROTEM®-guided use of blood

products reduces blood loss and alleviates the need for blood product transfusion during cardiac surgery more effectively than the empirical method[7,10,11]. On the other hand, some authors found that impaired haemostasis identified by ROTEM® was not always associated with significant post-operative bleeding and that ROTEM® analysis was not, therefore, useful for predicting which patients would bleed excessively after cardiac surgery[12,13]. It should be noted, however, that the type of activators used for ROTEM® analysis, the timing of the measurement and the interventions differed among the studies.

The aims of this study were to assess the introduction of ROTEM® to guide the administration of fresh-frozen plasma (FFP) during cardiac surgery with CPB and to evaluate the effectiveness of the extrinsic test (EXTEM) and fibrin clot strength test (FIBTEM) -measured approximately 20 minutes before aortic declamping- at determining blood loss and transfusion requirements by comparing the results with those of a retrospective control group who underwent empirical management of haemostasis.

Materials and methods

Ethics committee approval

Approval for this study (N. 2,775) was provided by the ethics committee of Tokyo Women's Medical University (Shunichi Miyazaki, Chair of Tokyo Women's Medical University) on 22nd March, 2013. Written informed consent was obtained from each patient enrolled in the prospective part of the study.

Study population

A total of 82 patients undergoing cardiac surgery with CPB between April 2013 and September 2015 were included in this prospective interventional study (ROTEM® group). Exclusion criteria included a history of any known coagulopathies, liver dysfunction, re-operations, abnormal pre-operative coagulation profiles (international normalised ratio ≥1.3, activated partial thromboplastin time >40 seconds), and/or recent exposure to anticoagulant and/or antiplatelet agents which should have been stopped during the pre-operative period. In all, 14 patients in the ROTEM® group were excluded from analysis because of predefined exclusion criteria. As a result, the ROTEM®-guided algorithm for FFP transfusion was applied to a total of 68 patients (Figure 1). A retrospective group of 81 patients who had undergone cardiac surgery between January 2011 and April 2012 with the same clinical team as for the ROTEM® group was also assessed (control group). The patients in the control group were selected for having received the same haemostatic strategy (i.e., routine administration of tranexamic acid, Hepcon-HMS Plus heparin/protamine management and cell-saver use as described below) except that ROTEM® was not used. Overall, 12 patients in the control group were excluded from analysis due to predefined exclusion criteria. Finally, 68 patients in the ROTEM® group and 69 patients in the control group were included in the data analysis.

Study protocol

The database comprises information on patients' demographics and characteristics including age, sex, and body mass index; pre-operative coagulation laboratory results; details of the surgery performed; time in the operating room including cross-clamping and bypass times; packed red blood cell (PRBC), FFP, and platelet administration; haemoglobin concentration after surgery; and patients' outcome data.

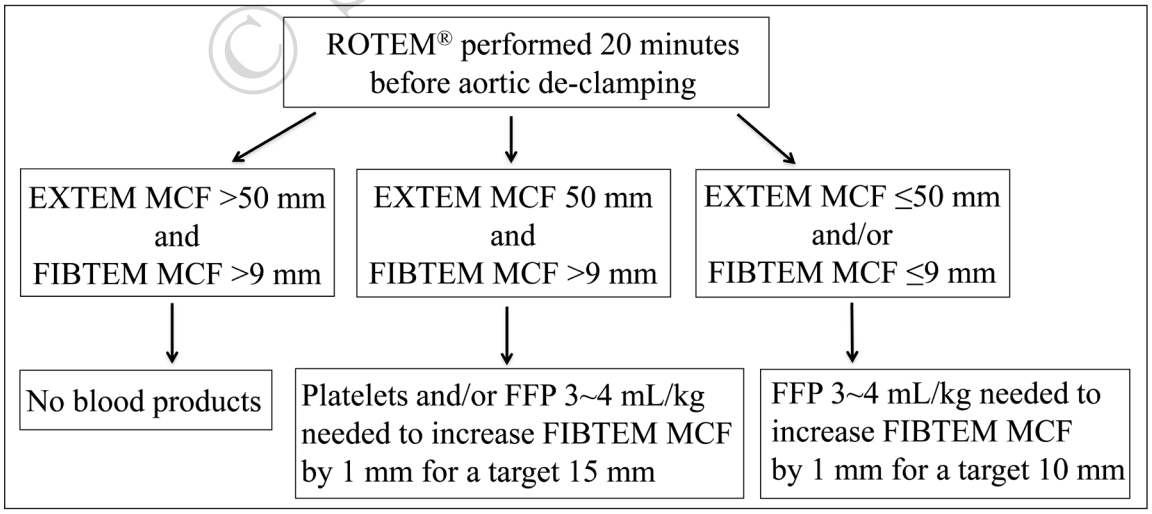

Figure 1 - ROTEM® diagnostic flow chart.
ROTEM: rotational thromboelastometry; EXTEM: extrinsic test; FIBTEM: fibrin clot strength test; MCF: maximum clot firmness.

PRBC transfusion was indicated when the haematocrit dropped below 20% during CPB and below 30% after extracorporeal circulation. PRBC were occasionally transfused despite a haematocrit of more than 30% when the patients' clinical condition dictated or in accordance with the surgeons' instructions. Platelet transfusion was performed in the case of pre-operative thrombocytopenia and/or clinically relevant diffuse bleeding after heparin reversal. Before the introduction of ROTEM®, FFP was transfused without a standardised transfusion protocol based on visual assessment of empirical microvascular bleeding. After the introduction of ROTEM®, FFP was administered based on the ROTEM® results.

Blood samples for ROTEM® analysis (1.8 mL) were obtained via an indwelling arterial catheter and were collected immediately into 3.2% sodium citrate tubes (Venoject II; Terumo Corporation, Tokyo, Japan). Samples were obtained approximately 20 minutes before aortic de-clamping and after coagulation therapy. The primary end-point of the study was 24-hour post-operative blood loss. The secondary end-points were transfusion of allogeneic blood products after CPB in the 24 hours after surgery and post-operative complications (documented until the patient was discharged).

ROTEM® measurements

The coagulation trigger used in the extrinsic test (EXTEM), which reflects thrombin-mediated platelet activation and fibrin polymerisation, was tissue factor. The following variables were measured in the EXTEM assays: clotting time (CT, in seconds); clot formation time (CFT, in seconds); alpha angle, the angle between the baseline and a tangent to the clotting curve through the 2 mm amplitude, in degrees); and maximum clot firmness (MCF, in millimetres). The MCF measurement was also used in FIBTEM, which provides information about the quality of the fibrin-based clot. In FIBTEM, cytochalasin D is added to the EXTEM test to inhibit the contribution of platelets to fibrin clot formation. Figure 1 shows the MCF values derived from the ROTEM®-guided algorithm for the administration of FFP. The ROTEM® measurements were analysed 20 minutes before aortic de-clamping. A FIBTEM MCF ≤9 mm was set as the threshold for FFP administration for a target FIBTEM MCF of 10 mm[14,15]. An EXTEM MCF ≤50 mm and an FIBTEM MCF >9 mm were set as the thresholds for FFP transfusion for a target FIBTEM MCF of 15 mm[14,15]. FFP, equivalent to a fibrinogen dose of 7.5 mg/kg, was administered in the CPB circuit to increase the FIBTEM MCF by 1 mm. The volume of FFP was calculated based on the assumption that FFP contains 2-2.5 mg/mL fibrinogen. Accordingly, 3-4 mL/kg FFP was administered for a targeted increase of 1 mm in FIBTEM MCF. If bleeding continued, further FFP was administered intravenously.

Other measurements

Blood counts and coagulation factors were measured at the same time that the ROTEM® analyses were performed. Complete blood counts and coagulation studies, such as the prothrombin time, activated partial thromboplastin time, international normalised ratio, and fibrinogen concentration, were performed by the central haematology laboratory according to the institutional protocol. Complete blood counts were determined using an LH 780 (Beckman, Brea, CA, USA) and coagulation studies were conducted on an ACL TOP (Instrumentation Laboratory, Bedford, MA, USA).

Anaesthesia (haemostatic strategy) and cardiopulmonary bypass

No attempt was made to standardise the anaesthesia, as standard practice varies widely among professionals. Tranexamic acid was routinely infused intravenously before CPB at a dosage of 1 g. No further continuous infusion was given. A second intravenous dose of 1 to 2 g was administered only if the CPB was prolonged (>140 minutes). We used the Hepcon HMS Plus (Medtronic, Minneapolis, MN, USA) for all patients. Heparin (LEO Pharma, Ballerup, Denmark) and protamine sulphate were administered based on the results. A kaolin-activated clotting time of 450 seconds was determined to be the target value for the heparin dose–response measured on the Hepcon system. A cell-saver collection device (Cell Saver; Haemonetics Corporation, Braintree, MA, USA) was also used in all patients.

All patients underwent CPB using a membrane oxygenator and biocompatible circuits (Capiox, RX-15 or 25; Terumo Corporation, Tokyo, Japan) driven by a centrifugal pump with a mean flow of 2.5 L/min/m^2. Depending on the size of the patient, the extracorporeal circuit was primed with 550 mL Ringer's solution, 30 g mannitol, and 5 mg betamethasone per kilogram of body weight when the body surface area was <2.08 m^2, or 800 mL of Ringer's solution when the body surface area was ≥2.08 m^2.

Data analysis

Data are presented as the mean ± standard deviation or the median and interquartile range (IQR) for continuous variables and percentages for categorical variables. The Kolmogorov-Smirnov test was used to analyse the normal distribution of continuous variables. To detect differences between the ROTEM® and control groups, either an unpaired *t*-test or the Mann-Whitney U-test was performed, depending on the underlying distribution. Chi-squared tests were used to analyse absolute

frequencies (e.g., sex, complications, surgery performed, re-exploration, post-operative hospitalisation, 30-day mortality, and numbers of patients transfused with PRBC, FFP, and/or platelets).

The criterion for rejection of the null hypothesis was $p<0.05$. All the statistical analyses, except the statistical power analyses which were determined using G*Power 3.1 (www.gpower.hhu.de/en.html), were performed using SPSS software (version 11.0; SPSS, Chicago, IL, USA).

Sample size

In a recent retrospective study[16] it was shown that the introduction of a thromboelastometry-guided algorithm was associated with a 43% decrease in the mean amount of blood loss. Because the algorithm used in that study was almost identical to the algorithm used in the current study, we anticipated a reduction in peri-operative blood loss of at least 33%. Considering the average blood loss of 900 mL in a comparable cohort of patients and time period at our hospital, the anticipated discrepancy between the two groups would consequently be at least 300 mL. Sample size analysis (300 mL expected difference of mean blood losses with an expected standard deviation of 700, a desired power of 0.8, and an α error of 0.05) revealed that at least 136 patients (68 per group) would be needed to detect statistically significant differences between the groups.

Results

The patients' characteristics and pre-operative laboratory results are summarised in Table I. Demographic parameters were similar before and after implementation of ROTEM® except for haemoglobin concentration. The mean pre-operative haemoglobin concentration was significantly lower in patients in the ROTEM® group than in patients in the control group (11.7 *vs* 12.5 g/dL p=0.015).

Surgical variables and transfusion data for the two groups during surgery are summarised in Table II). There were no differences between groups regarding the frequencies of the types of surgery, CPB time (ROTEM® *vs* control group; 132.1±53.6 *vs* 142.8±56.6 minutes; p=0.359), or aorta cross-clamping time (ROTEM® *vs* control group: 98.1±43.0 *vs* 100.9±44.3 minutes; p=0.82). Although the ROTEM® patients received less PRBC (mean volume 840 *vs* 1,120 mL; p=0.031) and FFP (mean volume 480 *vs* 720 mL; p=0.007), the intra-operative blood loss (ROTEM® *vs* control group: 695.5±638.4 *vs* 956.3±1,053.2 mL; p=0.103) and post-operative haemoglobin levels (ROTEM® *vs* control group: 10.4±1.3 *vs* 10.1±1.4 g/dL; p=0.435) were similar in the two groups.

Transfusion requirements after surgery, blood loss within 24 hours after admission to the intensive care

Table I - Patients' characteristics and pre-operative laboratory results.

Parameter	ROTEM®	Controls	p
Age (years)	70.0±12.3	66.8±13.3	0.099
Sex (male/female)	34/34	33/36	0.799
Height (cm)	157.3±8.6	157.4±9.8	0.866
Weight (kg)	56.3±11.0	57.3±11.1	0.507
Hypertension (n, %)	30 (44.1)	38 (55.1)	0.272
Diabetes (n, %)	14 (20.6)	10 (14.5)	0.348
Cerebrovascular disease (n, %)	5 (7.4)	9 (13.0)	0.272
Atrial fibrillation (n, %)	10 (14.7)	12 (17.4)	0.669
Renal failure (n, %)	17 (25.0)	12(17.4)	0.276
Pre-operative laboratory parameters			
Haemoglobin (g/dL)	11.7±1.7	12.5±1.9	0.015
Platelet count (10×10^9/L)	172±59	185±59	0.226
Fibrinogen (mg/dL)	399.1±100.8	386.8±130.9	0.797
INR	1.03±0.1	1.09±0.22	0.138
APTT (s)	32.5±4.6	33.6±5.3	0.85

Data are shown as the mean ± standard deviation or n (%). ROTEM: rotational thromboelastometry; INR: international normalised ratio; APTT: activated partial thromboplastin time.

Table II - Surgical variables and transfusion data for the two groups during surgery.

Parameter	ROTEM®	Controls	p
Surgical variable			
Surgery performed	68	69	
Valve surgery	45	45	0.807
Combined valve/ bypass surgery	7	8	0.979
Aortic surgery	10	10	0.972
Others	6	6	0.979
Transfusion data			
CPB time (min)	132.1±53.6	142.8±56.6	0.359
Aortic cross-clamp time (min)	98.1±43.0	100.9±44.3	0.82
Autologous blood product transfusion (n, %)	13 (19.1)	18 (26.0)	0.420
Patients transfused with PRBC (n, %)	47 (69.1)	48 (69.6)	0.955
PRBC transfused (mL)	840 (560)	1,120 (880)	0.031
Patients transfused with FFP (n, %)	39 (57.4)	48 (69.6)	0.138
FFP transfused (mL)	480 (540)	720 (480)	0.007
Patients transfused with platelets (n, %)	8 (11.8)	11 (15.9)	0.479
Platelets transfused (units)	20 (40)	20 (20)	0.904
Discharge haemoglobin (g/dL)	10.4±1.3	10.1±1.4	0.435
Intra-operative blood loss	695.5±638.4	956.3±1,053.2	0.103

Platelets transfused are presented as median (range). Other values are shown as the mean ± standard deviation or n (%). ROTEM: rotational thromboelastometry; CPB: cardiopulmonary bypass; PRBC: packed red blood cells; FFP: fresh-frozen plasma.

unit (ICU), and post-operative outcomes are summarised in Table III. In addition to significantly reduced blood loss (369.5±261.6 *vs* 706.4±444.0 mL; p<0.001), and less frequent requirement for PRBC (30.8 *vs* 62.3%; p<0.001) and FFP (25.0 *vs* 56.5%; p<0.001), the amounts of PRBC (mean volume 315 *vs* 840 mL; p<0.001) and FFP (mean volume 480 *vs* 840 mL; p=0.001) administered during the first 24 hours after ICU admission were significantly reduced in the ROTEM® group. Although there was not a statistically significant difference in post-operative adverse events or bleeding complications requiring re-exploration between the two groups, the duration of hospitalisation after operation was significantly shorter in the ROTEM® group (mean days 11 *vs* 14 days; p=0.002).

ROTEM® parameters, blood counts, and coagulation factors before weaning from CPB and at the end of surgery before admission to the ICU are presented for the ROTEM® group only (Table IV). Of the 68 patients in this group, 18 (26.5%) showed alterations only of FIBTEM MCF, and seven (10.3%) had decreases in both FIBTEM MCF and EXTEM MCF. After administration of FFP, the median FIBTEM MCF increased significantly from 10.0 to 11.0 mm, and an EXTEM MCF of 55.5 mm was maintained. Although five of the 68 patients (7.4%) who had reduced EXTEM MCF in spite of a normal FIBTEM MCF were administered FFP for the target level of FIBTEM MCF 15 mm, the median FIBTEM MCF before and after FFP administration was the same (12 mm) showing that a targeted FIBTEM MCF level of 15 mm cannot be reached by FFP transfusion. Of the 68 patients, nine (13.2%) required FFP after weaning from CPB, even though the FIBTEM MCF and EXTEM MCF were within their respective normal ranges. As a result, of the 39 (57.4%) patients who were given FFP, 31 (45.6%) were given only FFP and eight patients (11.8%) were given both FFP and platelets.

After coagulation therapy, the fibrinogen concentration (232.2±83.1 *vs* 286.1±62.5 mg/dL; p=0.006), haemoglobin level (8.9±0.94 *vs* 9.9±1.1 g/dL; p<0.001), and haematocrit (26.8±2.9% *vs* 30.1±3.1%;

Table III - Transfusion requirements after surgery, blood loss within 24 hours after ICU admission and post-operative outcomes.

Parameter	ROTEM®	Controls	p
Incidence of transfusion in ICU			
Patients without allogeneic blood transfusion on first day (n, %)	40 (58.8)	25 (36.2)	0.008
Patients transfused with PRBC (n, %)	21 (30.8)	43 (62..3)	<0.001
PRBCs transfused (mL)	315 (280)	840 (560)	<0.001
Patients transfused with FFP (n, %)	17 (25.0)	39 (56.5)	<0.001
FFP transfused (mL)	480 (450)	840 (720)	0.001
Patients transfused with platelets (n, %)	5 (7.4)	3 (4.3)	0.453
Platelets transfused (units)	20 (8)	20 (0)	0.77
24-hour blood loss in the ICU, adverse events, mortality			
Drainage volume (mL) during the first 24 h in ICU	369.5±261.6	706.4±444.0	<0.001
Re-exploration for bleeding (n, %)	2 (2.9)	2 (2.9)	0.988
Prolonged ventilatory support (n, %)	1 (1.5)	2 (2.9)	1
Stroke (n, %)	3 (4.4)	2 (2.9)	0.637
Post-operative atrial fibrillation (n, %)	19 (27.9)	12 (17.4)	0.140
Renal failure (n, %)	2 (2.9)	3 (4.3)	0.661
Post-operative hospitalisation (days)	11 (16.2)	14 (20.3)	0.533
30-day mortality (n,%)	2 (2.9)	1 (1.5)	0.551

Drainage volume during the first 24 hours in ICU is presented as mean ± standard deviation. Other values are n (%) or median (range). Prolonged ventilatory support means mechanical ventilation beyond the first day after surgery. ROTEM: rotational thromboelastometry; ICU: intensive care unit; PRBC: packed red blood cells; FFP: fresh-frozen plasma.

Table IV - ROTEM® parameters, blood count, and coagulation factors of all 68 patients in the ROTEM® group before weaning from CPB and at the end of surgery before ICU admission.

Parameter	End of CPB	After coagulation therapy	p
EXTEM			
CT (s) (normal range 38-79 s)	68.0 (28.5)	74.0 (17.5)	0.574
CFT (s) (normal range 34-59 s)	122.0 (64.5)	127.0 (42)	0.953
MCF (mm) (normal range 50-72 mm)	55.0 (8.0)	56.0 (7.5)	0.543
Alpha angle (normal range 63°-83°)	67.0 (12.5)	65.0 (8.5)	0.219
Maximum lysis (%) (normal range ≤15% within 1 h)	7.0 (6.0)	10.0 (5.0)	<0.001
FIBTEM			
MCF (mm) (normal range 9-25 mm)	10.0 (8.0)	11.0 (5.5)	<0.001
Haematocrit (%)	26.8±2.9	30.1±3.1	<0.001
Haemoglobin (g/dL)	8.9±0.94	9.9±1.1	<0.001
PT (s)		14.6±1.4	
APTT (s)		40.3±13.8	
Platelet count ($\times 10^9$/L)	98±46	99±34	0.861
Fibrinogen (mg/L)	232.2±83.1	286.1±62.5	0.006

Data are shown as the mean ± standard deviation or median (range). ROTEM: rotational thromboelastometry; ICU: intensive care unit; CPB: cardiopulmonary bypass; EXTEM: extrinsic test; CT: clotting time; CFT: clot formation time; MCF: maximum clot firmness; FIBTEM: fibrin clot strength test; PT: prothrombin time; APTT: activated partial thromboplastin time.

p<0.001) were significantly higher than those at the end of CPB. We excluded 11 patients whose fibrinogen levels were less than 40 mg/dL because fibrinogen levels cannot be assessed accurately by a prothrombin time-derived method during CPB. The median maximum lysis was 10% within 1 hour of the end of surgery, although it was significantly increased compared with that before weaning from CPB. A second intravenous dose of tranexamic acid 1-2 g was administered to 28 (41.1%) patients in the ROTEM® group and 26 (37.7%) patients in the control group (p=0.676).

Discussion

Our study shows that the introduction of ROTEM®-guided coagulation management is associated with reduced post-operative bleeding, decreased peri-operative PRBC and FFP transfusion and a reduction in the percentage of cardiosurgical patients receiving post-operative PRBC and FFP transfusions.

Our findings are in agreement with those of others[6-10] who have shown a beneficial effect of POC coagulation management during cardiac surgery. Although it is common to use haemostatic algorithms based on POC tests, it is important to note that the POC devices, measurement timing, and interventions differ among reports. Proper timing of coagulation tests is necessary to detect a patient's actual coagulation status, because it undergoes dynamic changes during CPB, and to predict excessive bleeding due to a coagulopathy. Although the introduction of a POC-based transfusion algorithm was similar to that implemented in other studies[6-10], in our study, FFP administration in the CPB reservoir based only on EXTEM and FIBTEM MCF values, 20 minutes before aortic de-clamping, significantly decreased peri-operative use of blood components compared with usage in the retrospective, conventionally managed treatment group.

Fibrinogen is the coagulation factor that first decreases below a critical concentration during massive haemorrhage[17,18]. Görlinger *et al.* found that first-line administration of fibrinogen concentrate was associated with decreased peri-operative bleeding and a lower incidence of blood transfusion[19]. In Japan, fibrinogen concentrate is not available for massive bleeding; it was available only for congenital fibrinogen deficiency due to the spread of hepatitis C virus infection up to 1998 caused primarily by virus-contaminated fibrinogen products[20]. A cryoprecipitate that contains a higher concentration of fibrinogen than FFP is not generally supplied by the Japanese Red Cross but may be used depending on the institution. Because cryoprecipitate is not yet available at our institution, we had to use FFP as a source of fibrinogen.

In our study, the timely availability of ROTEM® results enabled early and specific first-line therapy with FFP, minimising not only FFP requirements but also the amount of PRBC given during surgery. In addition, despite patients in the ROTEM® group starting with a significantly lower haemoglobin concentration pre-operatively and receiving fewer PRBC and FFP transfusions, their mean discharge haemoglobin level was comparable to that in the control group. POC-guided coagulation management might be associated with administering a calculated amount of FFP to patients with coagulopathy not for prophylaxis but for therapeutic purposes. Prophylactic administration of FFP to patients without coagulopathy who are undergoing elective cardiac surgery increases the overall need for PRBC[21]. Although POC tests showed that the clotting process was improved by the use of prophylactic FFP, the difference was too small to make a difference in clinical practice[22].

Coagulopathy after CPB is caused by multiple factors, including disturbed haemostatic function due to haemodilution, coagulation factor depletion, platelet dysfunction, heparin rebound, and activation of the fibrinolytic system[4,5,23]. In this study, heparin and protamine sulphate were administered to all patients based on Hepcon-HMS Plus results. In our study, although all the patients had measurable heparin levels at 2 hours after protamine administration based on the Hepcon-HMS Plus results, an elevated heparin concentration was not correlated with post-operative bleeding[24]. In one patient maximum lysis in EXTEM was more than 15% within 1 hour, but analysis did not show typical ROTEM® tracings of hyperfibrinolysis. The timely use of EXTEM and FIBTEM enables early, specific identification of a coagulopathy after CPB. These tests show the functional status of the fibrinogen and platelet-fibrin interactions. In addition, they allow for a more accurate diagnosis of haemostatic defects even during complete anticoagulation with heparin during CPB[25]. The fibrinogen level in this study was estimated using a prothrombin time-derived method in which a clotting process was triggered by tissue thromboplastin on an automated coagulometer[26]. This method significantly overestimates fibrinogen levels after dilution with albumin and hydroxyethyl starch and is affected by a high concentration of heparin[27]. The significant hypofibrinogenaemia, below 40 mg/dL, in 11 patients in this study might have been caused by a high concentration of heparin. The Clauss method also cannot be used reliably during CPB because the results are decreased significantly by high heparin concentrations[28]. Our therapy was not focused on maintaining exact plasma fibrinogen levels but on fibrin polymerisation and the adherence of platelets to polymerising fibrin. We administered 7.5 mg/kg fibrinogen[14,15] to maintain fibrin intra-operative polymerisation at a level of 10 mm,

which is approximately equivalent to a plasma fibrinogen concentration of 200 mg/dL[29]. Higher fibrinogen levels are necessary to control the multifactorial microvascular bleeding associated with dilutional and consumptive coagulopathies during cardiac surgery with CPB.

Because thrombocytopenia deteriorates platelet contractile forces and increases the risk of bleeding[30], it could be useful to perform EXTEM A5, A10, and MCF tests, which show comparable correlations with the platelet count[17]. Considering the potential for platelet dysfunction and the unexpected or ongoing bleeding during cardiac surgery, we decided to set a platelet count of [(50×10^9/L)–(100×10^9/L)] as the threshold for FFP administration. In a past study[31], the threshold level of EXTEM MCF for predicting platelet counts $<100\times10^9$/L was 53 mm. When the EXTEM MCF was reduced to less than 50 mm, despite the normal FIBTEM MCF, the target level of FIBTEM MCF was set at 15 mm because previous studies demonstrated that high fibrinogen concentrations might compensate for a decreased platelet count with regard to clot formation[32]. We used this approach since timely availability of platelet concentrates is often an issue in Japan. Karlsson *et al*. reported that fibrinogen substitution for platelet concentrates can control haemorrhage and reduce the need for transfusion of allogeneic blood products[33]. This seems to be based on an interaction between platelets with fibrinogen and fibrin to achieve haemostasis[34].

Despite the large amounts of FFP administered, it was not possible to reach the target FIBTEM MCF level of 15 mm, defined in the protocol. This can be explained by the low concentration of fibrinogen in FFP and by the fact that transfusing large volumes of FFP carries a high risk of transfusion-associated circulatory overload. FFP had to be given after CPB to 12 patients who had high targeted MCF values in EXTEM and FIBTEM because of surgical haemostasis and/or difficulty in forming a haemostatic clot in the operating field after CPB. After ROTEM®-guided FFP transfusion, their mean concentration of fibrinogen was 286.1±62.5 mg/dL, which is higher than the threshold of 150 mg/dL commonly used in transfusion algorithms.

Although ROTEM® analysis was performed only during surgery and was not, therefore, included in post-operative management, it did not only decrease intra-operative but also post-operative transfusion requirements. This is in line with the results of other studies[16,35,36] showing that post-operative outcome can be profoundly influenced by meticulous control of bleeding in the operating theatre. We, therefore, stress the importance of achieving a well-balanced post-operative coagulation status in the operating theatre before transfer to the ICU.

Blood transfusions are known to cause inflammation[37] especially in the pulmonary system, acute haemolytic and non-haemolytic reactions[38], transmission of viral and bacterial disease, transfusion-associated circulatory overload, and immunosuppression[39] for which there is a strong dose–response relation[1]. Thus, peri-operative haemorrhage, requiring transfusion, in patients undergoing cardiac surgery is related to a marked deterioration of the prognosis. Knowledge about the amount of blood to transfuse is necessary. We found that the time spent in hospital was significantly shorter after introduction of the ROTEM®-guided use of FFP. There were no particular differences in neurological, cardiac, renal and/or respiratory complications in the post-operative period, which is concordant with the findings of other studies[14,40]. Notably, this study was not powered to show any differences in transfusion-associated adverse events. Further studies are, therefore, needed to assess outcomes in patients undergoing complex cardiac surgery with longer perfusion times, which put patients at risk of excessive peri-operative blood loss.

Our study does have several limitations. First, it was a single-centre study and was not randomised or controlled. The data comparing the two time-periods were analysed and were chosen to have matching sample sizes. There were no changes in senior staff during these two periods, which might have influenced transfusion practices over the study period.

Second, low clot strength in FIBTEM and EXTEM might be better corrected by cryoprecipitate/fibrinogen concentrate and platelet transfusion, respectively. Since these blood products are not or not always promptly available in Japan, we used FFP transfusions instead, being aware of the limited efficacy of such transfusions. The optimal fibrinogen level for haemostasis is not yet known, and a potential association between abnormally elevated MCF in ROTEM® parameters and hypercoagulability is controversial[41,42]. FFP administration for a target FIBTEM MCF of 15 mm to compensate for thrombocytopenia might enhance the risk of post-operative thromboembolic complications. Accordingly, the use of cryoprecipitate/fibrinogen concentrate and platelet transfusions in the ROTEM®-guided algorithm might even improve its efficacy and safety[43].

Conclusions

Correctly timed ROTEM®-guided FFP administration during cardiac surgery reduced post-operative blood loss and overall blood product use compared to that with a transfusion regimen based solely on the clinician's experience. Our findings suggest that these observations are mainly attributable to implementation of an algorithm based on monitoring since no additional

therapeutics were used. It would be interesting to make some modifications to the algorithm and study another prospective group.

Authorship contributions

JI designed and participated in the study, collected and analysed data and wrote the manuscript, reviewed the original study data and data analysis and was the author responsible for maintaining records of the study; KG analysed the data and wrote the manuscript and reviewed the original study data and data analysis; TM, KN, MKod, MO and MKom participated in the study and collected data. All the Authors approved the final version of the manuscript.

The Authors declare no conflicts of interest.

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