Original Article

Safety of Fibrinogen Concentrate and Cryoprecipitate in Cardiovascular Surgery: Multicenter Database Study

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Objectives: To investigate whether administering fibrinogen concentrate or cryoprecipitate is associated with increased postoperative thromboembolic events and improved mortality in patients undergoing thoracic aortic surgery.

Design: Multicenter retrospective cohort study using propensity-score analyses and multivariate logistic regression analysis to control for confounders.

Setting: Four hospitals (1 national cardiovascular center and 3 university hospitals).

Participants: Patients undergoing thoracic aortic surgery with cardiopulmonary bypass between January 2010 and October 2012 (n = 1,047).

Interventions: Outcomes in patients treated with fibrinogen concentrate or cryoprecipitate (fibrinogen group) were compared with those who did not receive these products (no fibrinogen group) based on propensity-score matching. Multivariate logistic regression analysis then was performed to confirm the results.

Measurements and Main Results: Among 1,047 patients enrolled in this study, 247 patients received fibrinogen concentrate or cryoprecipitate. The median amount of administered fibrinogen was 3 g (interquartile range 2-4 g). Eighty-seven patients were excluded from the propensity-score matching because of missing data. Propensity-score–matched analysis showed no significant difference in the incidence of thromboembolic events or 30-day mortality rate between the groups. Multivariate analysis revealed that the fibrinogen group showed no significant difference in thromboembolic events (odds ratio 1.22; 95% confidence interval 0.76-1.95; p = 0.408) or mortality rate (odds ratio 0.44; 95% confidence interval 0.18-1.12; p = 0.081) compared with those in the no fibrinogen group.

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Conclusions: Administering fibrinogen concentrate or cryoprecipitate was associated with neither thromboembolic events nor 30-day mortality in patients undergoing thoracic aortic surgery. Administering fibrinogen concentrate or cryoprecipitate is safe and does not appear to increase thromboembolic events and mortality in thoracic aortic surgery patients.

Key Words: fibrinogen; fibrinogen concentrate; cryoprecipitate; massive bleeding; cardiovascular surgery

COMPLEX CARDIOVASCULAR surgery with cardio-pulmonary bypass (CPB) can be associated with excessive bleeding. Because several previous studies reported an association between bleeding and mortality, an optimal hemostatic strategy is desirable. Fibrinogen, which reaches critically low levels first among the clotting factors during major blood loss and volume replacement, is a promising hemostatic target in cardiovascular surgery. The Japanese Red Cross, which is the only organization in Japan to collect and supply blood for use in transfusion, does not provide cryoprecipitate, and fibrinogen concentrate is approved in Japan only for patients with congenital fibrinogen deficiency. Therefore, some hospitals produce cryoprecipitate in their own transfusion divisions, or they administer fibrinogen concentrate off-label.

Theoretically, administering fibrinogen concentrate or cryoprecipitate would raise plasma fibrinogen levels rapidly without volume overload, reversing coagulopathic bleeding by enhancing the strength of blood clot formation, resulting in less intraoperative bleeding. However, recent results of randomized controlled trials studying this issue are contradictory, likely because of their relatively small sample sizes and the difficulty involved in enrolling patients with severe bleeding into randomized controlled trials. An added concern is potential thromboembolic complications that worsen patients’ outcomes because fibrinogen concentrate and cryoprecipitate are procoagulatory drugs. In fact, several studies have shown an association between elevated plasma fibrinogen and risk of arterial and venous thrombosis. However, there is only limited evidence regarding the safety of fibrinogen concentrate and cryoprecipitate in patients undergoing cardiac surgery.

The authors hypothesized that concentrated fibrinogen products (fibrinogen concentrate and cryoprecipitate) are associated with improved mortality without increased postoperative thromboembolic events. The goal of this multicenter study was to investigate the authors’ hypothesis using the database from the Japanese nationwide registry for cardiovascular surgery, which was combined with data on the administration of fibrinogen concentrate or cryoprecipitate retrieved from electronic medical records in each hospital, analyzing the data using propensity-score matching and logistic regression analysis.

Materials and Methods

Patients and Study Design

This retrospective, multicenter, cohort study involved the following 4 hospitals: National Cerebral and Cardiovascular Center (Osaka, Japan); Keio University Hospital (Tokyo, Japan); Kobe University Hospital (Hyogo, Japan); and Nagoya University Hospital (Aichi, Japan). This study was approved by the ethics committee of each institution and met the guidelines of the Helsinki Declaration. Written, informed consent was waived by the board because of the anonymous nature of the data. Patients with ages ≥20 years undergoing thoracic vascular surgery with CPB between January 2010 and December 2012 were enrolled in the study. Thoracic vascular surgery was divided into the following 4 groups: root surgery, arch surgery, thoracic surgery, and combined surgery. Root surgery included mainly ascending artery replacement with or without additional surgeries such as valve replacement or coronary artery bypass grafting. Arch surgery included mainly total arch replacement with or without additional surgeries such as valve replacement or coronary artery bypass grafting. Thoracic surgery included mainly descending thoracic aneurysm and thoracoabdominal aneurysm repairs. Combined surgery included mainly patients undergoing total arch replacement and thoracoabdominal aneurysm repair.

Data Collection

Data were collected from the hospitals’ electronic medical databases, which are uploaded to the Japan Adult Cardiovascular Database. This database consists of clinical information for all patients undergoing cardiovascular surgery in almost all hospitals in Japan, the details of which were described elsewhere. The variables contained in the Japan Adult Cardiovascular Database are almost identical to those in the Society for Thoracic Surgeons’ National Database, which collects detailed clinical information about patients undergoing cardiac surgery. However, the Japan Adult Cardiovascular Database lacks data on the administration of fibrinogen concentrate or cryoprecipitate; therefore, the authors retrieved these data from electronic medical records in each hospital and incorporated the data into the analyses.

Outcomes

The primary outcome was thromboembolic events (postoperative stroke, myocardial infarction, pulmonary embolism, and limb ischemia) during intensive care unit (ICU) stay. For this study, thromboembolic events are defined as postoperative stroke, newly emerged paralysis of the central nerve system persisting more than 72 hours before discharge, postoperative myocardial infarction, newly elevated cardiac biomarkers (creatine phosphokinase isoenzymes or creatine kinase MB
isoenzyme greater than twice the upper limit of the reference range or elevated troponin), postoperative pulmonary embolism diagnosed using lung perfusion scintigraphy or angiography, limb ischemia, and any complication caused by limb ischemia. The secondary outcome was 30-day mortality.

**Management of Anticoagulation and Cardiopulmonary Bypass**

This was an observational study, and anticoagulation and CPB management were neither controlled nor standardized. Usually, the authors administer 300 to 400 U/kg of unfractionated heparin as a priming dose for anticoagulation for CPB to achieve an activated clotting time >400 seconds. After CPB discontinuation, protamine is used to neutralize heparin.

Postoperatively, patients were transferred to the ICU for monitoring and mechanical ventilation; patients were extubated when standard criteria were met. Dynamic mechanical thromboprophylaxis (intermittent compression devices or pneumatic compression devices) or graduated compression stockings normally were used postoperatively if there were no contraindications.

**Transfusion Practices**

This was an observational study, and transfusion practices were neither controlled nor standardized. The authors normally administer red blood cells with a target hemoglobin level of 9 to 10 g/dL, and this policy did not change through the study period. The administration of fresh frozen plasma (FFP) and platelet concentrate was at the discretion of attending anesthesiologists and cardiac surgeons. FFP normally is administered for international normalized ratios >1.5, and platelet concentrate usually is administered for platelet counts <100,000 platelets/μL. In the National Cerebral and Cardiovascular Center, cryoprecipitate was transfused if fibrinogen was <150 mg/dL. Usually, one pool of cryoprecipitate was prepared from 1,440 mL of FFP, and the pool contained approximately 2 g of fibrinogen. In Nagoya University Hospital and Kobe University Hospital, fibrinogen concentrate (Fibrinogen HT; Japan Blood Products Organization, Tokyo, Japan) was administered if fibrinogen was <150 mg/dL at weaning from CPB or when the attending surgeon believed that fibrinogen concentrate was required because of surgical bleeding. In Keio University Hospital, neither fibrinogen concentrate nor cryoprecipitate was used intraoperatively or postoperatively; only FFP was administered, targeting a fibrinogen concentration of 120 to 150 mg/dL based on surgical hemostasis. As an antifibrinolytic agent, tranexamic acid was used at the anesthesiologist’s discretion.

**Statistics**

First, patients with missing characteristics data were excluded from the study (Fig 1). Then, propensity-score (PS) matching was performed to balance patients’ backgrounds between the fibrinogen administration group (patients receiving fibrinogen concentrate or cryoprecipitate) and no fibrinogen group (patients not receiving fibrinogen concentrate or cryoprecipitate). PS was calculated to predict the probability of receiving fibrinogen concentrate or cryoprecipitate based on the predictors in Table 1 using a logistic regression model. One-to-one patient matching between fibrinogen and no fibrinogen groups was performed, with the closest estimated PS within 1 caliper (≤0.2 of the pooled standard deviation of estimated logits) using the nearest-neighbor method. The balance in baseline variables was estimated using standardized differences, where >10% was considered imbalanced. Sixty-day mortality and perioperative thromboembolic events were compared between the groups using the chi-square test.

Second, multivariate logistic regression analysis was performed to confirm the results. To calculate odds ratios (OR) and 95% confidence intervals (95% CIs) for 30-day mortality and thromboembolic events during ICU stay, variables with a p value <0.2 with univariate logistic regression analysis were selected for the multivariate logistic regression model with a forced entry of use of fibrinogen concentrate or cryoprecipitate. Regarding “age,” odds per 10 years was calculated, and for “duration of surgery” and “duration of CPB,” odds per 1-hour increase were calculated for easier understanding, clinically. Multiple imputation was used for the multivariate logistic regression analyses to account for variables with missing data (n = 1,047).

All statistical analyses were performed using IBM SPSS, version 22 (IBM Corp., Armonk, NY).
Results

During the study period, 1,047 patients were enrolled. Post-operative outcome parameters in the 4 hospitals are shown in the Supplementary Table. To perform PS matching, 87 patients were excluded because of missing characteristics data, and data for 960 study patients were analyzed. PS matching created 191 pairs of patients with and without fibrinogen concentrate or cryoprecipitate administration (see Fig 1). The median amount of administered fibrinogen was 3 g (interquartile range 2-4 g) in the fibrinogen group, which was calculated by assuming that 1 pool of cryoprecipitate contained 2 g of fibrinogen.

Table 1 shows the baseline characteristics of the unmatched and PS-matched groups. After PS matching, standardized differences for the measured covariates, except degree of urgency, type of surgery, and hospitals, were <0.1, suggesting that groups generally were well-balanced. Table 2 shows the
proportion of 30-day mortality and the incidence of thromboembolic events between the PS-matched groups. No significant difference was found in the incidence of both outcomes between the groups. Even with 1:2 and 1:3 matching, no significant difference in the incidence of both outcomes between the groups was found (data not shown).

Next, to confirm these results, multivariate logistic regression analysis was performed. Several variables that differed between patients who experienced perioperative thromboembolic events (n = 105) and those who did not (n = 942) were identified (Table 3). Multivariate analysis revealed that carotid vessel disease (OR 2.25; 95% CI 1.24-4.07; p = 0.008) and duration of surgery (per 1-hour increase: OR 1.17; 95% CI 1.05-1.29; p = 0.003) were significantly associated with thromboembolic events. However, administering fibrinogen concentrate or cryoprecipitate was not associated with thromboembolic events. Similarly, age (per 10-year increase: OR 1.43; 95% CI 1.03-1.97; p = 0.031), preoperative resuscitation (OR 14.07; 95% CI 3.77-52.5; p < 0.001), and duration of surgery (per 1-hour increase: OR 1.20; 95% CI 1.02-1.40; p = 0.028) were independent risk factors for 30-day mortality (35 of 1,047 patients died). However, administering fibrinogen concentrate or cryoprecipitate was not associated with 30-day mortality (OR 0.44; 95% CI 0.18-1.12; p = 0.081) (Table 4).

Discussion

This study investigated whether administering fibrinogen concentrate or cryoprecipitate to treat bleeding is associated with increased postoperative thromboembolic events or improved mortality in patients undergoing thoracic vascular surgery with CPB. In this multicenter retrospective study using national registry data, PS matching revealed that administering fibrinogen concentrate or cryoprecipitate was associated with neither thromboembolic events nor 30-day mortality, which was confirmed using multivariate logistic regression models with a multiple imputation method for missing data.

Previous randomized controlled trials have attempted to confirm the efficacy, but not the safety, of fibrinogen concentrate.9–12 These studies, given a low event rate of adverse events, are rarely powered to address safety issues. For example, death was reported in only 2 of 60 patients in the fibrinogen group, and none occurred in the control group in a recent randomized controlled trial.12 Another randomized controlled trial reported thromboembolic events in 6 of 78 patients (7.7%) in the fibrinogen group and 10 of 74 patients (13.5%) in the placebo group.11 A recent retrospective, single-center cohort study suggested that perioperative administration of fibrinogen concentrate to bleeding patients undergoing cardiac surgery is not associated with increased incidence of major adverse cardiac and thromboembolic events and mortality,17 which is consistent with the findings of the present study. Contrasting with the previous study, which investigated patients undergoing cardiac surgery (with the exception of patients

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate Logistic Regression Analysis of Patients’ Thrombosis Events in the Intensive Care Unit</td>
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<td>Covariates</td>
</tr>
<tr>
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<tr>
<td>Fibrinogen/cryoprecipitate use</td>
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<tr>
<td>Age (per 10-y increase)</td>
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<tr>
<td>Sex (male)</td>
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<tr>
<td>Smoking (missing 1)</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>Carotid vessel disease</td>
</tr>
<tr>
<td>COPD moderate to severe</td>
</tr>
<tr>
<td>Peripheral vascular disease (missing 51)</td>
</tr>
<tr>
<td>Old myocardial infarction (missing 2)</td>
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<tr>
<td>Redo surgery</td>
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<tr>
<td>Duration of surgery (per 1-h increase)</td>
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<td>Duration of CPB (per 1-h increase) (missing 77)</td>
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<tr>
<td>Type of cardiac surgery (missing 31)</td>
</tr>
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<td>Arch</td>
</tr>
<tr>
<td>Thoracic</td>
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<td>Combined</td>
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NOTE: Missing number (n) represents missing data for that number of patients.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; DM, diabetes mellitus; OR, odds ratio.

Table 2
Postoperative Outcome Parameters in the Propensity-Score Matched Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrinogen/Cryoprecipitate Group (n = 191)</th>
<th>No Fibrinogen/Cryoprecipitate Group (n = 191)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis (%)</td>
<td>27 (14.1)</td>
<td>28 (14.7)</td>
<td>0.884</td>
</tr>
<tr>
<td>30-d mortality (%)</td>
<td>6 (3.1)</td>
<td>10 (5.2)</td>
<td>0.307</td>
</tr>
</tbody>
</table>

NOTE. Categorical data are presented as number (%).
undergoing surgery of the ascending aorta\textsuperscript{17}), the present study investigated patients undergoing thoracic aortic surgery, which can be a more complex surgery with a higher risk of massive bleeding. In addition, patients from 4 different institutions were enrolled, which potentially contributed to external validity.\textsuperscript{18} The ideal clinical situation in which to use fibrinogen concentrate or cryoprecipitate remains unknown. Theoretically, fibrinogen is the first coagulation factor to reach critically low levels during major blood loss and volume replacement, functioning both as a source of fibrin and as a mediator of platelet aggregation.\textsuperscript{4} Therefore, it is reasonable to hypothesize that rapid increases in fibrinogen levels would be more beneficial in patients undergoing complex surgery with a high risk of massive bleeding. To test this hypothesis, the present study was conducted to investigate patients who underwent thoracic aortic surgery. Fibrinogen concentrate and cryoprecipitate were not used at all in 1 hospital, which may have worked in favor of PS matching because neither fibrinogen concentrate nor cryoprecipitate was used, even in severe cases. Results of the present study confirm the safety of fibrinogen concentrate or cryoprecipitate in the chosen patient population. Multivariate logistic regression analysis revealed that the OR of fibrinogen or cryoprecipitate use for 30-day mortality missed statistical significance (OR 0.44; 95% CI 0.18-1.12; \(p = 0.081\)). In the additional logistic regression analysis dividing fibrinogen concentrate and cryoprecipitate as explanatory variables, it was observed that fibrinogen concentrate may effectively reduce mortality (OR 0.20; 95% CI 0.05-0.84). Additional studies with a higher study power may clarify the effect of using fibrinogen concentrate or cryoprecipitate.

Several limitations of this study must be acknowledged. First, because of the observational nature of the study, inference of causality is limited. Also, patients may have left the study, and misdiagnosis of rare adverse events is possible. For example, spinal cord ischemia might present as stroke and be misidentified as a thrombotic complication. It also is possible that some events could have been missed because of the absence of standardized protocols. Second, although this study was based on multicenter data, the data were collected retrospectively. Despite using PS matching to reduce bias related to confounding, the possibility that there may be unobserved confounders such as differences in perioperative management among hospitals, practices, and other blood product management systems and the high likelihood that bleeding patients receive fibrinogen cannot be eliminated. The PS matching results are generalizable only among patients in the PS range included in the paired analysis, and these results may not be applicable to patients with scores outside this range. However, multivariate logistic regression analysis was conducted using a multiple imputation method for missing data, and the authors confirmed the robustness of the results. Third, the authors’ database lacked data on antifibrinolytic agents such as tranexamic acid used intraoperatively and anticoagulation therapy with antiplatelet or anticoagulation agents preoperatively, which also may have affected the results. Fourth, laboratory data for perioperative fibrinogen levels or viscoelastic tests are lacking, which may be useful in guiding appropriate use of fibrinogen products, and this may have affected the results. Fifth, 105 thrombotic events and 35 deaths occurred. Considering the small number of deaths, the logistic regression analysis may have been affected by overfitting.
In conclusion, this study revealed that treatment with fibrinogen concentrate or cryoprecipitate was associated with neither thromboembolic events nor 30-day mortality in patients undergoing thoracic aortic surgery.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2018.06.001.

References