Journal of Cardiothoracic and Vascular Anesthesia 38 (2024) 80–85

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Prospective, Randomized Study of Fibrinogen Concentrate Versus Cryoprecipitate for Correcting Hypofibrinogenemia in Cardiac Surgery Patients

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Objective: Cardiac surgery with cardiopulmonary bypass (CPB) is associated with hypofibrinogenemia and severe bleeding requiring transfusion. Guidelines recommend cryoprecipitate or fibrinogen concentrate (FC) for the treatment of acquired hypofibrinogenemia. This study compared cryoprecipitate and FC for the correction of acquired hypofibrinogenemia and the associated costs.

Design: A single-center, prospective, randomized study evaluating patients with hypofibrinogenemia after cardiac surgery. The primary endpoint was direct treatment cost. Secondary endpoints included the change in fibrinogen level after FC and/or cryoprecipitate dosing.

Setting: A single-center study in Astana, Kazakhstan.

Participants: Participants who underwent CPB from 2021 to 2022 and developed clinically significant bleeding and hypofibrinogenemia.

Interventions: Patients were randomized to receive cryoprecipitate or FC.

Measurements and Main Results: Eighty-eight adult patients with acquired hypofibrinogenemia (<2.0 g/L) after CPB were randomized to receive cryoprecipitate (N = 40) or FC (N = 48), with similar demographics between groups. Overall, mean ± SD 9.33 ± 0.94 units (range, 8-10) cryoprecipitate or 1.40 ± 0.49 g (1-2) FC was administered to the 2 groups. From before administration to 24 hours after, mean plasma fibrinogen increased by a mean ± SD of 125 ± 65 and 96 ± 65 mg/dL in the cryoprecipitate and FC groups, respectively. At 48 hours after administration, there was no significant difference in fibrinogen levels between groups. The mean direct cost of treatment with FC was significantly lower than with cryoprecipitate ($p < 0.0001$): $1,505.06 ± $152.40 and $631.75 ± $223.67 per patient for cryoprecipitate and FC, respectively.

Conclusion: Analysis of plasma fibrinogen concentration showed that cryoprecipitate and FC had comparable effectiveness. However, FC is advantageous over cryoprecipitate due to its ease of handling, lower cost, and high purity.

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CARDIAC SURGERY with cardiopulmonary bypass (CPB) is associated with severe bleeding. Although the cause is usually multifactorial, hypofibrinogenemia (plasma fibrinogen level <150-200 mg/dL) is common.[1] Fibrinogen is the major structural component in clot formation, and is essential for effective hemostasis, but fibrinogen is the first factor to fall to critically low levels in situations such as major hemorrhage and surgical bleeding.[2] Causes of hypofibrinogenemia during CPB include the consumption of coagulation factors, exacerbated through contact with the CPB circuit, as well as hemodilution and hyperfibrinolysis.[1,3,4] There is a close association between low fibrinogen levels and severe postoperative bleeding.[5] Moreover, blood component transfusion after cardiac surgery is associated strongly with increased morbidity, mortality, and hospital costs.[6]

Recent guidelines from the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology recommend the use of cryoprecipitate or fibrinogen concentrate (FC) for the treatment of acquired hypofibrinogenemia during cardiac surgery.[3] Cryoprecipitate is precipitated by thawing leuko-depleted fresh frozen plasma from donors, which is centrifuged and resuspended in plasma; whereas FC is a plasma-derived, highly

Editorial assistance for the writing of the article was provided by Portland Medical Communications Ltd and funded by Octapharma AG. The funding source was not involved in study design, data collection, data analysis or interpretation, or the decision to submit the article for publication.

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https://doi.org/10.1053/j.jvca.2023.10.031

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purified, virus-inactivated preparation. There is a high degree of variability in the concentration of fibrinogen in cryoprecipitate, which is reported to contain between 3-to-30 g/L units of fibrinogen.[7-9] One study found that 2 units of cryoprecipitate per 10 kg body weight raised the plasma fibrinogen concentration by 1 g/L[10]; however, the fibrinogen content of the cryoprecipitate is not standardized. In contrast, reconstituted FC contains a standardized content of 200 mg/dL of fibrinogen.

Other important differences between cryoprecipitate and FC include ease and speed of use, pathogen removal, and content. Cryoprecipitate must be stored at −20°C and has a shelf life of 1 year when frozen, and 4-to-6 hours when thawed. In contrast, FC is lyophilized and can be stored for up to 3 years at room temperature before reconstitution.[11] Cryoprecipitate must be thawed before use, whereas FC can be reconstituted and administered rapidly.[7] Fibrinogen concentrate undergoes pathogen reduction steps during its manufacture. Although a pathogen-reduced preparation of cryoprecipitate recently became available (INTERCEPT Fibrinogen Complex, Cerus Corporation, Concord, CA), the mainstay of cryoprecipitate does not undergo pathogen reduction, and, in comparison to this, FC is considered to be a safer option.[7] Finally, cryoprecipitate is a complex solution containing varying concentrations of von Willebrand factor, fibronectin, fibrinogen, factor (F) VIII, FXIII, and platelet microparticles and, therefore, addresses multiple aspects of coagulopathy, whereas FC administration only addresses fibrin polymerization due to its highly purified nature.[11]

Fibrinogen concentrates do contain FXIII, although the concentration varies among preparations. For example, Fibryga (Octapharma, Lachen, Switzerland) was found to contain a higher concentration of FXIII versus Haemocomplettan (also sold under the brand name of RiaSTAP; CSL Behring, King of Prussia, PA; 0.2 *v* 0.055 IU FXIII/mg fibrinogen), which may explain the increased maximum clot firmness via thromboelastometry.[12]

Cryoprecipitate remains the main choice for fibrinogen replacement in some countries, including the United States, whereas FC is now the predominant choice of therapy in most European countries. In Kazakhstan, where this study was conducted, both FC and cryoprecipitate are available and form the standard of care. The authors performed this prospective, randomized study to directly compare the ability of the 2 therapies to correct acquired hypofibrinogenemia and the costs of the 2 therapies in patients with hypofibrinogenemia after CPB in Kazakhstan.

Methods

This was a pragmatic, single-center, prospective, randomized study carried out in patients who underwent cardiac surgery from 2021 to 2022 and developed clinically significant bleeding and hypofibrinogenemia after CBP. Due to the emergency nature of the condition being studied (ie, bleeding after surgery), the trial only included patients who were incapable of providing informed consent at the time the therapy was needed and in whom delays in obtaining surrogate consent would have been severely detrimental to their well-being and survival. In addition, both cryoprecipitate and FC were standard of care at the authors' institution. Thus, this study qualified for a waiver of informed consent, followed by a postoperative debriefing to patients or their surrogate decision-maker, providing them the opportunity to withdraw from the study, in accordance with subparagraph 104 of paragraph 1 of Article 7 of the Code of the Republic of Kazakhstan dated September 18, 2009.

Patients

Patients were recruited from a single tertiary-care center in Kazakhstan. The study included all adult patients aged ≥18 years who were undergoing cardiac surgery with CPB for whom fibrinogen supplementation was ordered in accordance with accepted clinical standards (ie, significant hemorrhage and hypofibrinogenemia, defined as fibrinogen plasma level <200 mg/dL as confirmed by the Clauss method). Definitions of bleeding included chest drain output >150 mL/h or >600 mL per 12 hours postoperatively.

Patients who had received fibrinogen-containing products, including FC or cryoprecipitate, within 24 hours before surgery, those with a history of severe allergic reaction to cryoprecipitate or FC, and those who refused FC or cryoprecipitate due to religious or other reasons, were excluded from the study.

Treatment

After enrollment, once bleeding was detected and the coagulation assay showed a Clauss fibrinogen level below 2 g/L, patients were randomized via computer-generated randomization into 2 groups. Patients in the first group received FC (Fibryga), whereas those in the second group were treated with cryoprecipitate. For patients in the FC group, the dose of FC was calculated using the following formula: dose of FC (mg/kg body weight) = [target fibrinogen level (mg/dL) − measured fibrinogen level (mg/dL)] / 1.8 (mg/dL per mg/kg body weight), as per the manufacturer's recommended dosing,[13] with a target fibrinogen level of 2.0 g/L. Minimum rounded doses were administered from 1- g vials at the discretion of the treating physician. Patients in the cryoprecipitate group received 1 unit of cryoprecipitate per 5-to- 10 kg body weight, as per the standard of care at the authors' institution. One dose of FC or cryoprecipitate was administered as per the randomization schedule during the first 24 hours after termination of CPB. All other treatment was performed as per the institution's standard of care.

Cost

The primary endpoint of the study was the mean direct cost of treatment with cryoprecipitate and FC. The mean direct cost of treatment was calculated by multiplying the cost per gram or unit by the mean number of grams or units administered to that group. Prices were based on purchase documents for

January 2022, and the United States dollar exchange rate was calculated using rates from January 2022. Only direct costs were analyzed.

Change in Fibrinogen Levels

Fibrinogen levels were assessed before surgery (preoperative), after surgery upon administration of FC or cryoprecipitate (postoperative), and at 24 and 48 hours after administration of FC or cryoprecipitate. Change in fibrinogen level after dosing with FC or cryoprecipitate was a secondary endpoint of the study.

Safety

Adverse events were recorded by the treating physician until 48 hours after the study drug administration, with a specific focus on vascular thromboses, ischemic stroke, and anaphylaxis. Thromboses and vascular events were diagnosed via ultrasound (which was available 24 hours per day) upon suspicion by the investigator, based on typical clinical symptoms. In addition, patients with vascular devices (eg, catheters) were monitored routinely via ultrasound once daily. Anaphylaxis was defined as sudden changes in breathing and hemodynamic assessments, in which cardiogenic and pulmonary causes had been excluded, including ultrasound to check for pulmonary embolism. Computerized tomography scans, magnetic resonance imaging, and urgent angiography were also available 24 hours a day if clinically justified, with electrocardiogram and breathing monitoring performed routinely, as per the standard of care. Data on the length of time spent in the intensive care unit and overall in-hospital mortality during the study also were collected.

Statistical Analyses

For continuous variables, arithmetic mean, SD, median, and range were calculated. For binary or categorical variables, absolute and relative frequencies (n, [%]) were calculated. To assess intergroup differences, *t* tests were performed using pooled analyses for equal variances, and Satterthwaite analyses for unequal variances. Any p values < 0.05 were taken to indicate significance.

The sample size for this single-center, pragmatic study was based on logistic and economic considerations. The study authors estimated that it would be possible to enroll 100 patients per group from 2021 to 2022, with planned interim assessments of the endpoints and group size. After 35 patients were randomized and treated in each group, the authors performed a planned assessment, and found that fibrinogen replacement with FC cost significantly less than that of cryoprecipitate, whereas effectiveness in terms of their ability to increase fibrinogen levels was comparable. Taking into consideration the cost of treatment (which is an important factor for treatment choice in Kazakhstan), the comparable efficacy, and the improved speed and convenience of using FC in an emergency setting, the decision was made to end the study, by which point 40 cryoprecipitate patients and 48 patients requiring FC had been randomized and treated and were included in the final analysis.

Results

A total of 40 patients were included in the cryoprecipitate group, and 48 were included in the FC group. Demographics are shown in Table 1. Attributes were generally similar between groups.

Overall, the mean ± SD of cryoprecipitate administered to patients in the cryoprecipitate group was 9.33 ± 0.94 (range, 8-10), whereas 1.40 ± 0.49 g (1-2) of FC were administered to the patients in the FC group.

Table 1
Demographics

Demographic	Cryoprecipitate Group, N = 40	FC Group, N = 48
Age, median (range), y	59 (29-77)	58 (21-81)
Sex, n (%)		
Female	21 (52.5)	19 (39.9)
Male	19 (47.5)	29 (60.4)
Body measurements, median (range)		
Weight, kg	70.5 (24-96)	69.5 (46-118)
BMI, m^2	26.6 (9.5-34.2)	26.4 (16.7-37.5)
BSA, m^2	1.8 (1.0-2.2)	1.8 (1.5-2.4)
Comorbidity history, n (%)		
Stroke	10 (25.0)	9 (18.8)
MI	19 (47.5)	16 (33.0)
Diabetes	11 (27.5)	14 (29.0)
Type of surgery, n (%)		
Bentall-de Bono	6 (15.0)	5 (10.4)
CABG	12 (30.0)	16 (33.3)
HM3 LVAD	2 (5.0)	2 (4.2)
HTX	1 (2.5)	2 (4.2)
Intimectomy	-	1 (2.1)
Intimthrombectomy from pulmonary arteries	1 (2.5)	-
Valsalva sinus plasty	-	1 (2.1)
Valve surgery	18 (45.0)	20 (41.7)
Valve surgery + CABG	-	1 (2.1)
Surgery timings, median (range), min		
CBP time	83.0 (27.0-198.0)	78.5 (46.0-156.0)
Aortic cross-clamp time	51.0 (0.0-115.0)	48.5 (19.0-93.0)
Baseline levels, median (range)		
Hemoglobin	99.0 (62.0-127.0)	99.0 (62.0-127.0)
Hematocrit	29.0 (20.0-35.1)	29.0 (20.0-37.1)
INR	1.0 (0.8-1.5)	1.0 (0.8-2.3)
Platelet count	253.0 (140.0-410.0)	251.5 (131.0-420.0)

Abbreviations: BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CBP, cardiopulmonary bypass; FC, fibrinogen concentrate; HM3 LVAD, HeartMate 3 left ventricular assist device; HTX, heart transplantation; INR, international normalized ratio; MI, myocardial infarction.

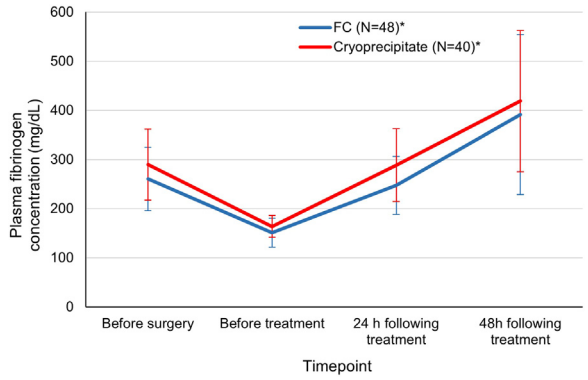

Fig 1. Plasma fibrinogen levels over time following administration of cryoprecipitate or fibrinogen concentrate. FC, fibrinogen concentrate. *N = 33 at 48 hours following treatment, N = 33 for the cryoprecipitate group, and N = 41 for the FC group.

Before surgery, plasma fibrinogen levels were numerically slightly lower in the FC group (Fig 1). Patients in the cryoprecipitate group had a mean fibrinogen level of 289 mg/dL (range, 117-420), and patients in the FC group had a mean fibrinogen level of 260 mg/dL (170-448) (p = 0.0511 for equal variances; p = 0.0542 for unequal variances; Table 2), with the majority of patients falling within the normal range of 200-to-450 mg/dL. After CPB and before study treatment was administered, all patients had a plasma fibrinogen level <200 mg/dL, indicating that they had acquired hypofibrinogenemia; however, patients in the cryoprecipitate group had a significantly higher mean fibrinogen level than patients in the FC group (p = 0.0288 for equal variances; p = 0.0250 for unequal variances). After administration of cryoprecipitate or FC, mean fibrinogen levels increased in both groups. From before administration to 24 hours after administration, the mean plasma fibrinogen level increased by a mean± SD of 125 ± 65 mg/dL in the cryoprecipitate group, and 96 ± 65 mg/dL in the FC group (between groups, p = 0.4409 for equal variance; p = 0.0410 for unequal variances; Table 2). By 48 hours after administration of the study drug, fibrinogen levels had increased further in both groups, and there was no significant difference in fibrinogen levels between patients in the cryoprecipitate and FC groups.

Rates of reexploration and bleeding were similar between groups. Reexploration postoperatively was carried out in 6 (12.5%) of patients in the FC group and 8 (20.0%) of patients in the cryoprecipitate group. Bleeding in the first 12 hours after treatment infusion was median (min, max) 605.0 mL (470.0, 1,600.0) in the FC group and 575.0 mL (400.0, 3,500.0) in the cryoprecipitate group. Furthermore, levels of postoperative infusion of red blood cells were similar between groups, required by 13 (27.0%) patients in the FC group and 12 (27.5%) patients in the cryoprecipitate group.

No adverse reactions or adverse events related to treatment were recorded in patients in either group. Length of stay in the intensive care unit was 5.13 days for patients in the FC group and 6.15 for patients in the cryoprecipitate group, and in-hospital mortality rates were similar (3 [6.25%] patients in the FC group and 3 [7.5%] patients in the cryoprecipitate group).

For patients in this study, the mean direct cost of treatment with FC was significantly lower than with cryoprecipitate (p < 0.0001): the mean ± SD direct cost of treatment with FC was $631.75 ± $223.67 and $1,505.06 ± $152.40 per patient with cryoprecipitate (Table 3).

Table 3
Cost of Treatment With Fibrinogen Concentrate and Cryoprecipitate

Treatment	Cryoprecipitate Group N = 40	FC Group N = 48	p Value*
Mean dose	9.33	1.40	-
Cost per dose, USD	161.40	452.60	-
Cost of treatment per patient, mean ± SD, USD	1,505.06 ± 152	631.75 ± 223.67	< 0.0001

Abbreviations: FC, fibrinogen concentrate; USD, United States dollar.
* p values correct for equal and unequal variances.

Discussion

Results from this study showed that cryoprecipitate and FC were both effective in increasing plasma fibrinogen levels in patients requiring cardiac surgery with CPB, with significant hemorrhage and known or presumed hypofibrinogenemia. No safety concerns were reported for either drug. The direct cost of fibrinogen replacement therapy for patients on FC was less than half for patients who received cryoprecipitate.

Similar results for plasma fibrinogen levels to those observed in the authors' study were seen in the recent FIBRES

Table 2
Plasma Fibrinogen Levels

Plasma fibrinogen	Cryoprecipitate Group N = 40	FC group N = 48	Between Groups p Value (Equal Variances)	Between Groups p Value (Unequal Variances)
Preoperative, mean ± SD, mg/dL	289 ± 72	260 ± 64	0.0511	0.0542
Pre-treatment, mean ± SD, mg/dL	165 ± 19	152 ± 29	0.0288*	0.0250*
24 h after treatment, mean ± SD, mg/dL	288 ± 74	247 ± 59	0.0043*	0.0053*
48 h after treatment, mean ± SD, mg/dL	410 ± 143	390 ± 160	0.4450	0.4388

Abbreviation: FC, fibrinogen concentrate.
* p < 0.05 indicates statistical significance.

study.[14] FIBRES was a randomized, controlled phase 3 study that aimed to determine the non-inferiority of FC versus cryoprecipitate in adult patients experiencing clinically significant bleeding and hypofibrinogenemia after cardiac surgery. The primary endpoint of the FIBRES study, the number of units of blood components administered during the first 24 hours after CPB, was met. Before FC or cryoprecipitate was administered, plasma fibrinogen concentration was similar between study groups. After infusion of FC or cryoprecipitate, the increase in plasma fibrinogen level was greater in the FC group versus the cryoprecipitate group (90 *v* 70 mg/dL; $p < 0.001$). In the authors' study, mean fibrinogen levels after transfusion were higher in patients in the cryoprecipitate group compared to the FC group; however, their study used a lower mean dose of FC than the FIBRES study (mean, 1.40 g *v* 2.1 g, respectively), and a slightly higher mean dose of cryoprecipitate (9.33 *v* 8.5 U, respectively). The FORMA-05 study,[15] which included patients undergoing cytoreductive surgery for pseudomyxoma peritonei, also examined plasma fibrinogen levels in patients with acquired hypofibrinogenemia. The mean dose of FC was 6.48 g, and patients in the cryoprecipitate group received 4.09 pools (equal to 20.45 units). For the Per-Protocol population, the mean ± SD increase in plasma fibrinogen observed after each dose of FC was 78 ± 34 mg/dL, and the mean increase after each dose of cryoprecipitate was 35 ± 29 mg/dL ($p < 0.0001$).

One of the known disadvantages of cryoprecipitate is uncertainty over its fibrinogen content. In both the FIBRES and FORMA-05 studies, intervention with cryoprecipitate and FC was based on near-equivalent doses of fibrinogen.[14,15] Unexpectedly, the plasma fibrinogen level posttreatment in these studies was lower in the cryoprecipitate group compared to the FC group. It is possible that the concentration of fibrinogen in cryoprecipitate, which is not standardized, was lower than anticipated. The authors' results confirmed that the fibrinogen content of cryoprecipitate provided by their blood service in Kazakhstan was estimated, based on the incremental increase in plasma fibrinogen concentration, to be around 200 mg fibrinogen per unit. This is higher than the minimum specified level (140 mg), but this difference does not equate to a cost advantage once the cost of each treatment episode is taken into account. In general, the absence of standardization of the fibrinogen content of cryoprecipitate makes dosing unpredictable and inconsistent across different countries and institutions.

Results from this study showed that in Kazakhstan, the direct cost of fibrinogen replacement with FC is lower than with cryoprecipitate. A recent study by Abrahamyan et al.[16] examined all in-hospital resource utilization costs and allogeneic blood product transfusion costs incurred within 28 days of surgery for a subset of 485 adult patients requiring cardiac surgery in Canadian hospitals from the FIBRES study. Overall mean treatment costs were similar between the cryoprecipitate and FC groups (38,180 CAD *v* 38,790 CAD, respectively). The groups in the FIBRES study were unbalanced, with the FC group including more critically ill patients who presumably required more resources and costs to treat. When excluding these patients, total costs were 35,390 CAD for the FC group versus 37,890 CAD for the cryoprecipitate group.

These results have shown that at the authors' institution, cryoprecipitate and FC result in similar changes in plasma fibrinogen levels after CPB, whereas the direct cost of FC is lower. Other important factors in selecting a fibrinogen replacement therapy include logistics. The preparation of FC for injection is simpler and faster than that of cryoprecipitate, which makes it advantageous in cases of bleeding that need immediate treatment. At the time of writing, FC is now the sole therapy used for fibrinogen replacement at the authors' institution due to its ease of preparation, including the lack of need to defrost, the ability to store at room temperature, and the low volume with quick infusion time.

Study limitations

Limitations of this study included that it was not possible to administer equivalent fibrinogen doses for FC and cryoprecipitate in this pragmatic study because of the necessity to use established protocols and adhere to the existing standard of care. Another limitation was that the costs may differ across different institutions and in different countries. In addition, the authors' cost analysis only assessed direct costs. A cost analysis using activity-based costing,[17] including the indirect costs of devices, processes and procedures, and expenses for storage and testing, and costs in different countries could be investigated in future studies.

In conclusion, the results from this study showed that FC and cryoprecipitate were both effective for increasing plasma fibrinogen levels in patients requiring cardiac surgery with CPB, who suffered significant hemorrhage and hypofibrinogenemia. No safety concerns were reported for either drug. Fibrinogen concentrate was found to be significantly cheaper than cryoprecipitate and advantageous due to the speed and ease of preparation.

Declaration of Competing Interest

None.

Acknowledgments

Editorial assistance was provided by Portland Medial Communications Ltd, funded by Octapharma AG.

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