SciMedCentral

International Journal of Clinical Anesthesiology

Research Article

The Use of Concentrated Fibrinogen in Cardiac Surgery Patients: a Retrospective Chart Review

Antonio Weingartshofer[1], Heather Mingo[1], Blaine Kent[1], Jean-Francois Legare[2], Karen Buth[2], and Myron M. Kwapisz[1]*

[1]Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University, Canada

[2]Department of Surgery, Dalhousie University, Canada

*Corresponding author

Myron Kwapisz, Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University, 1278 South Park St, Halifax, N.S, B3H 2Y9, Canada, Tel: 902-473-4326; Fax: 902-473-3820; Email: myron.kwapisz@nshealth.ca

Submitted: 14 November 2016

Accepted: 28 February 2017

Published: 06 March 2017

ISSN: 2333-6641

Keywords

- Cardiac surgery
- Fibrinogen concentrate
- Perioperative blood management
- Transfusion

Abstract

Purpose: A retrospective chart review was performed to evaluate the effectiveness and safety of fibrinogen concentrate as an additional treatment option for excessive bleeding in cardiac surgery.

Methods: Data from patients receiving fibrinogen concentrate between January 2010 and June 2013 was retrospectively collected from the Maritime Heart Centre database for Cardiac Surgery and from patients' electronic charts at the Queen Elizabeth II Health Sciences Centre.

Results: In total, data for 50 patients receiving fibrinogen concentrate were collected. On average, patients were 60.7 years of age and 68% were male. Baseline laboratory characteristics were slightly lower than reference ranges, possibly due to the high number of urgent or emergency procedures (36%). Patients received fibrinogen concentrate as an additional line of treatment for bleeding and also received, on average, a total of 8.8 units of blood products: 4.3 units of packed red blood cells, 2.5 units of fresh frozen plasma, 1.5 units of platelets and 0.5 units of cryoprecipitate. The overall transfusion rate was 94%. Two patients (4%) suffered from in-hospital stroke and the overall mortality rate was 18%.

Conclusion: Patients received a relatively high number of blood components despite receiving fibrinogen concentrate as an additional line of treatment for blood loss. As the study was retrospective in nature, it has significant limitations and demonstrates the importance of considering confounding variables, including different transfusion triggers among anesthetists. However, the study does demonstrate the need for a larger-scale randomized prospective study to fully understand the effects of fibrinogen concentrate.

ABBREVIATIONS

CPB: Cardio Pulmonary Bypass; FFP: Fresh Frozen Plasma; RBCS: Red Blood Cells; MHC: Maritime Heart Centre; ACT: Activated Clotting Time; CVICU: Cardiovascular Intensive Care Unit; IMCU: Intermediate-Care Unit

INTRODUCTION

Cardiac surgery is often accompanied by excessive perioperative bleeding. Contributing factors are hemodilution, reduced and dysfunctional platelets, hyperfibrinolysis and low levels of coagulation factors caused by prolonged cardiopulmonary bypass (CPB) [1,2]. Severe cases of hemorrhage in a surgical setting could prove to be life threatening. Fibrinogen plays a key role in hemostasis and, as a precursor to fibrin, adequate levels of fibrinogen are necessary to improve clot strength via the interaction between fibrin and platelets [3,4]. Fibrinogen is the first coagulation factor to reach critical levels during major bleeding, therefore making it important to supplement plasma fibrinogen levels to limit blood loss in the perioperative and trauma settings [5,6,7-11]. Clinical and in vitro data from Lang and colleagues demonstrates that even in the presence of reduced platelet count and thrombin levels (e.g. after extensive CPB), administration of fibrinogen increases clot strength [12].

Previous methods of treating perioperative bleeding, namely the use of fresh frozen plasma (FFP), platelets and cryoprecipitate, have revealed a number of disadvantages [13-15]. For example, as FFP and cryoprecipitate are provided as frozen allogeneic blood components, they can require substantial thawing time prior to administration and there is also the need for donor-recipient AB-compatibility [16]. Furthermore, inconsistentfibrinogen concentrations and the risk of transfusion-related complications, including viral transmission and immune-related adverse events, have shifted the focus towards fibrinogen concentrate as a potential alternative to the conventional treatments [14,16,17].

Several advantages to using fibrinogen concentrate have made it a point of interest to physicians. Its powdered nature allows rapid reconstitution, easy administration to patients, and provides more control over fibrinogen concentrations

and dosing [5,7,14,17,18].Viral inactivation by pasteurization and additional purification steps during production minimizes the risk of immunological adverse events [16]. Additionally, a systematic review by Warmuth and colleagues reported that administration of fibrinogen concentrate improved clot firmness, as measured by thrombelastometry (e.g. ROTEM®), significantly reduced postoperative bleeding, and subsequently significantly decreased the need for transfusion of other blood products (e.g. red blood cells [RBCs]) [19].

In this retrospective chart review of patients undergoing cardiac surgery, the aim was to provide a description of the blood transfusion requirements in those patients receiving fibrinogen concentrate as an additional treatment for excessive bleeding. Moreover, we investigated the occurrence of adverse events with the use of fibrinogen concentrate in cardiac surgery.

MATERIALS AND METHODS

In 2010, our institution became one of the first Canadian heart centers using fibrinogen concentrate. At that time, the product was only available via the 'Special Access Program' through Health Canada. In 2012, it became freely available as RiaSTAP® (CSL Behring, Marburg, Germany) through our local blood bank. Review ethics board approval was obtained, and the study was performed as a retrospective chart review. Patient data was collected from the Maritime Heart Centre (MHC) database for Cardiac Surgery, and from patients' electronic charts (HPF clinical portal) at the Queen Elizabeth II Health Sciences Centre (QEII HSC), Halifax, Canada.

Anesthesia management

As per the standard of care in this surgical population, all patients underwent general anesthesia and were induced with midazolam, fentanyl or sufentanil, propofol and rocuronium. General anesthesia was maintained with sevoflurane titrated to maintain an end-tidal concentration of 1-2% and boluses of fentanyl or sufentanil, until initiation of CPB. Tranexamic acid (Sandoz Canada Inc.) was infused at a rate of 2-5 mg/kg/h following an initial bolus of 1000-2000 mg. During the CPB run, propofol was infused with subsequent boluses of fentanyl or sufentanil. Prior to CPB, patients were given unfractionated heparin (500 units/kg; PPC, Pharmaceuticals Partners of Canada Inc.) to maintain an activated clotting time (ACT) >480 seconds. The CPB circuit included a membrane oxygenator and roller pumps to maintain a non-pulsatile perfusion technique. Depending on the procedure, deep or moderate hypothermia (nasopharyngeal temperature of 18°C or 32-34°C) was utilized and cardioprotection was maintained using antegrade and retrograde cold blood cardioplegia when possible. Separation from CPB was achieved once the patient was re-warmed to a nasopharyngeal temperature of 36.5°C. Following separation from CPB, heparin was reversed with protamine (1 mg protamine/100 units heparin; protamine sulphate, Sandoz Canada Inc.). A hemoglobin concentration <65-70 g/L was treated with RBCs to maintain a hemoglobin concentrate ≥ 65-70 g/L throughout the procedure.

Surgical technique

Surgery was performed in a standardized manner with CPB. During CPB, the mean arterial pressure target was 60-70 mmHg and the body temperature was allowed to drift to approximately 32°C or lower. Intermittent cold blood cardioplegia (1:4 bloods to crystalloid with maximal K^+concentration 22 meq/L) was delivered ante grade via the aortic root unless otherwise indicated. No special blood conservation technique was utilized other than: non-hemic prime, retransfusion of all contents of the oxygenator at the end of CPB, and acceptance of normovolemic anemia.

Postoperative management

All postoperative cardiac surgery patients were taken immediately to a dedicated cardiovascular intensive care unit (CVICU).All patients received respiratory and hemodynamic support as needed. Each patient was required to meet standard hospital criteria both prior to extubation and prior to transfer to the intermediate-care unit (IMCU).Discharged patients were transferred to an IMCU or general-care ward under the care of the same cardiac surgical team. All patients were monitored continuously for a minimum of 24 hours.In case of surgical bleeding; a re-sternotomy was performed. Diffuse bleeding was treated with blood components.

RESULTS AND DISCUSSION

Data from 54 patients who were admitted to the QEII HSC for cardiac surgery and received fibrinogen concentrate from January 2010 to June 2013 were considered. Of these, patients were excluded for the following reasons: one died before surgery in the CVICU, one had incomplete chart data and two Jehovah's Witness patients were also excluded, due to their inability to accept blood products, leaving 50 patients in the study group. Of the 50 patients receiving fibrinogen concentrate, average age was 60.7 years and 68% were male. Baseline laboratory characteristics were slightly lower than reference ranges for hemoglobin (118.1 g/L), platelets (206.54×10^9/L), and hematocrit (0.36) which may be attributed to the high number of urgent or emergency procedures in the study group (36%) (Table 1).

While the observed group was receiving fibrinogen concentrate as an additional line of treatment for bleeding, each patient also received, on average, a total number of 8.8 units of blood products. Individual components accounted for the following: 4.3 units of packed RBCs, 2.5 units of FFP, 1.5 units of platelets and 0.5 units of cryoprecipitate (Table 2). The overall transfusion rate was 94%. This is higher than the all-case transfusion rate at our institution of 28% ($p < 0.001$, 95% CI 83.45 to 98.75) from all cardiac surgeries in 2013.

Post-operative laboratory values for the group, on average, declined with average values being 91 g/L for hemoglobin, 164×10^9/L for platelets, 0.27 for hematocrit, 40 sec for PTT and INR increased to 1.6 (Table 3).

Median time for CPB was 173 min (IQR 118, 243) with total length in ICU of 96.5 hours (IQR 43, 195.5) and a total hospital length of stay of 13.5 days (IQR 7, 27).

There were two patients (4%) with a stroke, defined as a persisting deficit at discharge and there was an observed mortality rate of 18% (Table 3).

Table 1: Patient and procedure characteristics.

Characteristic	Fibrinogen concentrate group (n=50)
Age (years), mean	60.7
Sex, male (%)	34 (68)
Indication (%) Elective Urgent or emergency	 32 (64) 18 (36)
CABG (%)	13 (26)
CABG and valve(s) (%)	6 (12)
Other (%)	12 (24)
Other and valve(s) (%)	19 (38)
Redo (%)	10 (20)
Baseline hemoglobin (g/L), mean	118.1
Baseline platelets (10^9/L), mean	206.54
Baseline hematocrit, mean	0.355
Baseline INR, mean	1.257
Baseline PTT (sec), mean	41.714

Abbreviations: CABG: Coronary Artery Bypass Graft; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time

Table 2: Number of blood products received.

Number of units transfused in OR and ICU, mean per patient	Fibrinogen concentrate group (n=50)
RBC	4.26
FFP	2.50
Platelets	1.54
Cryoprecipitate	0.54
Total number of units transfused	8.84

Abbreviations: FFP: Fresh Frozen Plasma; ICU: Intensive Care Unit: OR: Operating Room; RBC: Red Blood Cells

Table 3: Postoperative laboratory values.

Characteristics	Fibrinogen concentrate group (n=50)
Hemoglobin post-op (g/L), mean	91
Platelets post-op (10^9/L), mean	164
Hematocrit post-op, mean	0.27
PTT post-op (sec), mean	40
INR post-op, mean	1.6
ICU stay (h), median (IQR 25^{th}, 75^{th})	96.5 (43, 195.5)
Hospital LOS (days), median (IQR 25^{th}, 75^{th})	13.5 (7, 27)
CPB time (min), median (IQR 25^{th}, 75^{th})	172.5 (118, 243)
Vent time (h), median (IQR 25^{th}, 75^{th})	28 (14.5, 116)
Overall transfusion rate (%)	47 (94)
In-hospital mortality (%)	9 (18)
In-hospital stroke (%)	2 (4)

Abbreviations: CPB: Cardiopulmonary Bypass; ICU: Intensive Care Unit; INR: International Normalized Ratio; IQR: Interquartile Range; LOS: Length Of Stay; PTT: Partial Thromboplastin Time

Our results demonstrate a relatively high number of blood components transfused despite patients receiving fibrinogen concentrate as an additional line of treatment for blood loss. This might suggest that administering fibrinogen concentrate did not necessarily lower blood transfusion requirements perioperatively in this specific patient population. These results are similar to a larger retrospective study performed by Bilecen et al., where 264 patients over a 4-year study period receiving a median dose of 2 g fibrinogen concentrate showed an increase in blood transfusion rates with no observable adverse events, when compared to those not receiving fibrinogen concentrate [20].

Because both our study and that by Bilecen et al., were retrospective and had many confounding parameters with a high level of patient heterogeneity, there is no clear interpretation possible. However, the results obtained are important as a description in terms of thromboembolic complications and post-operative adverse events for the first patients treated with fibrinogen concentrate in our center.

Since 36% of our study patients had an emergency procedure, the mortality rate of 18% is not surprising. Many patients came to the operating room (OR) in cardiogenic shock. Additionally, a significant amount of those patients had received potent anti-platelet medication, like clopidogrel. All these factors contribute to a higher risk for bleeding and transfusion which leads to increased morbidity and mortality.

As fibrinogen concentrate was newly introduced to our institution during the study period, it was possibly used for hemostatic management when other interventions had been exhausted. Despite our efforts to start using fibrinogen concentrate in a controlled and standardized manner, the chart review revealed that dosing and timing was not standardized.

As the study was retrospective in nature it has significant limitations.It is important to take confounding variables into consideration, including different transfusion triggers among different surgeons and anesthetists, as well as inconsistent timing and dosing. For example, some anesthetists started blood product transfusion when hemoglobin levels dropped below 75 g/L, while others waited until it dropped below 65 g/L. The decision to transfuse was also based on the patient's co-morbidities pre-operatively and the clinical situation during the procedure. As cryoprecipitate administration in the past was not standardized and fibrinogen concentrate was sometimes used as an alternative or an add-on, the interpretation of the results is quite challenging. As we did not include a control group that did not receive fibrinogen concentrate, we are unable to draw definitive conclusions regarding the amount of blood products transfused and the use of fibrinogen concentrate. These limitations show the importance of a prospective randomized controlled trial which uses an established transfusion algorithm to ensure better consistency of treatment among patient populations.

Dosing and administration of fibrinogen concentrate has been heterogeneous in the past and much has been learned about proper and more efficient dosing since the initial 50 patients were observed. Quicker reconstitution of the lyophilized powder (using pre-warmed sterile water instead of cold sterile water) along with faster administration in bleeding situations has

made it more useful to anesthetists and surgeons. The process of transferring the fibrinogen concentrate to the OR has been significantly facilitated at our institution (e.g. pre-printed order sheets, short distance from Blood Bank to OR). Some anesthetists and surgeons previously used thrombelastography (TEG®5000, Haemonetics, Braintree, USA) as a guidance for transfusion and fibrinogen concentrate dosing. For mild to moderate bleeding, the dosing was calculated at 50 mg/kg bodyweight, and for more severe bleeding a higher dose was given (70 mg/kg).

With more experience using fibrinogen concentrate, we developed a ROTEM®-based transfusion algorithm for perioperative bleeding at our institution. This algorithm and pre-operative fibrinogen levels are now used routinely to optimize and individualize perioperative blood management.

CONCLUSION

In this study, the administration of fibrinogen concentrate during cardiac surgery possibly did not minimize the transfusion rate of blood components. This is most likely due to the patient population being more susceptible to heavy bleeding. While prospective randomized controlled studies could yield more accurate results due to better administration triggers and could eliminate some confounding factors that may have skewed our results, there are important observations from our study. It served as a learning curve and highlighted the importance of streamlining processes such as optimizing reconstitution time and dosing of fibrinogen concentrate. Additionally, it demonstrates that the risk for post-operative adverse events appears to be low. Furthermore, this study emphasizes the ongoing importance of perioperative blood management, and demonstrates the need for larger-scale randomized prospective studies to fully assess the efficacy of fibrinogen concentrate.

ACKNOWLEDGEMENTS

Editorial assistance was provided by Meridian HealthComms Ltd., funded by CSL Behring.

CONFLICT OF INTEREST

M.K. received speaker honoraria from CSL Behring. The studywas financially supportedby CSL Behring (Marburg, Germany) and Nova Scotia Health Authority (Halifax,Canada).

REFERENCES

1. Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion. 2008; 48: 2152-2158.
2. Kestin AS, Valeri CR, Khuri SF, Loscalzo J, Ellis PA, Mac Gregor H, et al. The platelet function defect of cardiopulmonary bypass. Blood. 1993; 82: 107-117.
3. Blome M, Isgro F, Kiessling AH, Skuras J, Haubelt H, Hellstern P, et al. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost. 2005; 93: 1101-1107.
4. Nalla BP, Freedman J, Hare GM, Mazer CD. Update on blood conservation for cardiac surgery. J Cardiothorac Vasc Anesth. 2012; 26: 117-133.
5. Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus. 2012; 10: 23-27.
6. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg. 1995; 81: 360-365.
7. Ranucci M. Fibrinogen supplementation in cardiac surgery: where are we now and where are we going? J Cardiothorac Vasc Anesth. 2013; 27: 1-4.
8. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012; 10: 1342-1351.
9. Schlimp CJ, Schöchl H. The role of fibrinogen in trauma-induced coagulopathy. Hamostaseologie. 2014; 34: 29-39.
10. Schöchl H, Voelckel W, Grassetto A, Schlimp CJ. Practical application of point-of-care coagulation testing to guide treatment decisions in trauma. J Trauma Acute Care Surg. 2013; 74: 1587-1598.
11. Schöchl H, Voelckel W, Schlimp CJ. Management of traumatic haemorrhage--the European perspective. Anaesthesia. 2015; 70: 102-107, 35-37.
12. Lang T, Johanning K, Metzler H, Piepenbrock S, Solomon C, Rahe-Meyer N, et al. The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg. 2009; 108: 751-758.
13. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest. 2007; 131: 1308-1314.
14. Sørensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol. 2010; 149: 834-843.
15. Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion. 2004; 44: 1143-1148.
16. Rahe-Meyer N, Sørensen B. For: Fibrinogen concentrate for management of bleeding. J Thromb Haemost. 2011; 9: 1-5.
17. Bevan DH1. Cryoprecipitate: no longer the best therapeutic choice in congenital fibrinogen disorders? Thromb Res. 2009; 124: 12-16.
18. Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. Anesth Analg. 2012; 114: 261-274.
19. Warmuth M, Mad P, Wild C. Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. Acta Anaesthesiol Scand. 2012; 56: 539-548.
20. Bilecen S, Peelen LM, Kalkman CJ, Spanjersberg AJ, Moons KG, Nierich AP. Fibrinogen concentrates therapy in complex cardiac surgery. J Cardiothorac Vasc Anesth. 2013; 27: 12-17.

Cite this article

Weingartshofer A, Mingo H, Kent B, Legare JF, Buth K, et al. (2017) The Use of Concentrated Fibrinogen in Cardiac Surgery Patients: a Retrospective Chart Review. Int J Clin Anesthesiol 5(1): 1062.