Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: A randomized pilot trial

Filomena R. B. G. Galas, MD, PhD, Juliano P. de Almeida, MD, PhD, Júlia T. Fukushima, MSc, Jean Louis Vincent, MD, PhD, Eduardo A. Osawa, MD, PhD, Suely Zeferino, RN, Lígia Câmara, RN, Vanessa A. Guimarães, MD, Marcelo B. Jatene, MD, PhD, and Ludhmila A. Hajjar, MD, PhD

Objectives: Acute acquired hypofibrinogenemia in children undergoing cardiac surgery is a major concern because it often results in perioperative bleeding and high rates of allogeneic blood transfusion. Fibrinogen concentrate has been proposed as an alternative to cryoprecipitate (the gold standard therapy), with minimal infectious and immunologic risks. Our objective was to investigate the efficacy and safety of fibrinogen concentrate in children undergoing cardiac surgery.

Methods: In this randomized pilot study, patients were allocated to receive fibrinogen concentrate (60 mg/kg) or cryoprecipitate (10 mL/kg) if bleeding was associated with fibrinogen levels <1 g/dL after cardiopulmonary bypass weaning. The primary outcome was postoperative blood losses during the 48 hours after surgery.

Results: A total of 63 patients were included in the study, 30 in the fibrinogen concentrate group and 33 in the cryoprecipitate group. The median 48-hour blood loss was not significantly different between the 2 groups (320 mL [interquartile range, 157-750] vs 410 mL [interquartile range, 215-510], respectively; $P = .672$). After treatment, plasma fibrinogen concentration increased similarly following administration of both products. There were no differences in allogeneic blood transfusion after intervention treatment.

Conclusions: A large trial comparing fibrinogen concentrate and cryoprecipitate in the management of children with acute acquired hypofibrinogenemia during heart surgery is feasible. The preliminary results of our study showed that the use of fibrinogen concentrate was as efficient and safe as cryoprecipitate in the management of bleeding children undergoing cardiac surgery. (J Thorac Cardiovasc Surg 2014;148:1647-55)

Bleeding is a significant cause of mortality after cardiac surgery. It is associated with high rates of allogeneic blood transfusion, which in turn results in worse outcomes.[1] In cardiac surgery, reduced fibrinogen levels increase bleeding due to compromise in fibrin production and platelet aggregation.[2-4] Fibrinogen can be supplemented by the administration of fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate. FFP and cryoprecipitate are both allogeneic blood products that require cross-matching and thawing before administration and are also related to increased risk of pathogen transmission and immunologic reactions.[2,5] Alternatively, fibrinogen concentrate is a plasma-derived submitted to pasteurization that minimizes the risk of immunologic and allergic reactions.[5,6]

Previous studies have demonstrated that fibrinogen concentrate effectively increases plasma fibrinogen levels and controls perioperative bleeding in adult patients undergoing cardiopulmonary bypass (CPB) surgery.[3,7] However, the clinical efficacy of fibrinogen concentrate for management of perioperative bleeding has not been compared directly with cryoprecipitate.

We hypothesized that fibrinogen concentrate would be similar to cryoprecipitate in reducing bleeding in children undergoing cardiac surgery without increasing the rate of adverse effects.

METHODS

Study Design

This study was designed as a pilot trial. It was a prospective, randomized controlled trial conducted during 2 consecutive years at the Heart Institute of the University of Sao Paulo, Brazil. The study was approved by the Heart Institute Ethics Committee, Clinics Hospital, University of Sao Paulo, and written informed consent was obtained from parents or legal guardians. The authors designed the trial protocol, collected the data, directed the statistical plan, and wrote the manuscript. CSL Behring provided the study medication and supported the laboratory analysis.

Participants

Patients younger than age 7 years scheduled for elective cardiac surgery with CPB were preoperatively screened for eligibility. Exclusion criteria

From the Surgical Intensive Care Unit, InCor Heart Institute, University of Sao Paulo, Sao Paulo, Brazil.

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Address for reprints: Ludhmila Abrahão Hajjar, MD, PhD, Heart Institute, Av Dr Eneas Carvalho Aguiar, 44, Sao Paulo, Brazil 05403000 (E-mail: ludhmila@usp.br).

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
FFP = fresh frozen plasma
FIBTEM = fibrin-based thromboelastometric clotting assay
ICU = intensive care unit
RBC = red blood cell
ROTEM = rotational thromboelastometry

were inability to receive blood products, enrolment in another study, chronic anemia (preoperative hemoglobin < 10 g/dL), a history of coagulopathy or preoperative coagulopathy (platelet count < 100,000 mL/mm^3 or prothrombin time > 14.8 seconds), active infection, or hypersensitivity to fibrinogen concentrate.

Eligible patients were included in the study after heparin neutralization if 2 inclusion criteria were fulfilled: diffuse bleeding from capillary beds at wound surfaces requiring haemostatic therapy and plasma fibrinogen concentration < 1 g/L.

Patients were randomly assigned in a 1:1 ratio to receive 60 mg/kg pasteurized human fibrinogen concentrate (Haemocomplettan P, CSL Behring, Marburg, Germany) or 10 mL/kg cryoprecipitate. In our hospital, the cryoprecipitate is available in single bags, in a total mean volume of 25 mL per bag. Each unit of cryoprecipitate has approximately 150 mg fibrinogen.

Opaque envelopes arranged using a random-number table were prepared by the chief statistician and opened sequentially to determine the patient's treatment group. The research coordinator enrolled the participants and obtained informed consent. Outcome assessors and patients were unaware of study group assignments.

Anesthesia, CPB, and Surgery Methods

For all patients, anesthesia, CPB, and surgery were performed by the same team of cardiac surgeons, perfusionists, and anesthetists. Anesthesia was induced with fentanyl (3-5 μg/kg), ketamine (1 mg/kg), and pancuronium bromide (0.1 mg/kg). Maintenance was performed with sevoflurane in oxygen and fentanyl as needed. All patients were monitored using arterial and central venous catheters.

Dobutamine or milrinone were used as inotropic drugs, and norepinephrine or epinephrine as vasopressors. Methylprednisolone (10 mg/kg) and cefuroxime (50 mg/kg) were administered intravenously at the introduction of anesthesia. All patients received antifibrinolytic prophylaxis with ε-aminocaproic acid (100 mg/kg) as a loading dose given before anesthetic induction, followed by a 50 mg/kg/h infusion, which continued until the end of surgery.

Anticoagulation therapy was established with an initial dose of 4 mg/kg heparin in the central venous line before bypass initiation, with a target activated clotting time of 480 seconds, using kaolin as the activating agent (ACT II HemoTec; Medtronic, Rueil Malmaison, France). Additional heparin was administered intermittently to titrate clotting times during bypass. A centrifugal pump (Medtronic Biomedicus; Medtronic, Minneapolis, Minn) was used for bypass. An extracorporeal circuit containing a microporous polypropylene membrane oxygenator (Braile; Sao Jose do Rio Preto, São Paulo, Brazil) with an integrated venous cardiotomy reservoir was used. The oxygenator was primed with lactated Ringer's solution containing 0.5 g/kg mannitol and 2500 U heparin. Packed red blood cells (RBCs) were added to the solution to maintain the CPB hematocrit value at 25%, and 8.4% sodium bicarbonate was added to correct the pH to 7.35 to 7.40. A hypothermic temperature management strategy (28°C-32°C) with α-stat blood gas management was used in all patients during bypass. After aortic crossclamping the heart was arrested by anterograde infusion of a cold blood cardioplegic solution. Fluid management was performed with lactated Ringer's solution and adjusted according to filling pressures, urine output, and central venous saturation.

Following surgery, patients were rewarmed to 36°C and weaned from CPB. To reverse the anticoagulant effect of heparin, protamine chloride was administered intravenously (30 U/kg). Additional protamine was administered as required to return activated clotting times to preoperative values. Patients were transferred to the intensive care unit (ICU) before recovery from anesthesia.

Coagulation Tests

Laboratory coagulation tests, including platelet count, hemoglobin and hematocrit, fibrinogen concentration, prothrombin time, international normalized ratio, and activated partial thromboplastin time, were performed using the fully automated analyzers STA-R Evolution (Roche AG, Grenzach-Wyhlen, Germany) and Sysmex XE 2001 (Sysmex GmbH, Norderstedt, Germany). These results were immediately available to be applied to the care of bleeding patients during the study.

Clotting activities of factor II, VII, IX, X, and XIII were determined by a 1-stage method on a Thrombolyzer ChromEquipment (Benk Electronic, Norderstedt, Germany), using plasmas deficient in factor II, VII, X, and X (Cryocheck, Dartmouth, Canada) as substrate, and recombinant human tissue factor (Innovin; Dade Behring GmbH, Marburg, Germany) or Platelin LS (Biomerieux, Herlev, Denmark) as the activating agent. Factor XIII transglutaminase activity was determined using the Berichrom FXIII kit, on an automated coagulation analyzer (Dade Behring Coagulation Timer; Dade Behring GmbH). Coagulation tests were performed in both groups at fixed time points: before randomization (T0) and 1 hour after study drug infusion (T1). These results were not available to the patients. They were evaluated post-hoc. Fibrinogen levels were dosed in both groups at fixed timed points: T0; T1; and 2 hours, 24 hours, and 48 hours (T4) after study drug infusion.

Thromboelastometry was performed using the rotational thromboelastometry (ROTEM) device (Tem International GmbH, Munich, Germany). ROTEM plastic cups prewarmed to 37°C were loaded with 300 μL whole blood and 20 μL investigational hemostatic agent. The coagulation process was activated with tissue factor (Innovin; Dade Behring GmbH). Standard ROTEM reagents were used for intrinsic, extrinsic, and fibrin-based (FIBTEM) thromboelastometric clotting assays. Clotting time, clot formation time, and maximum clot firmness parameters were recorded. The tests were performed in both groups at fixed time points: T0, T1, 24 hours, and T4.

Treatment Groups

After randomization, bleeding patients with fibrinogen levels <1 g/L were allocated to 1 of 2 treatments: fibrinogen concentrate (Haemocomplettan P, CSL Behring GmbH) in a intravenous dose of 60 mg/kg or cryoprecipitate in a dose of 10 mL/kg (Figure 1). The trigger of fibrinogen levels <1 g/L was chosen based on previous studies showing an association between these values and bleeding after cardiac surgery.[8,9]

During pump weaning in the operating room, in all cases, both fibrinogen concentrate and cryoprecipitate were both already prepared and available to be administered. After randomization, fibrinogen concentrate or cryoprecipitate was administered immediately after bleeding identification and the other 1 was dropped out. Both fibrinogen concentrate and cryoprecipitate were used as a first-line therapy for hemostasis, and no other products were given before this first intervention.

Data Collection

Demographic and clinical data for the calculation of the risk-adjusted classification for congenital heart surgery were obtained for each patient at the time of randomization.[10] Data regarding the type of surgical procedure, bypass duration, number and type of allogeneic units transfused (including RBC, platelets, FFP, and additional cryoprecipitate) were