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Fibrinogen concentrate in the treatment of severe bleeding after aortic aneurysm graft surgery

Niels Rahe-Meyer*

Clinic for Anesthesiology and Intensive Care Medicine, Hannover, Germany

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ABSTRACT

Aortic aneurysm graft surgery involving cardiopulmonary bypass is often associated with substantial coagulopathic perioperative bleeding, requiring hemostatic intervention with allogeneic blood products, such as fresh frozen plasma, platelet concentrate, and red blood cells. We conducted a pilot study to determine the effects of fibrinogen concentrate in patients with microvascular bleeding during aortic valve surgery with ascending aorta replacement. Dosing of fibrinogen concentrate was individualized based on thromboelastometry. First-line therapy with fibrinogen concentrate reduced the need for allogeneic blood product support, including transfusions of fresh frozen plasma, platelet concentrate, and red blood cells. Similar results were seen in a second cohort study conducted in patients undergoing thoraco-abdominal aortic aneurysm surgery: patients who received fibrinogen concentrate required significantly less allogeneic blood product support following surgery. These results prompted the initiation of a randomized placebo-controlled trial in patients undergoing thoraco-abdominal aortic aneurysm surgery, aortic valve surgery with ascending aorta replacement, or aortic arch surgery. Results are expected to be published soon. Larger, multicenter studies are needed to determine the exact role of fibrinogen concentrate in the management of perioperative bleeding following cardiac surgery and cardiopulmonary bypass.

Abbreviations

AV-AA:	aortic valve surgery with ascending aorta replacement
CPB:	cardiopulmonary bypass
FFP:	fresh frozen plasma
MCF:	maximum clot firmness
PC:	platelet concentrate
RBC:	red blood cell
TAAA:	Thoraco-abdominal aortic aneurysm

Cardiac surgery is often associated with excessive perioperative bleeding caused by impairment of the coagulation system [1]. Use of cardiopulmonary bypass (CPB) can cause further disruptions in hemostasis via impaired platelet function, fibrinolysis, and other pathways [2,3]. Excessive bleeding during cardiac surgery has been linked to increased morbidity and mortality [4]. Conventional intervention involves one or more transfusions of fresh frozen plasma (FFP) and/or other allogeneic blood products, including platelet concentrate (PC) or red blood cells (RBC). While FFP is widely available and relatively inexpensive, repeated use of FFP can increase the risk of volume overload [5]. Moreover, the hemostatic efficacy of FFP has not been established in the cardiac surgery setting [6]. Studies evaluating pharmacologic interventions have generally focused on the ability to reduce blood loss, and few studies have been sufficiently powered to assess other more clinically relevant outcomes, such as surgical re-exploration, transfusion requirement, myocardial infarction, and mortality [4]. In a review of trials evaluating pharmacologic interventions, aprotinin and lysine analogs were found to reduce blood loss and possibly transfusion requirement, whereas desmopressin increased the risk of myocardial infarction despite a moderate reduction in blood loss [4]. However, aprotinin has been withdrawn from the market. Clearly, new approaches to the control of perioperative bleeding in cardiac surgery patients are needed.

Fibrinogen is the precursor to fibrin and plays an important role in primary and secondary hemostasis [7,8]. It is also an important determinant of blood viscosity and blood flow. The minimum plasma fibrinogen concentration needed for non-surgical hemostasis is 0.5–1 g/L, and during surgery substitution therapy with fibrinogen concentrate is usually recommended when levels fall below 1.0–2.0 g/L [9,10]. However, physiologic fibrinogen levels are generally higher than this threshold (2.0–4.5 g/L) [11], and the optimal trigger for substitution therapy may be considerably higher in special populations, such as women with postpartum bleeding (4 g/L) [12] or cardiac surgery (3.9 g/L) [13].

Plasma-derived fibrinogen concentrate has been commercially available for many years and has been used in patients with congenital fibrinogen deficiency [11,14–16]. Relatively less is known about the efficacy and safety of fibrinogen concentrate in patients with acquired fibrinogen deficiency, particularly in relation to cardiac surgery. Here we present a series of clinical studies conducted at the Hannover Medical School in Germany evaluating the effects of fibrinogen concentrate when used perioperatively in patients undergoing aortic aneurysm graft surgery with CPB.

*Corresponding author. N. Rahe-Meyer, Department of Anesthesiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
*Tel.: +49 521 589 1601; fax: +49 521 589 1604.
E-mail address: rahe-meyer.niels@mh-hannover.de (N. Rahe-Meyer).

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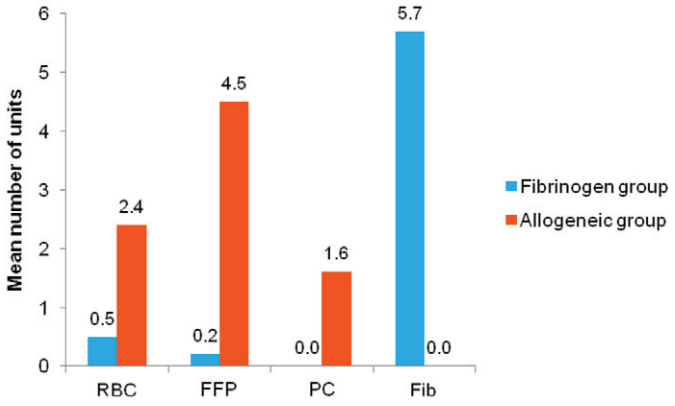

Fig. 1. Transfusion of allogeneic blood products within 24 hours after ascending aorta surgery [17]. RBC, red blood cell; Fib, fibrinogen concentrate; FFP, fresh frozen plasma; PC, platelet concentrate. $p < 0.05$ fibrinogen vs. allogeneic groups for comparisons between all blood product groups.

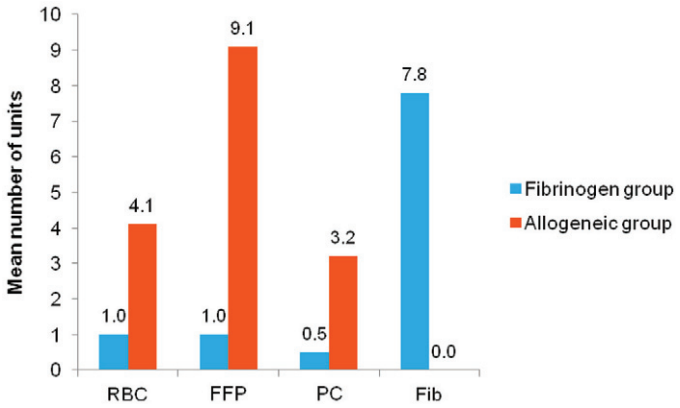

Fig. 2. Transfusion of allogeneic blood products within 24 hours after surgery for thoraco-abdominal aortic aneurysm [18]. RBC, red blood cell; Fib, fibrinogen concentrate; FFP, fresh frozen plasma; PC, platelet concentrate. $p < 0.05$ fibrinogen vs. allogeneic groups for comparisons between all blood product groups.

Cohort studies evaluating fibrinogen concentrate

Aortic valve and ascending aorta surgery

Our initial pilot study assessed the effects of fibrinogen concentrate as first-line therapy for perioperative bleeding in patients undergoing aortic valve surgery with ascending aorta replacement (AV-AA), which is expected to induce moderate coagulopathy [17]. A prospective group of 10 patients received fibrinogen concentrate, and the results were compared with a retrospective group of 42 patients who received standard treatment with FFP and PC. Dosing of fibrinogen concentrate was individualized based on thromboelastometry results, and FFP and PC were added as needed after the administration of fibrinogen concentrate.

Patients treated with fibrinogen concentrate received a mean of 5.7 g of fibrinogen (Figure 1) [17]. The mean number of units of allogeneic blood products transfused within 24 hours after surgery was significantly lower in patients treated with fibrinogen concentrate, compared with those who received standard therapy (0.7 units versus 8.5 units; $p < 0.05$; Figure 1). The reduction in transfusion requirement was seen across all allogeneic blood products (FFP, PC, and RBC). Notably, 80% of patients in the standard treatment group received allogeneic blood product support, whereas 90% of patients treated with fibrinogen concentrate required no postoperative transfusions. These findings suggest that individualized dosing of fibrinogen concentrate can reduce postoperative bleeding and transfusion requirement in patients undergoing AV-AA.

Thoraco-abdominal aortic aneurysm surgery

Based on the encouraging findings from the pilot study of fibrinogen concentrate in patients undergoing AV-AA [17], we decided to conduct a second cohort study in patients undergoing a more extreme form of elective aortic graft surgery [18]. Thoraco-abdominal aortic aneurysm surgery (TAAA) is associated with excessive perioperative bleeding due to considerable impairment of the coagulation system, including reductions in fibrinogen and factors II, V, VII, VIII, IX, X, and XII [1]. The greater disruption of the coagulation system seen with this procedure is due to the extensive graft size, the need for multiple anastomoses, and prolonged surgical time. Using a design similar to that of the pilot study, we compared the effects of fibrinogen concentrate on transfusion requirement with that of standard treatment with allogeneic blood products in patients undergoing TAAA. A prospective group of six patients received fibrinogen concentrate as first-line hemostatic treatment, and a retrospective group of 12 patients received standard treatment with FFP and PC. As before, the dose of fibrinogen concentrate was determined on an individual basis with thromboelastometry. Those who received fibrinogen concentrate were allowed to receive subsequent FFP and PC as needed.

Patients received a mean of 7.8 g of fibrinogen concentrate (Figure 2) [18]. As expected, the need for allogeneic blood product was considerably higher in this study than in the previous pilot study, due to the extensive nature of TAAA. Nevertheless, use of fibrinogen was associated with a significant reduction in the amount of allogeneic blood product needed within the first 24 hours after surgery (2.5 units versus 16.4 units; $p < 0.05$; Figure 2). All 12 patients who received standard therapy required some form of allogeneic blood product support within 24 hours after surgery, while four of the six patients treated with fibrinogen (67%) did not require any transfusions. Outcomes with fibrinogen therapy were impressively good, given the severity of bleeding typically associated with TAAA, and suggest that fibrinogen concentrate may effectively reduce bleeding and transfusion requirement in patients undergoing extensive cardiac surgery.

Individualized dosing of fibrinogen

The promising results achieved in the two cohort studies described above may be attributed in part to the novel method of individualized dosing of fibrinogen concentrate that was used, based on point-of-care assessment of plasma fibrinogen levels using thromboelastometry [19–21]. After CBP, a typical patient has a relatively low maximum clot firmness (MCF) of about 8 mm [18]. Our goal was to increase this value to about 22 mm, which corresponds to a plasma fibrinogen level of approximately 3.6 g/L; this level is higher than the currently recommended trigger for fibrinogen substitution therapy [9,10,22]; but within the normal range [11,23], and possibly a more suitable target for patients undergoing cardiac surgery [13]. The dose of fibrinogen needed to achieve this target was calculated using a formula that accounted for baseline MCF and body weight. In general, a 70-kg patient requires a fibrinogen dose of approximately 0.5 g to increase the MFC by approximately 1 mm [18].

Quantification of perioperative bleeding

Importantly, patients prospectively assigned to receive fibrinogen concentrate in these trials had to meet certain requirements to establish that they had clinically relevant microvascular bleeding. After weaning from CPB, neutralization of heparin, and completion of surgical hemostasis, all blood was removed from the surgical field by suction, and surgical swabs were then inserted for 5 minutes to absorb any additional blood that arose from active bleeding. Blood mass was calculated by weighing swabs before and after use. To be included in the study, patients had to have a blood mass of 60–250 g, which was considered high-level bleeding that warranted hemostatic intervention. Patients with a blood mass less than 60 g were considered to have sufficient hemostatic control that did not require intervention. A blood mass greater than 250 g was considered life-threatening and warranted

surgical re-exploration and emergency intervention. The cut-off values of 60 g and 250 g were based on previous experience and have not been described in the literature. Blood mass assessment was also repeated periodically after administration of fibrinogen concentrate to determine whether additional supportive therapy with FFP and PC was necessary.

Randomized proof-of-concept trial

The encouraging results from the two cohort studies described above prompted the initiation of a prospective proof-of-concept trial to determine whether fibrinogen concentrate sufficiently reduces transfusion requirement following cardiac surgery. In this single-center, double-blind, placebo-controlled trial, 80 patients undergoing elective TAAA, AV-AA, or aortic arch graft surgery were randomized to fibrinogen concentrate or placebo, with dosing of fibrinogen concentrate guided by thromboelastometry results. The results of this study are expected to be published at the beginning of 2012.

Summary

Cardiac surgery involving CPB is often associated with a substantial amount of coagulopathic perioperative bleeding. A pilot study in patients undergoing AV-AA, for which a moderate amount of coagulopathy is expected, indicated that thromboelastometry-guided administration of fibrinogen concentrate as first-line therapy for perioperative bleeding reduced the need for allogeneic blood product support, including transfusions of FFP, PC, and RBC. A second cohort study in patients undergoing TAAA, for which maximal coagulopathy is expected, yielded similar results: patients who received fibrinogen concentrate required significantly less allogeneic blood product support following surgery. In these trials, results from a prospective group treated with fibrinogen concentrate were compared with results from a retrospective group of patients who received FFP and PC. To overcome this potential bias, we conducted a prospective, randomized, placebo-controlled proof-of-concept trial in patients undergoing TAAA, AV-AA, or aortic arch graft surgery. Results are expected to be published in 2012. We are currently developing a protocol for a larger, multicenter trial that may confirm the promising efficacy and safety results achieved in these studies.

Conflict of interest

None declared

Role of the funding source

CSL Behring GmbH, Marburg, Germany.

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