Therapy with fibrinogen concentrate: clinical and ethical considerations

We are concerned that a recent report of Solomon and colleagues[1] regarding changes in fibrinogen concentration through administration of fibrinogen concentrate utilized approaches not in harmony with appropriate guidelines.[2]

The study compared different methods of fibrinogen concentration analysis and correlated these with rotational thrombelastometry, a functional test measuring the mechanical properties of the fibrin clot. The correlation was good, but became less significant with increasing fibrinogen concentration; one reason for this may have been confusion between plasma and blood concentrations in some instances. The authors also appear to be confused about the normal concentration of fibrinogen, mentioning fibrinogen values "up to approximately the limit of normal values (4.5 g/L)" or "at concentrations to and above normal value 4.5 g/L." However, in fact, the normal range for plasma fibrinogen concentration is (related to different methods) 1.5 to 4.0 g/L with a mean of 2.75 g/L[2]. Aliberti and coworkers[3] found in 4116 normal value outpatients a mean fibrinogen concentration of 3.24 (2.3-3.9) g/L. Solomon and colleagues surprisingly do not comment on their own findings demonstrating fibrinogen concentrations in four volunteers between 2 and 3 g/L (their Fig. 4) and 1.8 g/L (mean) in 33 cardiac patients. In addition, as stated by Urwyler and colleagues,[4] if fibrinogen concentration were determined by point-of-care thrombelastometry (ROTEM) instead of the standard method according to Clauss, "the use of fibrinogen concentrate would increase significantly."

The study of Solomon and colleagues reported the effects of the use of fibrinogen concentrate in their patients. We want to emphasize that fibrinogen concentrate is extremely expensive and not completely harmless; its indiscriminate use should be avoided as there is no solid evidence for any benefit when given prophylactically.[5] The applicable regulation for the study of Solomon and colleagues are the *German* guidelines,[2] which state in issue 2008, Chapter 7.1.7. that "After fibrinogen substitution plasma concentration should be at least 1.0 g/L. In the adult normally 3-6 g fibrinogen concentrate are necessary."

For us, the reported use of fibrinogen concentrate in 33 cardiac surgical patients is a matter of concern. The *clinical* need for fibrinogen concentrate therapy may be assumed in special trauma cases with massive bleeding, but is a rare exception in cardiac surgical patients.[5,6] The authors do not explain the indication for fibrinogen concentrate based on the appropriate guidelines or comprehensible evidence. Instead we learn that 6 g was given to 33 consecutive patients with "diffuse bleeding" after bypass, increasing the fibrinogen plasma concentration up to 3.3 g/L; the clinical situations were not explained any further, and they were not mentioned in the discussion either. In fact, the initial mean fibrinogen level in these 33 patients was 1.8 g/L, which is comfortably within normal range, as described above. In addition they had been treated with aprotinin, an antifibrinolytic agent. Platelet (PLT) count, aPTT, and PT were also within acceptable range after bypass, without being affected by fibrinogen administration.

We doubt therefore that fibrinogen concentrate was given with legitimate indication. Diffuse bleeding after bypass is not unknown, but up to now there is no evidence that this situation is mainly related to fibrinogen deficiency; hemodilution, PLT dysfunction, or inadequate heparin reversal also have to be considered.[6] As stated in the article, one patient required 2 units of red blood cells (RBCs), 6 units of plasma, and 3 units of PLTs; one patient required a single unit of RBCs, and the remaining 31 patients had no need for transfusions at all! This does not sound like urgent need for treatment of coagulation disorder. The authors should have described the clinical situations in more detail, such as the amount of blood loss and the site(s) of bleeding, for example, vents, sternum, and pericardium. Additionally, the authors should have discussed the potential hazardous side effects of fibrinogen concentrate infusion, such as venous thromboembolism, anaphylactic reaction, or transmission of viral diseases.[5]

The authors appropriately note the approval of their ethics committee and the patients' informed consent. May we ask if the patients had been informed about the possibility of fibrinogen application, and did they know about the potential side effects of this medication? This is not an unfair question since 33 cases needing fibrinogen concentrate after bypass within a period of 10 months exceeds the likely number of unpredictable emergencies and thus suggests that the routine consent of all patients for fibrinogen use should be obtained when they are scheduled for cardiac surgery.

TRANSFUSION appropriately requires authors to state their conflicts of interest. Five of the eight authors of the article by Solomon and colleagues reported conflicts with various manufacturers related to the study, and one was an employee of the company manufacturing the fibrinogen concentrate. This observation makes us even more wary of the approaches described.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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In reply:

We fear that von Bormann and colleagues[1] have misinterpreted our study, which was *not* an investigation of fibrinogen concentrate. We designed the study to compare different fibrinogen concentration measurement methods with maximum clot firmness (MCF) assessed by thromboelastometry (FIBTEM), and we felt it clinically relevant to do this using samples taken before and after hemostatic treatment. Our conclusions concern diagnostic issues, not the role of fibrinogen concentrate as hemostatic therapy. If the authors wish to debate the latter, we feel strongly that a letter in reply to our study is not the appropriate forum; we refer von Bormann and colleagues to a separate publication which provides detailed clinical descriptions and evaluates the efficacy and safety of fibrinogen concentrate,[2] topics that were beyond the scope of our article.[3]

It is not clear which are the approaches used in our diagnostic study that von Bormann and colleagues believe to be inconsistent with their second citation (Biscoping, 2009) or how they reached this conclusion; furthermore, this reference is not a guideline but an editorial offering opinion on a guideline, so the citation is inappropriate. Fibrinogen concentrate was not administered prophylactically in our study but was given only after confirmation of coagulopathic bleeding in the surgical field, as first-line therapy to avoid or minimize transfusion of allogeneic blood products. This approach is on-label and standard of care in a lot of Austrian, Swiss, and German hospitals and therefore does not require separate consent. Nevertheless, patients were informed about the possible administration of the hemostatic interventions, including fibrinogen concentrate. In our study, the only "intervention" beyond standard of care was an additional blood draw from a central line to obtain samples for analysis; consent was obtained for this.

Contrary to the opinion of von Bormann and colleagues, and despite the extensive use of antifibrinolytics, we observe that bleeding is common during complex cardiac surgery and in cardiac surgery patients receiving platelet inhibitors. Among cardiac surgery patients, 80% of blood product transfusions are consumed by a subset (10%-20%) of high-risk patients, and complex procedures and intake of antiplatelet medication are among the high-risk indicators.[4] In most patients in our study, bleeding stopped after administration of fibrinogen concentrate, and transfusion of allogeneic blood products was therefore avoided for many patients. As stated, our study did not involve *prophylactic* use of fibrinogen concentrate.

There is no confusion between plasma and blood concentrations in our article, and von Bormann and colleagues are wrong to suggest that this might have affected the observed correlations. In one part of the study, fibrinogen was added to whole blood samples to obtain prespecified increases in plasma fibrinogen concentration. We assumed a base hematocrit value of 45% for all volunteers. The prespecified increases (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 g/L; values shown on the *x*-axis of Fig. 4)[3] refer to plasma concentration *additional* to the starting value of 2.5 g/L. Therefore, all fibrinogen concentration data in our article are plasma values, in g/L.

Different studies have used different normal ranges for plasma fibrinogen concentration, and there is variation between normal ranges used by different hospital laboratories. In our laboratory, the normal range is defined as 2 to 4.5 g/L. This is consistent with the normal range of 1.63 to 4.58 g/L (5th to 95th percentile; data from 1379 individuals; age range, 25-74 years) published by Lowe and coworkers.[5] By defining the range as mean ± 2 SD, Grannis[6] derived a similar range of 1.7 to 4.1 g/L (data from 88 individuals; age, <45 years). There are numerous other publications that state values similar to 4.5 g/L for the upper limit of the normal range.[7-11] These include a study by Karlsson and coworkers,[8] which used a preopera-

tive plasma fibrinogen level of not more than 3.8 g/L as a trigger for inclusion in the study and treatment with fibrinogen concentrate or control. This trigger level is higher than the *target* plasma fibrinogen concentration (approx. 3.6 g/L; FIBTEM MCF of 22 mm) used in our study. Both the EMEA Core Summary of Product Characteristics for human fibrinogen products and the package insert for Haemocomplettan P also state the normal range for plasma fibrinogen concentration as 2 to 4.5 g/L.

Von Bormann and colleagues introduce confusion concerning measuring fibrinogen concentration with thromboelastometry. The FIBTEM assay measures the shear elastic modulus (strength) of the whole blood clot under platelet inhibition. A given value of FIBTEM MCF does not demonstrate a particular fibrinogen concentration because fibrinogen is not the only determinant of the strength of the fibrin-based clot. The SI unit of shear modulus is dyne/cm^2 (gigapascal); the SI units of fibrinogen concentration, g/L or mol/L, are entirely different.[12] In most perioperative settings, the Clauss assay is not relevant because the turnaround times are too long and would delay hemostatic therapy.

Finally, we are surprised that von Bormann and colleagues express concern about the declaration of the authors' conflicts of interest, and we find their position confusing. In a very similar situation as exists on our article, Dr Zander has recently coauthored a publication alongside employees of a manufacturer whose products are mentioned in the publication, declaring his work as a consultant for that manufacturer as a conflict of interest.[13] We acted in line with the requirements of the journal and accepted standards for ethical reporting of research.[14] For full transparency, we feel that von Bormann and colleagues should have done the same in their letter. We also suggest that Dr Zander provides more detail regarding his professional affiliation—we find it inadequate to list what appears to be a personal website on which he offers paid consultancy through a toll number.

CONFLICT OF INTEREST

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Neonatal alloimmunization: a rare case of multiple alloantibody formation in a patient with disseminated histoplasmosis

Neonatal alloimmunization is exceedingly rare and reported in only isolated case reports.[1-3] Relative immunodeficiency of the neonatal state, as well as poor interactions between antigen-presenting cells and T lymphocytes, may be causative.[4] The exact pathophysiologic mechanism, with additional costimulatory or contributory factors, is unknown.

We report a case of multiple alloantibody formation in a 4-month-old female with disseminated histoplasmosis. The patient was admitted with fever and found to be coagulopathic with pancytopenia and hepatosplenomegaly. She had no known immunodeficiency state or pertinent family history, nor had she ever received a blood transfusion. At admission, she was typed as A D+ (tube testing, Immucor, Norcross, GA) and her antibody screen (ID-MTS gel testing, Ortho Clinical Diagnostics, Raritan, NJ) was negative. The patient subsequently received five approximately 65-mL total volume simple transfusions of leukoreduced red blood cells (RBCs) from three separate units (Fig. 1). On Hospital Day 14, an antibody panel using gel testing (Ortho Clinical Diagnostics) demonstrated anti-E and anti-K1 and the direct antiglobulin test showed a 4+ positive reaction with immunoglobulin (Ig)G and a 1+ positive with anti-C3d. The acid elution was positive with IgG anti-Jkª specificity. Retained RBC segments from the transfused products were antigen typed and positive for the E, Jkª, and K1 antigens. Molecular genotyping demonstrated the patient was K1-antigen, E-antigen, and Jkª-antigen negative.

This 4-month-old female developed three distinct alloantibodies within 12 days of exposure to 3 units of RBCs, a rare occurrence in this age group. Passive transfer of antibodies was ruled out by negative donor antibody screens at the time of whole blood collection and negative maternal antibody screens.

The patient underwent comprehensive genetic, immunodeficiency, and infectious evaluations. Immunology studies (Hospital Day 3) showed soluble interleukin (IL)-2R (Cincinnati Children's Molecular Genetics, Cincinnati, OH) to be markedly elevated at 28,840 units/mL (normal, 334-3026 units/mL) indicating ongoing, significant T-cell activation. *Histoplasma* urine antigen was 14.89 ng/mL (positive, moderate) and she was treated
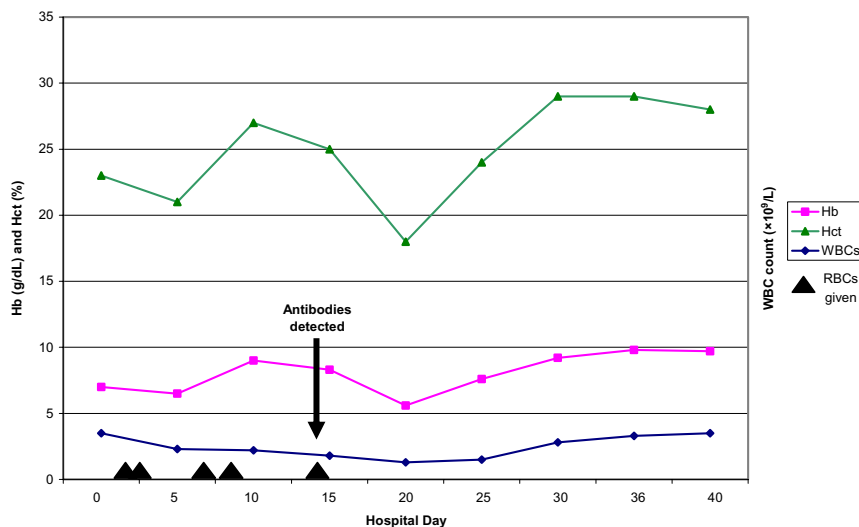

Fig. 1. Timeline of transfusion to antibody identification.