Anesthesiology 2009; 110:239–45

Factor XIII Substitution in Surgical Cancer Patients at High Risk for Intraoperative Bleeding

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Background: **Excessive intraoperative bleeding is associated with significant morbidity and mortality. The authors and others have shown that fibrin monomer allows preoperative risk stratification for intraoperative blood loss, likely due to an imbalance between available factor XIII and prothrombin conversion. The authors hypothesized that the use of factor XIII would delay the decrease of clot firmness in high-risk patients.**

Methods: **The concept was tested in a prospective, randomized, double-blind, placebo-controlled trial in elective gastrointestinal cancer surgery. Patients were randomized to receive factor XIII (30 U/kg) or placebo in addition to controlled standard therapy.**

Results: **Twenty-two patients were evaluable for a planned interim analysis. For the primary outcome parameter maximum clot firmness, patients receiving factor XIII showed a nonsignificant 8% decrease, and patients receiving placebo lost 38%, a highly significantly difference between the two groups ($P = 0.004$). A reduction in the nonprimary outcome parameters fibrinogen consumption (–28%, $P = 0.01$) and blood loss (–29%, $P = 0.041$) was also observed in the factor XIII group. Three patients experienced adverse events that seemed unrelated to factor XIII substitution. The trial was stopped early after a planned interim analysis with the primary endpoint reached.**

Conclusions: **This proof of concept study confirms the hypothesis that patients at high risk for intraoperative blood loss show reduced loss of clot firmness when factor XIII is administered early during surgery. Further clinical trials are needed to assess relevant clinical endpoints such as blood loss, loss of other coagulation factors, and use of blood products.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

This article is accompanied by an Editorial View. Please see: Spahn DR, Asmis LM: Excessive perioperative bleeding: Are fibrin-monomers and factor XIII the missing link? ANESTHESIOLOGY 2009; 110:212–3.

BLEEDING is an inevitable and thus expected phenomenon during surgical procedures, but excessive intraoperative and perioperative blood loss is associated with significant morbidity and mortality.[1,2] Blood loss during surgical procedures is a dynamic phenomenon, and it is therefore difficult to define the exact point at which bleeding becomes excessive. Intraoperative coagulopathic bleeding can usually be identified on clinical findings, which subsequently triggers procoagulant therapy. Searching for improved preoperative risk stratification tools, we have shown that coagulopathic intraoperative bleeding in a high-risk population is associated with an increase in preoperative fibrin monomer concentration.[3] Inadequate cross-linking capacity due to reduced factor XIII availability per unit of thrombin generated explains this seemingly paradoxical finding. The decrease in cross-linking capacity precedes and later escorts the otherwise unexplained intraoperative coagulopathic bleeding.[3] This association between preoperative fibrin monomer concentration and intraoperative blood loss was confirmed in a second independent and prospectively evaluated patient population undergoing general visceral surgery.[4] Similar findings were independently reported by other investigators.[5]

While indications to perform cancer surgery are increasingly extended,[2,6,7] this type of surgery carries an increased risk of coagulopathic bleeding.[1,2,8–10] Given the results of our studies, we hypothesized that patients with increased preoperative fibrin monomer concentrations undergoing surgery for gastrointestinal cancer would benefit from early supplementation of factor XIII, *i.e.*, that the use of factor XIII would delay their loss of clot firmness observed earlier.[3] Acquired factor XIII deficiency is frequent in the surgical setting.[11–13] Our hypothesis was that the use of factor XIII would increase cross-linking capacity and thus reduce loss of clot firmness, which was the primary outcome. Published data on factor XIII application in cancer patients are scarce; to the best of our knowledge, the use of factor XIII in cancer patients has not been prospectively evaluated. The few available data, however, seem not to suggest an increased risk for thromboembolism.[14–16]

In this proof of principle study, we evaluated the effect of standard of care therapy with or without early administration of factor XIII on maximum clot firmness in a

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Received from Institute for Clinical Chemistry and Haematology, Institute for Anaesthesiology, Department of Pharmacy, and Department of Surgery, Kantonsspital, St. Gallen, Switzerland, and CSL Behring, Bern, Switzerland. Submitted for publication January 22, 2008. Accepted for publication September 30, 2008. Supported by the Institute for Clinical Chemistry and Haematology, and the Institute for Anesthesiology, Kantonsspital St. Gallen, St. Gallen, Switzerland and by a grant-in-aid from CSL Behring, Bern, Switzerland. Dr. Korte has received support from Dade Behring, Marburg, Germany; Pentapharm, Basel, Switzerland; Novo Nordisk, Zurich, Switzerland; and CSL Behring, Hattersheim, Germany and Bern, Switzerland. Mr. Devay is an employee of CSL Behring, Bern, Switzerland. Presented in part at the XXIst Congress of the International Society on Thrombosis and Haemostasis, Geneva, Switzerland, July 6–12, 2007, and at Euroanaesthesia 2008, Copenhagen, Denmark, May 31–June 3, 2008.

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prospective, double-blind, placebo-controlled fashion in surgical cancer patients.

Materials and Methods

The study was approved by the ethical committee of the Canton of St. Gallen, Switzerland, and was registered with and approved by the Swiss Federal Regulatory Board (registration no. 2003DR4334, Swissmedic, Bern, Switzerland). Patients gave written informed consent.

Patients undergoing elective surgery for gastrointestinal cancer were eligible if they were 18 yr or older, were at risk for increased intraoperative blood loss (preoperative fibrin monomer > 3 μg/l; Enzymun FM, Roche Diagnostics, Rotkreuz, Switzerland),[3,4] and had an American Society of Anaesthesiology physical status classification score of 2 or higher. Exclusion criteria were known congenital bleeding disorder, intolerance to planned transfusion triggers (see transfusion target values in the next paragraph), contraindications to the use of plasma proteins (*e.g.*, history of allergic reactions), history of cerebrovascular or cardiovascular events, symptomatic peripheral artery disease, deep venous thrombosis or pulmonary embolism within the last 5 yr, body mass index greater than 35 kg/m^2, and pregnancy. All patients received regular thromboprophylaxis throughout hospitalization according to local guidelines, using low–molecular weight heparin (dalteparin), beginning the day before surgery.

Volume Support and Transfusion Triggers

Crystalloids (normal saline or Ringer solution) were to be used for the first 2000 ml of volume support needed. Thereafter, hydroxyethyl starch (130/0.4) was allowed to be used. To prevent a potential bias from dilution by volume support, transfusion triggers (*i.e.*, when to start blood product support) to maintain target values of 95 g/l for hemoglobin, 0.5 for the prothrombin time ratio, and 50×10^9/l for the platelet count were defined preoperatively for each patient according to the Leuven approach.[17] To maintain target values, red blood cell concentrates, fresh frozen plasma, and platelet apheresis products were to be used. A deviation from target values was only allowed if the senior anesthesiologist in charge deemed it necessary due to the patient's condition.

Randomization and Study Intervention

Randomization was performed by the Pharmacy Department and was kept blinded to any person outside the Pharmacy Department during the study period. Patients were randomized using a predefined, computer-based blockwise randomization plan. The study medication (verum or placebo) was prepared by the pharmacy and directly sent to the anesthesiologist in charge in the operating room. The medication was ready to use, and special care was taken that verum and placebo preparations were indistinguishable from each other. Fifteen minutes after the beginning of surgery, the study medication (factor XIII 30 U/kg [Fibrogammin] or placebo [Albumin ZLB], both CSL Behring, Bern, Switzerland) was applied in a double-blind fashion. No other coagulation factor concentrates were used.

Laboratory Analyses

Nonactivated plasma thrombelastography was performed using the Natem assay on a ROTEM thrombelastograph, Pentapharm, Munich, Germany. Factor XIII was measured using a chromogenic assay (Berichrom on a Behring Coagulation System analyzer), fibrinogen was measured using a nephelometric assay on a Behring Nephelometer II analyzer, and prothrombin fragments F1 + 2 (as a measure of prothrombin conversion/thrombin generation) were quantified by ELISA (Berichrom, Behring Coagulation System, Behring Nephelometer II, Enzygnost F1 + 2; Siemens, Dade Behring, Marburg, Germany).

Sample Size Calculation

Maximum clot firmness during surgery was the primary outcome parameter. The study was powered to detect a 30% difference in clot firmness between the verum and the placebo group (*i.e.*, prevention of loss of maximum clot firmness in the verum group and a 30% decrease in maximum clot firmness in the placebo group). With a potential 10% dropout rate, 42 patients were to be enrolled. An interim analysis was planned after at least 21 evaluable patients with a plan to stop further recruitment if differences for the primary outcome parameter were significant at $P < 0.05$. Analysis was planned as an intention to treat analysis.

Statistical Analysis of Effect of Factor XIII on Clot Firmness

At the time of designing this proof of concept study, no information regarding the development of the expected change of the primary outcome (clot firmness) over time was available. Initial analysis showed a linear relationship between clot firmness and time in both groups. We therefore described this relationship with linear regression models. Data were also censored when surgery lasted less than 195 min (last measurement), and some measurements were missing. The model was finally implemented as a linear mixed effects model for the mixed effect modeling software NONMEM (Globomax, Hanover, MD). With this statistical method, sparse, unbalanced, and censored data can be adequately analyzed. Whether treatment with factor XIII was significantly affecting the change of clot firmness over time was investigated by comparing the performance of the reduced and the full model (includes the treatment effect). This comparison was based on the improvement in

Table 1. Patient Properties

Sex	Age, yr	BMI, kg/m^2	ASA	Type of Surgery
M	64	24.3	2	Partial hepatic, rectal, and bladder resection, prostatectomy
M	71	25.2	2	Hepatic resection, cholecystectomy
M	67	33.1	2	Low anterior resection
M	62	22.1	3	Fascial resection of metastases
M	79	34.6	3	Osephageal resection
F	77	26.9	3	Hemicolectomy, cholecystectomy
F	54	18.0	3	Small intestine resection, adhesiolysis, colostomy
F	85	21.6	2	Rectal resection
F	70	18.4	2	Adhesiolysis, rectal resection
M	64	27.7	2	Hemicolectomy
F	57	26.3	2	Debulking, peritonectomy
M	36	18.7	2	Hemicolectomy
M	65	24.2	2	Partial gastral resection
M	38	21.2	2	Hepatic resection, cholecystectomy
M	73	30.8	2	Hemicolectomy
F	48	20.0	2	Low anterior resection, hysterectomy, adenexectomy
M	70	33.5	2	Low anterior resection, ileocecal resection, i.o. radiotherapy
M	64	26.0	2	Whipple's operation
M	69	29.7	2	Low anterior resection, cholecystectomy
F	52	27.2	2	Partial colonic resection
M	66	28.3	2	Anterior resection
M	74	33.0	2	Partial hepatic resection, cholecystectomy, i.o. radiotherapy

Detailed properties of the patients are displayed.

ASA = American Society of Anaesthesiologist Physical Status Classification (ASA classification); BMI = body mass index.

the NONMEM objective criterion (minus twice log likelihood; –2LL). The full model was expressed as:

$$CF = \theta_1 + \eta_1 + (\theta_2 + (\theta_3 \times GRP) + \eta_2) \times time$$

where CF is clot firmness, θ_1 is baseline clot firmness and θ_2 the slope of the line for the placebo group; θ_3 is the change in slope due to treatment with factor XIII; treatment or placebo group (GRP) is either 0 or 1. η_1 and η_2 are the (normally distributed) random interindividual variability of the intercept and slope respectively. Setting θ_3 to 0, the reduced model was derived as:

$$CF = \theta_1 + \eta_1 + (\theta_2 + \eta_2) \times time$$

Bayesian individual predictions were used for assessing the performance of the linear model. Median prediction errors and median absolute predictions errors were calculated. In addition, the residuals were also visually assessed. The significance of the treatment effect was based on the likelihood ratio test. An improvement of –2LL with the full model of 6.6 is indicating that the additional parameter (treatment) is significant at $P = 0.01$. It was also tested whether the estimated parameters ± 2 SE included 0.

The mixed effect model was calculated using NONMEM software.

Analysis of Nonprimary Outcome Data

The remaining data were compared for differences at a singular time point only: 195 min (for fibrinogen and prothrombin fragments F1 + 2) or upon completion of surgery (blood loss, blood product support). Results are presented as median values. Differences between the groups were evaluated by Mann–Whitney Rank Sum Test at an alpha level of 0.05. SigmaStat 3.5 (SPSS, Erkrath, Germany) was used.

Results

Twenty-five patients were enrolled; three patients were early dropouts due to rescheduling of their surgery on short notice (these patients were thus neither treated nor followed and could therefore not be evaluated). Two patients (one each in the placebo and the factor XIII group) have received study medication despite fibrin monomer levels below the cutoff of 3 μg/l; consequently, they were evaluated (intention to treat). Thus, 22 patients were evaluated. The factor XIII and placebo groups showed similar median body mass index, age, and American Society of Anesthesiologists physical status classification scores. Detailed patient properties are displayed in table 1. Two patients in the factor XIII group received aspirin preoperatively compared to none in the placebo group.

Clot Firmmess

The decrease in maximum clot firmness over time was significantly different ($P = 0.004$) between the control (fig. 1A) and the treatment groups (fig. 1B). With the full model, –2LL improved by 8.38. Mean baseline maximum clot firmness (Theta1) was 32.4 mm (SE 2.16), and the slope (Theta2) was –0.06 (SE 0.01) for the placebo group. Theta3 was 0.05 (SE 0.02). The coefficient of variation was estimated as 202% for the intercept and 2% for the slope. Figure 1C shows the fits through the measured data in the placebo and the factor XIII group

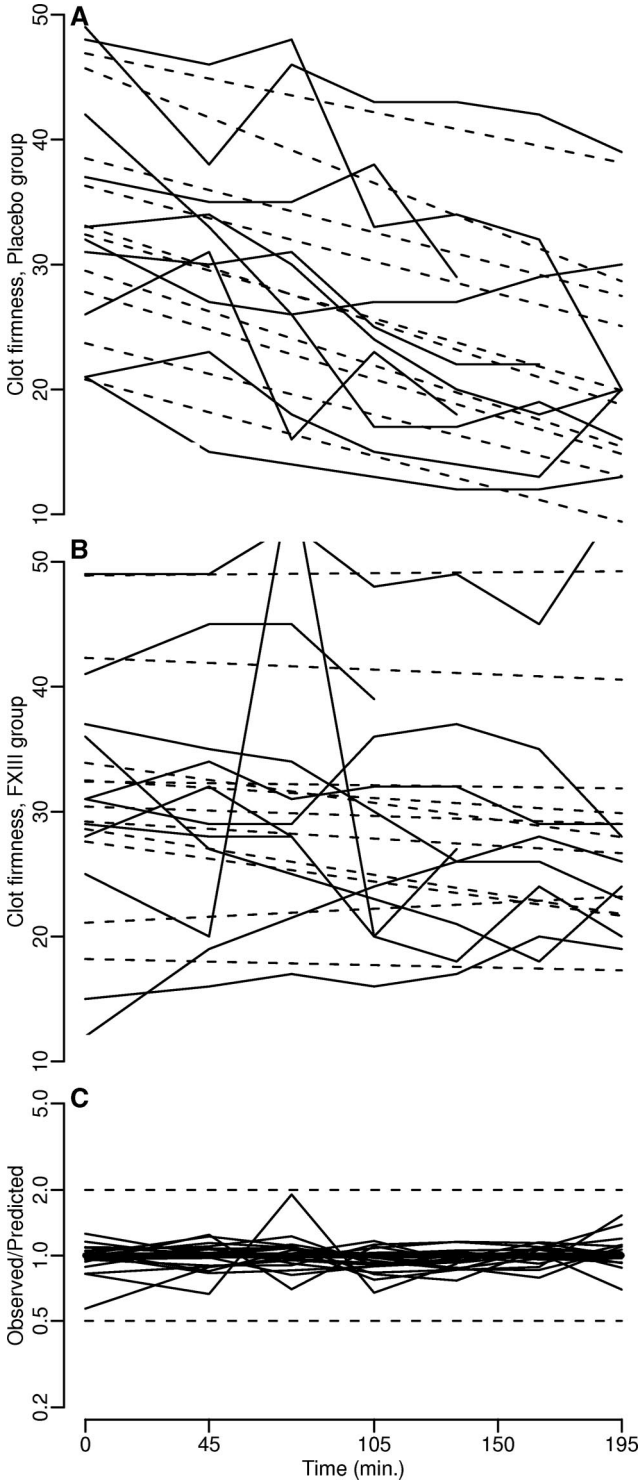

Fig. 1. Graphical display of the course of maximum clot firmness according to the linear mixed effects model in the (*A*) placebo group and (*B*) the factor XIII group. (*C*) Observed *versus* expected values during the study period, indicating a good fit between the model and the observed values.

and compares the (according to the model) expected and measured values. Figure 2 directly compares the clot firmness population prediction for the factor XIII and the placebo group. The graphs show that maximum clot

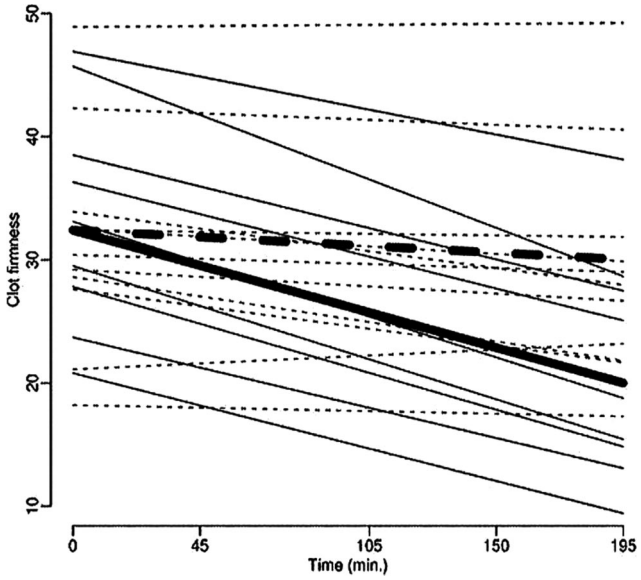

Fig. 2. Graphical display of the change of maximum clot firmness in the linear mixed effects model in the placebo group (*straight lines*) and the factor XIII group (*dashed lines*). The superimposed thick lines describe the course of maximum clot firmness for the placebo group (*straight line*) and the factor XIII group (*dashed line*). Maximum clot firmness behaves significantly different between the placebo group and the factor XIII group ($P = 0.004$).

firmness behaved uniformly over time within the groups, yet significantly different between the groups.

On the basis of the linear model, the reduction in clot firmness after 195 min was 38% in the placebo group and 7% in the treatment group ($P = 0.004$, direct graphic comparison in fig. 2).

The performance of the linear model shows that the model describes the data over the whole time course of the study. The median prediction error was −0.7%, and the median absolute prediction error 8%.

Non-primary Outcome Data

After application of the study medication, median factor XIII activity in the verum group increased to a maximal value of 1.11 U/ml (25th–75th percentile: 0.66–1.22), and it decreased to a minimum of 0.44 U/ml (0.42–0.52) in the placebo group.

Prothrombin conversion as measured by F1 + 2 was similar at baseline (factor XIII group: 244 pmol/l [178–280] *vs.* placebo group: 327 pmol/l [172–429]) and rose similarly in both groups during surgery (457% [270–544] *vs.* 313% [123–453], $P = 0.351$). The factor XIII and placebo groups had similar fibrinogen levels at baseline (3.51 g/l [2.61–4.05] *vs.* 3.61 g/l [2.89–5.83]), but the placebo group had a 28% greater decrease of fibrinogen as compared to the factor XIII group at + 195 min ($P = 0.01$).

Reduction in red blood cell support and infusion volume was not significant in the verum group. Lowest pH and lowest body temperature measured were not differ-

Table 2. Comparison between Factor XIII and Placebo Group

	Placebo	Factor XIII	*P*
IV fluids, ml	2450 (1900–3000)	2200 (1250–4975)	NS
FFP, ml	0 (0–800)	0 (0–0)	NS
Platelets, ml	0 (0–0)	0 (0–0)	NS
RBC, ml	200 (0–800)	150 (0–700)	NS
Blood loss, ml	1050 (700–1800)	750 (400–1000)	0.041
pH	7.34 (7.30–7.36)	7.33 (7.32–7.34)	NS
Temperature, C°	35.9 (35.3–36.1)	36.2 (36.0–36.7)	NS
Time, minutes	210 (150–230)	172 (100–415)	NS

Numbers in brackets describe the 25th and 75th percentiles.

FFP = fresh frozen plasma; RBC = red blood cell.

ent between the groups as was length of surgery (table 2). Median overall blood loss was lower in the factor XIII group (750 ml [400–1000] *vs.* 1050 ml [700–1800], $P = 0.04$).

No allergic responses were observed. One episode of hypotension occurred after application of factor XIII, but the respective patient was already in need for inotropic support due to hypotension repeatedly before the study medication was given. One patient in the verum group with extensive tumor surgery of the abdomen and pelvis (duration of surgery > 10 h) due to a metastasizing carcinoma of the rectum developed a symptomatic deep vein thrombosis 7 days after surgery (despite regular thromboprophylaxis). A diabetic patient in the verum group undergoing tumor debulking for colon cancer developed postoperative ascites and pleural empyema with sepsis, which developed progressively despite adequate therapy. A myocardical ischemia occurred 30 days postoperatively, and she died 2 days later.

With a median follow up of 340 days, 3 patients in the verum and 3 patients in the placebo group had died.

Discussion

We show that patients with increased preoperative fibrin monomer concentration (indicating an increased risk of intraoperative bleeding) have significantly decreased loss of clot firmness if they receive factor XIII early (15 min) into surgery.

Although the study was not powered for other endpoints, we observed a reduction in blood bloss and fibrinogen consumption, well in line with our hypothesis of the postulated meachanism.

Performing clinical trials in perioperative hemostasis is demanding, which might explain why only few prospective randomized trials have been performed on the use of procoagulant drugs. The strategy for the double-blind, placebo-controlled trial presented here was derived from a continuous line of evidence observed in different, independent patient populations. We have shown earlier that patients with increased preoperative fibrin monomer concentrations have a higher risk for increased intraoperative blood loss, seemingly a paradox at first sight.[3] Similar observations were independently made, however, by other investigators.[5] The reason for this is likely to be the inadequate availability of factor XIII in comparison to the amount of prothrombin converted, *i.e.*, thrombin generated, resulting in reduced fibrin cross-linking and clot firmness.[3] In a further clinical trial, we were able to demonstrate that increased preoperative fibrin monomer concentrations can be used to prospectively risk stratify for intraoperative blood loss.[4] Explaining this model in detail elsewhere,[18] we hypothesized that early intraoperative supplementation of factor XIII would allow to decrease the loss of clot firmness observed with standard of care therapy.

The current study was powered to detect a 30% difference in maximum clot firmness between patients receiving factor XIII or placebo. As this primary endpoint was reached upon the planned interim analysis, no further patients were recruited thereafter.

For nonprimary outcome parameters, the difference in use of red cell concentrates and volume support was not significant between the groups. However, a significant reduction for blood loss (–29%, $P = 0.041$) and loss of fibrinogen (–28%, $P = 0.01$) was observed. Given that the two groups showed similar prothrombin conversion during surgery (no differences in circulating F1 + 2 concentrations), the difference in loss of fibrinogen is not due to differences in systemic thrombin generation. Two explanations seem possible for this observation: the higher factor XIII concentration in the verum group might reduce fibrinogen consumption at the site of bleeding through increased clot firmness, and the use of factor XIII might lead to protection of fibrinogen from plasmin degradation.[19]

The results of this study confirm our hypothesis that early factor XIII substitution in high-risk patients (as identified by increased preoperative fibrin monomer) prevents early loss of clot firmness. In addition, our results suggest that the prevention of loss in clot firmness through factor XIII application results in a fibrinogen-sparing effect and in reduction of blood loss. How-

ever, as the results on blood loss and fibrinogen were not primary outcomes, confirmation of these observations is yet to be generated in adequately powered clinical trials.

Given these as well as other clinical observations[20,21] and other experiences with *in vitro* experiments using factor XIII,[22,23] it seems reasonable to believe that the observations made in our study were indeed the direct result of reducing cross-linking defects or cross-linking deficiency through factor XIII application.

Clinical observations of (by definition) potential side effects of the study drug were observed in three patients. One patient had a hypotensive episode after factor XIII application; however, he already had repeated need for inotropic support for hypotension before factor XIII was applied. It is therefore unlikely that the study drug was the primary cause for hypotension; rather, drug application and hypotension coincided.

One patient developed a deep venous thrombosis 7 days after surgery and the use of verum study medication. This patient had extensive surgery for abdominal and pelvic tumor resection (lasting more than 10 h); besides the study drug, he received a total of 9800 ml of red blood cells, platelets, and fresh frozen plasma during surgery. Given the length and extent of surgery, the amount of blood products used and the fact that the patient's course of factor XIII activity during surgery was below or in the low normal range, it seems unlikely that the study drug contributed to the development of the thrombosis. By definition, however, such a relationship can ultimately not be excluded.

The third patient was diabetic and undergoing extensive abdominal tumor resection at various sites as well as intraoperative chemotherapy. Unfortunately, she developed postoperative pleural empyema. Despite adequate and aggressive therapy, the empyema could not be controlled during the early postoperative course. The patient's status deteriorated due to the infection, and she therefore required intensive care. Despite intensive care measures, she developed myocardial ischemia 30 days after surgery and died 2 days later. Given the patient's intraoperative course of factor XIII activity during surgery, which was below the normal range, the postoperative complications that occurred between surgery and myocardial ischemia, and the time delay between the adverse event and the use of the study drug, it seems, again, very unlikely that the verum study drug contributed to the myocardial ischemia. As with the aforementioned patient, however, such a relationship can (by definition) ultimately not be excluded. Potential thrombogenicity of procoagulant factors used in clinical practice must be a concern; however, factor XIII supplementation has so far not been linked to an increased risk of thromboembolism to the best of our knowledge. In fact, prospective evaluations of recombinant factor XIII in deficient patients and healthy volunteers with doses 1.5- to 2-fold higher than the dose used in this trial have not shown any evidence of an increased risk of thromboembolism.[24–26]

Limitations and Strength of the Study

Our study is a small, single-center study. Thus, potential limitations in interpreting these single-center results have to be recognized. However, this prospective proof of principal and, in fact, pilot trial tested a clear-cut hypothesis that was developed from earlier, consecutive clinical trials performed in independent patient populations. Also, it was performed as a randomized, double-blind, placebo-controlled trial in an attempt to prevent introduction of selection and treatment bias as far as possible; additional precautions were taken to assure that all patients would receive similar standard of care treatment. Both groups of patients received identical volumes of fresh frozen plasma. Despite this fact, patients receiving factor XIII concentrate showed a clear-cut increase in factor XIII activity and maintained their clot firmness, and those receiving placebo showed a loss of factor XIII activity and clot firmness (fig. 2). Thus, changes observed in factor XIII activity are due to the use of the study medication (factor XIII concentrate or placebo), and the effects seen with regard to the prevention of clot firmness loss can be attributed to the use of factor XIII. Although there was a reduction in loss of fibrinogen and blood loss, it has to be recognized that these parameters were not primary outcome parameters and that other secondary outcome parameters were not significantly different between the two groups, likely due to the small sample size. To evaluate the potential clinical benefit of factor XIII application, adequately powered larger trials are needed.

In conclusion, this prospective, randomized, double-blind, placebo-controlled trial confirms our hypothesis that loss of clot firmness in patients at high risk for increased intraoperative blood loss can be prevented with early intraoperative factor XIII substitution. Conversely, the placebo arm of this trial confirms that high-risk patients (as identified by preoperatively increased fibrin monomer concentrations) indeed experience significant loss of clot firmness despite standard of care therapy. Additional studies are needed to confirm these results in a larger patient population in elective surgery, not only in terms of efficacy but also of safety. Also, it seems wise to further evaluate this strategy in other settings such as the postoperative period.

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