Reversing Dabigatran Anticoagulation with Prothrombin Complex Concentrate *versus* Idarucizumab as Part of Multimodal Hemostatic Intervention in an Animal Model of Polytrauma

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ABSTRACT

Background: Although idarucizumab is the preferred treatment for urgent dabigatran reversal, it is not always available. Prothrombin complex concentrate (PCC) may be an alternative and, with bleeding in trauma, additional hemostatic therapy may be required. The authors investigated multimodal treatment in a preclinical polytrauma model.

Methods: Dabigatran etexilate (30 mg/kg twice daily) was given orally to 45 male pigs for 3 days. On day 4, animals received a dabigatran infusion before blunt liver injury and bilateral femur fractures. After injury, animals were randomized 1:1:1:1:1 to receive placebo (control), tranexamic acid (TXA; 20 mg/kg) plus human fibrinogen concentrate (FCH; 80 mg/kg) (TXA–FCH group), PCC (25 U/kg or 50 U/kg) plus TXA plus FCH (PCC25 and PCC50 groups), or 60 mg/kg idarucizumab (IDA) plus TXA plus FCH (IDA group). Animals were monitored for 240 min after trauma, or until death.

Results: The degree of injury was similar in all animals before intervention. Control and TXA–FCH animals had the highest total postinjury blood loss (3,652 ± 601 and 3,497 ± 418 ml) and 100% mortality (mean survival time 96 and 109 min). Blood loss was significantly lower in the PCC50 (1,367 ± 273 ml) and IDA (986 ± 144 ml) groups, with 100% survival. Thrombin–antithrombin levels and thrombin generation were significantly elevated in the PCC50 group.

Conclusions: Idarucizumab may be considered the optimal treatment for emergency reversal of dabigatran anticoagulation. However, this study suggests that PCC may be similarly effective as idarucizumab and could therefore be valuable when idarucizumab is unavailable. **(ANESTHESIOLOGY 2017; 127:852-61)**

NON-VITAMIN K oral anticoagulants including dabigatran, rivaroxaban, apixaban, and edoxaban are increasingly prescribed for patients with atrial fibrillation.[1–3] Although non-vitamin K oral anticoagulants carry a low risk of bleeding, the risk cannot be eliminated and immediate reversal of the anticoagulant effects is occasionally needed (*e.g.*, emergency surgery or trauma).[4] Guidelines for the management of bleeding associated with non-vitamin K oral anticoagulants are based on limited evidence.[5–7]

Prothrombin complex concentrates and activated prothrombin complex concentrates are currently being used for reversing the anticoagulant effects of dabigatran.[8] Preclinical experiments have shown that these products are effective,[9–13] and a recent clinical study demonstrated the effectiveness of activated prothrombin complex concentrate for controlling dabigatran-associated major bleeding.[14] High doses have

What We Already Know about This Topic

- Idarucizumab is an antigen-binding fragment that binds to dabigatran and is approved in many countries for urgent anticoagulation reversal. However, in certain circumstances, other hemostatic therapies, including tranexamic acid and prothrombin complex concentrates, may be administered to treat the coagulopathy after trauma and hemorrhage, or when the specific antidote is not available.

What This Article Tells Us That Is New

- In a porcine polytrauma injury model, blood loss was lower with idarucizumab than with prothrombin complex concentrate (PCC) when administered for dabigatran reversal as part of multimodal therapy. However, survival was 100% in both groups. There were no hypercoagulability effects with idarucizumab, while PCC increased thrombin generation. Without idarucizumab or PCC, tranexamic acid and fibrinogen concentrate were ineffective at reducing bleeding in this model.

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been associated with a risk of thromboembolic complications,[8,15] although clinical data indicate that the risk is no higher with prothrombin complex concentrates than with therapeutic plasma.[16,17] Thromboembolic risk may persist for several days postoperatively[18] and it may be higher with activated prothrombin complex concentrates than with prothrombin complex concentrates.[19]

Idarucizumab, a humanized monoclonal antibody fragment, is the first specific antidote for reversing the anticoagulant activity of dabigatran.[20,21] Preclinical and clinical studies have shown that it achieves immediate and sustained reversal.[22] Since idarucizumab binds only to dabigatran, it has no intrinsic coagulation activity. However, in massive bleeding with complex coagulopathy, specific reversal of dabigatran may not be sufficient to achieve hemostasis; multimodal treatment with a range of hemostatic agents may be required. In central European countries, it is common for coagulation management to be based on coagulation factor concentrates (*e.g.*, fibrinogen concentrate, prothrombin complex concentrate), administered according to point-of-care coagulation monitoring.[23–25] In other countries such as the United States, there is more reliance upon treatment with allogeneic blood products (*e.g.*, cryoprecipitate, fresh frozen plasma), potentially using a fixed-ratio approach.[26,27] There is also international recognition that tranexamic acid can reduce mortality by preventing fibrinolysis.[28,29]

For the current study, we hypothesized that idarucizumab is more effective in reducing blood loss than prothrombin complex concentrate when administered together with tranexamic acid and fibrinogen concentrate in a porcine polytrauma model under dabigatran anticoagulation. We also investigated the thrombogenic potential of each intervention.

Materials and Methods

The methodology for this study was similar to that of several previous studies.[10,11,30] See Supplemental Digital Content (http://links.lww.com/ALN/B529) for additional details of methodology used in this study. Data from all animals were collected between March 12, 2015, and August 4, 2015.

Ethical Approval

Experiments were performed at RWTH Aachen University Hospital, Aachen, Germany, in accordance with German legislation governing animal studies following the Guide for the Care and Use of Laboratory Animals.[31] The protocol was approved by the government office for animal care and use (Landesamt für Natur, Umwelt und Verbraucherschutz, Recklinghausen, Germany).

Experimental Methodology

Forty-five German landrace pigs (weight [mean ± SD]: 41 ± 3 kg) were included in the study. Animals received dabigatran etexilate orally for 3 days (30 mg/kg twice daily), with the last dose given 12 h before surgery. On day 4, animals were anesthetized and prepared for surgery. Dabigatran (Boehringer Ingelheim, Germany) was infused intravenously for 90 min (1 mg/ml; rate: 0.77 mg · kg^{-1} · h^{-1} for 30 min, then 0.2 mg · kg^{-1} · h^{-1} for 60 min).

Before injury, dabigatran-treated animals were randomized using sealed envelopes (n = 9 per group) to receive: saline (control group); tranexamic acid (TXA; 20 mg/kg) plus fibrinogen concentrate (FCH; 80 mg/kg) (TXA–FCH group); prothrombin complex concentrate (PCC; 25 U/kg) plus tranexamic acid (20 mg/kg) plus fibrinogen concentrate (80 mg/kg) (PCC25 group); prothrombin complex concentrate (50 U/kg) plus tranexamic acid (20 mg/kg) plus fibrinogen concentrate (80 mg/kg) (PCC50 group); or idarucizumab (IDA; 60 mg/kg) plus tranexamic acid (20 mg/kg) plus fibrinogen concentrate (80 mg/kg) (IDA group). The following products were used: prothrombin complex concentrate, Beriplex P/N (CSL Behring, Germany; U.S. brand-name Kcentra; Lot 89270111A); tranexamic acid, Cyclocapron (Pfizer, USA; Lot Y05545); fibrinogen concentrate, Haemocomplettan P (CSL Behring; Lot 31169911A); idarucizumab, Praxbind (Boehringer Ingelheim, Germany; Lot 6001325).

A captive bolt gun (Karl Schermer and Co., Germany) was used to create bilateral femur fractures with a concomitant soft tissue injury at the midshaft, and a standardized blunt liver injury was induced. These procedures were performed by one investigator who was blinded to treatment allocation.

Five minutes after injury and after onset of hemorrhagic shock, animals were resuscitated with Ringer's solution. Twelve minutes after injury, blood loss was measured by suctioning intraperitoneal blood. Study treatments were then administered.

Animals surviving for the 240-min observation period after injury were euthanized with pentobarbital. Immediately after death, total postinjury blood loss was determined and internal organs (heart, lungs, liver, and kidneys) were examined macroscopically and histologically.

Blood Sampling and Analytical Methods

Analysis of blood samples included conventional coagulation testing (prothrombin time; activated partial thromboplastin time; and levels of fibrinogen, fibrinopeptide A, D-dimer, and thrombin–antithrombin complex); thromboelastometry; thrombin generation; and measurement of blood gases and plasma concentrations of dabigatran (using diluted thrombin time).[9,12,15] For animals that died before 240 min postinjury, the last regular assessment was evaluated.

Pathologic Examination

Immediately after death, internal organs (heart, lungs, liver, and kidneys) were removed, fixed in formalin, cut into slices (thickness: 5 mm), and examined by a pathologist who was unaware of treatment assignment.

Statistical Analysis

The primary endpoint of this study was the reduction in blood loss. The sample size was based on previous experience from a similar animal model with prothrombin complex concentrate monotherapy for the reversal of dabigatran.[10] Statistical analysis was performed using SPSS 22 (SPSS, USA) and GraphPad Prism 6.0h (GraphPad Software, USA) was used for graphing purposes. Differences in total blood loss between groups were assessed using analysis of variance, with *post hoc* Tukey adjustment. For comparison of coagulation variables, blood cell count, and hemodynamic variables, a repeated measure analysis of variance was used with intervention as group-factor and time as repeated-factor. The group by time interaction was also included to allow the group differences to vary over time. For significant effects, the Sidak method was used *post hoc*. Pairwise log-rank tests were used for survival analysis. Statistical tests were performed two-tailed and $P < 0.05$ was considered statistically significant. Data are shown as mean ± SD.

Results

Forty-five pigs were included in the study. Until the time of death, complete data were available for all animals with respect to all study variables. Baseline laboratory and hemodynamic parameters were comparable between the groups before injury.

Blood Loss and Survival

In the control group (dabigatran plus placebo), postinjury blood loss was 3,652 ± 601 ml ($P < 0.0001$ *vs.* PCC50 and IDA) and the mean survival time was 96 min (range, 62 to 148 min) (fig. 1A and B). Treatment with tranexamic acid and fibrinogen concentrate did not reduce blood loss (3,497 ± 418 ml), while mean survival time was 109 min (77 to 156 min). The mortality rate was 100% in the control and TXA–FCH groups. Administration of prothrombin complex concentrate 25 U/kg together with tranexamic acid and fibrinogen concentrate (PCC25 group) reduced the mortality rate to 56% (fig. 1B) and the total postinjury blood loss was reduced to 2,827 ± 864 ml ($P < 0.01$ *vs.* control and TXA–FCH; fig. 1A). Treatment with prothrombin complex concentrate 50 U/kg or idarucizumab (in addition to tranexamic acid and fibrinogen concentrate) resulted in significantly lower total blood loss (1,367 ± 273 and 986 ± 144 ml) with reductions of 61 to 62% and 72 to 73% *versus* control and TXA–FCH animals (all $P < 0.0001$; $P < 0.05$ *vs.* PCC25; no significant difference between the PCC50 and IDA groups). All animals given PCC50 or idarucizumab survived to 240 min ($P < 0.05$ *vs.* control, TXA–FCH and PCC25; fig. 1B). Stabilization of hemodynamic variables and lactate levels was also observed in these groups, with significant differences from the control and TXA–FCH groups (see Supplemental Digital Content, table 1, http://links.lww.com/ALN/B529).

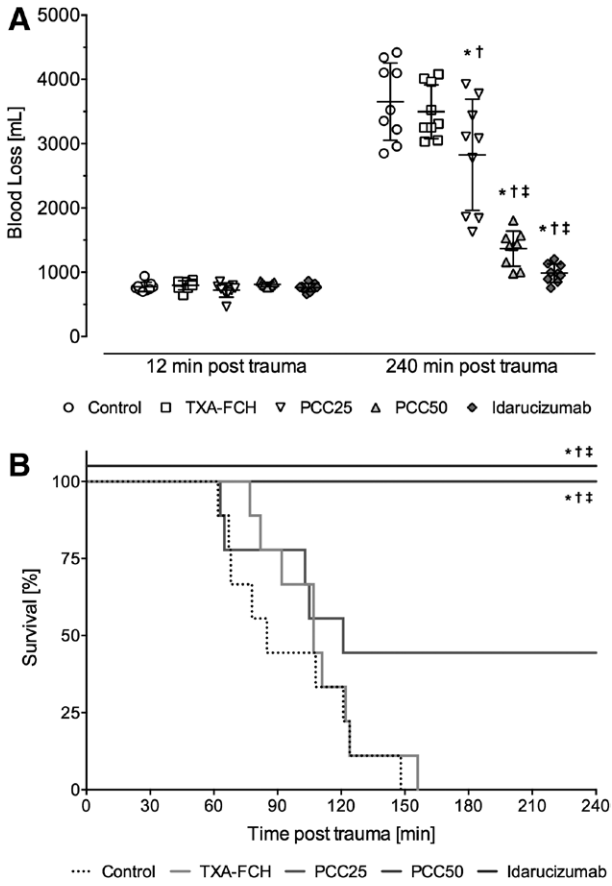

Fig. 1. Blood loss and survival. Blood loss 12 min after liver injury but before intervention, and at the end of the experiment (240 min after liver injury; *A*). Data are presented as mean ± SD; n = 9 per group. Survival data are presented as a Kaplan-Meier curve (*B*); initially n = 9 per group. *$P < 0.05$ *versus* control group; †$P < 0.05$ *versus* tranexamic acid (TXA) plus human fibrinogen concentrate (FCH) group (TXA–FCH); ‡$P < 0.05$ *versus* prothrombin complex concentrate (PCC) 25 U/kg group (PCC25). Between-group differences are presented hierarchically as follows: idarucizumab (IDA) and PCC 50 U/kg (PCC50) (‡†*) → PCC25 (†*) → TXA–FCH (*) → control.

Plasma Levels of Dabigatran and Resulting Anticoagulation before Infliction of Injury

After the 90-min infusion of dabigatran on day 4, the overall mean plasma dabigatran level (all animals) was 522 ng/ml, and plasma-based clotting tests (activated partial thromboplastin time and prothrombin time) were prolonged (table 1). Prolongations were also seen in the EXTEM clotting time and INTEM clotting time (table 2). A further effect of dabigatran was a reduction in thrombin generation (fig. 2).

Measurements after Standardized Polytrauma

Control Animals. Despite fluid resuscitation, controls and animals treated with only tranexamic acid and fibrinogen concentrate developed severe shock after injury, with low mean arterial pressure and cardiac output attributable to ongoing blood loss ($P < 0.01$ *vs.* IDA and PCC50 within 60 min posttrauma; see Supplemental Digital Content, table

Table 1. Dabigatran Levels, Coagulation Tests, Hemoglobin, and Platelet Counts

Timepoint	Study Group	Dabigatran (ng/ml)	aPTT (s)	Prothrombin Time (s)	Hemoglobin (g/dl)	Platelets (x10^3/μl)
Baseline	Control	—	15.8 ± 3.2	15.4 ± 7.8	10.6 ± 0.6	432 ± 63
	TXA–FCH	—	13.6 ± 2.9	12.0 ± 2.4	10.3 ± 0.5	395 ± 68
	PCC25	—	12.9 ± 2.7	11.6 ± 2.3	10.2 ± 0.8	388 ± 57
	PCC50	—	14.2 ± 3.0	11.8 ± 2.6	9.9 ± 0.8	415 ± 54
	IDA	—	14.2 ± 1.8	12.1 ± 1.9	10.6 ± 0.5	427 ± 47
After dabigatran	Control	508 ± 124	19.2 ± 1.3	22.5 ± 6.6	8.8 ± 0.3	358 ± 37
	TXA–FCH	490 ± 184	17.6 ± 3.9	21.7 ± 9.2	8.7 ± 0.4	345 ± 43
	PCC25	596 ± 213	18.6 ± 2.7	25.4 ± 10.0	9.3 ± 0.3	329 ± 81
	PCC50	494 ± 231	18.8 ± 3.4	22.1 ± 13.4	8.8 ± 0.6	372 ± 56
	IDA	519 ± 110	17.1 ± 2.3	20.7 ± 5.1	8.8 ± 0.5	376 ± 39
12 min posttrauma	Control	443 ± 198	21.8 ± 4.5	37.5 ± 15.9	6.4 ± 0.6	271 ± 37
	TXA–FCH	388 ± 127	19.0 ± 4.3	30.6 ± 18.2	6.6 ± 0.5	260 ± 50
	PCC25	553 ± 216	21.2 ± 4.2	37.3 ± 12.7	6.5 ± 0.4	247 ± 87
	PCC50	344 ± 124	20.8 ± 6.8	33.7 ± 10.8	6.7 ± 0.5	276 ± 42
	IDA	490 ± 207	19.5 ± 2.9	31.8 ± 12.0	6.8 ± 0.7	284 ± 43
30 min posttrauma	Control	448 ± 136	29.7 ± 10.6	62.9 ± 39.3	5.3 ± 0.6	236 ± 37
	TXA–FCH	472 ± 201	24.0 ± 5.4	52.9 ± 31.4	5.3 ± 0.5	239 ± 54
	PCC25	469 ± 130	29.8 ± 4.9	23.5 ± 8.0*†	4.9 ± 0.5	227 ± 132
	PCC50	424 ± 153	24.0 ± 4.4	14.4 ± 4.8*†	5.4 ± 0.4	222 ± 31
	IDA	0 ± 0*†‡§	11.0 ± 2.5	9.2 ± 0.5*†	5.6 ± 0.5	254 ± 41
60 min posttrauma	Control	381 ± 229	101.5 ± 10.6	109.3 ± 67.8	3.4 ± 0.9	150 ± 42
	TXA–FCH	415 ± 174	27.3 ± 5.6*	56.1 ± 31.2*	4.2 ± 0.6	189 ± 35
	PCC25	363 ± 107	28.0 ± 4.9*	26.6 ± 13.1*†	4.3 ± 0.7	195 ± 96
	PCC50	347 ± 143	21.0 ± 3.8*	12.8 ± 4.3*†	5.4 ± 0.6*†‡	222 ± 38
	IDA	66 ± 74*†‡§	11.1 ± 1.9*	9.9 ± 0.7*†	5.4 ± 0.5*†‡	251 ± 39*
120 min posttrauma	Control	277 ± 61	127.3 ± 115.6	196.4 ± 98.3	2.7 ± 0.4	98 ± 35
	TXA–FCH	296 ± 107	42.7 ± 10.2*	116.4 ± 32.2	2.6 ± 0.6	104 ± 25
	PCC25	350 ± 57	31.6 ± 5.6*	29.6 ± 21.1*†	4.1 ± 0.8*†	166 ± 36*
	PCC50	298 ± 90	22.4 ± 4.7*	13.4 ± 4.6*†	5.2 ± 0.6*†‡	217 ± 27*†
	IDA	86 ± 75*†‡§	12.3 ± 2.3*	10.6 ± 1.1*†	5.3 ± 0.5*†‡	238 ± 23*†
180 min posttrauma	Control	—	—	—	—	—
	TXA–FCH	—	—	—	—	—
	PCC25	327 ± 44	24.6 ± 4.2	20.8 ± 9.3	4.1 ± 0.5	154 ± 21
	PCC50	259 ± 92	21. 2 ± 4.6	12.2 ± 3.7	5.2 ± 0.6‡	206 ± 33
	IDA	142 ± 66‡	12.3 ± 2.3	11.2 ± 1.0	5.3 ± 0.4‡	242 ± 31‡
240 min posttrauma	Control	—	—	—	—	—
	TXA–FCH	—	—	—	—	—
	PCC25	282 ± 67	23.0 ± 4.6	14.4 ± 2.6	4.0 ± 0.6	151 ± 31
	PCC50	235 ± 96	20.2 ± 3.3	11.8 ± 3.4	5.2 ± 0.6‡	205 ± 33
	IDA	103 ± 63‡	12.8 ± 2.5	11.3 ± 1.1	5.3 ± 0.4‡	234 ± 32‡

Data are shown as mean ± SD. In each group, n = 9 animals initially.

*P < 0.05 *versus* control group; †P < 0.05 *versus* TXA–FCH group; ‡P < 0.05 *versus* PCC25 group; §P < 0.05 *versus* PCC50 group. Between-group differences are presented hierarchically as follows: IDA (§‡†*) → PCC50 (‡†*) → PCC25 (†*) → TXA–FCH (*) → control.

aPTT = activated partial thromboplastin time; IDA = idarucizumab; PCC25 = prothrombin complex concentrate 25 U/kg; PCC50 = prothrombin complex concentrate 50 U/kg; TXA–FCH = tranexamic acid plus human fibrinogen concentrate.

1, http://links.lww.com/ALN/B529). Controls and TXA–FCH animals also had the lowest platelet counts and hemoglobin levels (table 1). Control animals developed severe coagulopathy with deterioration over time in all coagulation parameters (significant differences *vs.* all other study groups except TXA–FCH; figs. 2 and 3; tables 1 and 2). EXTEM maximum clot firmness (MCF) and INTEM MCF were lowest in this group, while the plasma fibrinogen level was significantly lower than in the PCC25, PCC50, and IDA groups (table 2; fig. 3). The impairment of thrombin generation caused by dabigatran was sustained among control animals.

Substitution with Fibrinogen and Tranexamic Acid (TXA–FCH Group). Immediately after administration of fibrinogen concentrate (80 mg/kg), plasma fibrinogen levels were significantly higher in all intervention groups than in controls (P < 0.0001; fig. 3). The mean fibrinogen level subsequently decreased over time to reach comparability with controls at 120 min postinjury. All other coagulation parameters were similar to the control group.

Substitution with Fibrinogen, Tranexamic Acid, and Prothrombin Complex Concentrate (25 U/kg). In the PCC25 group, data from 240 min onward were from the four animals

Table 2. Thromboelastometry Results

Timepoint	Study Group	EXTEM CT (s)	EXTEM MCF (mm)	INTEM CT (s)	INTEM MCF (mm)
Baseline	Control	38 ± 6	76 ± 4	118 ± 13	72 ± 4
	TXA–FCH	42 ± 5	75 ± 4	140 ± 21	71 ± 4
	PCC25	34 ± 5	73 ± 2	96 ± 28	71 ± 3
	PCC50	39 ± 6	75 ± 3	144 ± 22	72 ± 4
	IDA	42 ± 7	74 ± 1	115 ± 21	70 ± 1
After dabigatran	Control	473 ± 189	76 ± 3	584 ± 127	71 ± 4
	TXA–FCH	510 ± 225	74 ± 8	600 ± 164	70 ± 4
	PCC25	492 ± 209	69 ± 18	592 ± 150	70 ± 4
	PCC50	432 ± 295	69 ± 21	605 ± 204	70 ± 5
	IDA	352 ± 82	77 ± 2	489 ± 76	71 ± 2
12 min posttrauma	Control	587 ± 350	59 ± 22	650 ± 184	64 ± 4
	TXA–FCH	552 ± 261	58 ± 24	674 ± 241	63 ± 3
	PCC25	612 ± 186	50 ± 28	716 ± 174	63 ± 5
	PCC50	486 ± 191	59 ± 27	680 ± 291	65 ± 4
	IDA	580 ± 220	64 ± 18	607 ± 96	65 ± 3
30 min posttrauma	Control	1010 ± 738	40 ± 31	823 ± 250	60 ± 5
	TXA–FCH	864 ± 340	39 ± 24	805 ± 230	67 ± 4*
	PCC25	171 ± 47*†	71 ± 3*†	482 ± 81*†	65 ± 3
	PCC50	108 ± 38*†	73 ± 3*†	353 ± 109*†	69 ± 3*
	IDA	33 ± 13*†	73 ± 2*†	172 ± 18*†‡	66 ± 2
60 min posttrauma	Control	1580 ± 699	26 ± 26	1049 ± 320	48 ± 9
	TXA–FCH	835 ± 246*	34 ± 25	794 ± 164*	61 ± 3*
	PCC25	176 ± 63*†	67 ± 6*†	420 ± 80*†	62 ± 5*
	PCC50	85 ± 37*†	72 ± 3*†	283 ± 80*†	67 ± 4*†
	IDA	48 ± 14*†	72 ± 2*†	186 ± 64*†‡	66 ± 2*†
120 min posttrauma	Control	2047 ± 473	Not detectable	1086 ± 63	36 ± 6
	TXA–FCH	1745 ± 592	12 ± 7	950 ± 132*	46 ± 5*
	PCC25	230 ± 122*†	60 ± 21†	479 ± 98*†	60 ± 7*†
	PCC50	84 ± 35*†	72 ± 2†	274 ± 70*†‡	66 ± 3*†‡
	IDA	61 ± 24*†	72 ± 3†	220 ± 90*†‡	67 ± 2*†‡
180 min posttrauma	Control	—	—	—	—
	TXA–FCH	—	—	—	—
	PCC25	171 ± 67	69 ± 1	436 ± 111	63 ± 3
	PCC50	78 ± 37	72 ± 2	254 ± 66‡	67 ± 2‡
	IDA	66 ± 18	72 ± 2	225 ± 76‡	67 ± 1‡
240 min posttrauma	Control	—	—	—	—
	TXA–FCH	—	—	—	—
	PCC25	154 ± 96	68 ± 2	409 ± 153	64 ± 5
	PCC50	73 ± 37	71 ± 2	249 ± 79‡	67 ± 3‡
	IDA	73 ± 22	72 ± 2	235 ± 80‡	68 ± 2‡

Measurements from whole-blood ROTEM, EXTEM, and INTEM assays are shown. Data are shown as mean ± SD; in each group, n = 9 animals initially.

*P < 0.05 *versus* control group; †P < 0.05 *versus* TXA–FCH group; ‡P < 0.05 *versus* PCC25 group. Between-group differences are presented hierarchically as follows: IDA and PCC50 (‡†*) → PCC25 (†*) → TXA–FCH (*) → control.

CT = clotting time; IDA = idarucizumab; MCF = maximum clot firmness; PCC25 = prothrombin complex concentrate 25 U/kg; PCC50 = prothrombin complex concentrate 50 U/kg; TXA–FCH = tranexamic acid plus human fibrinogen concentrate.

surviving the whole 240-min observation period. These animals may be considered to have recovered from trauma after administration of study treatment. Hemodynamic parameters in the PCC25 group exhibited only minor deterioration after fluid resuscitation (see Supplemental Digital Content, table 1, http://links.lww.com/ALN/B529). Improvements (decreases) over time were observed in the activated partial thromboplastin time and prothrombin time (table 1) as well as in EXTEM and INTEM clotting time (table 2). Despite increased thrombin generation compared with pretrauma levels, endogenous thrombin potential and peak height remained lower than baseline values in the PCC25 group and lower than values observed in PCC50 animals (fig. 2). The lag time was significantly shorter than in the control and TXA–FCH groups (P < 0.001), although this parameter did not return to baseline levels (fig. 2). Levels of fibrinopeptide A and thrombin-antithrombin complex in the PCC25 group were higher than those in the control and TXA–FCH groups but less than those in the PCC50 group (fig. 3).

We performed a subanalysis of animals in the PCC25 group based on plasma dabigatran concentrations immediately after trauma ($PCC25_{high}$, plasma dabigatran

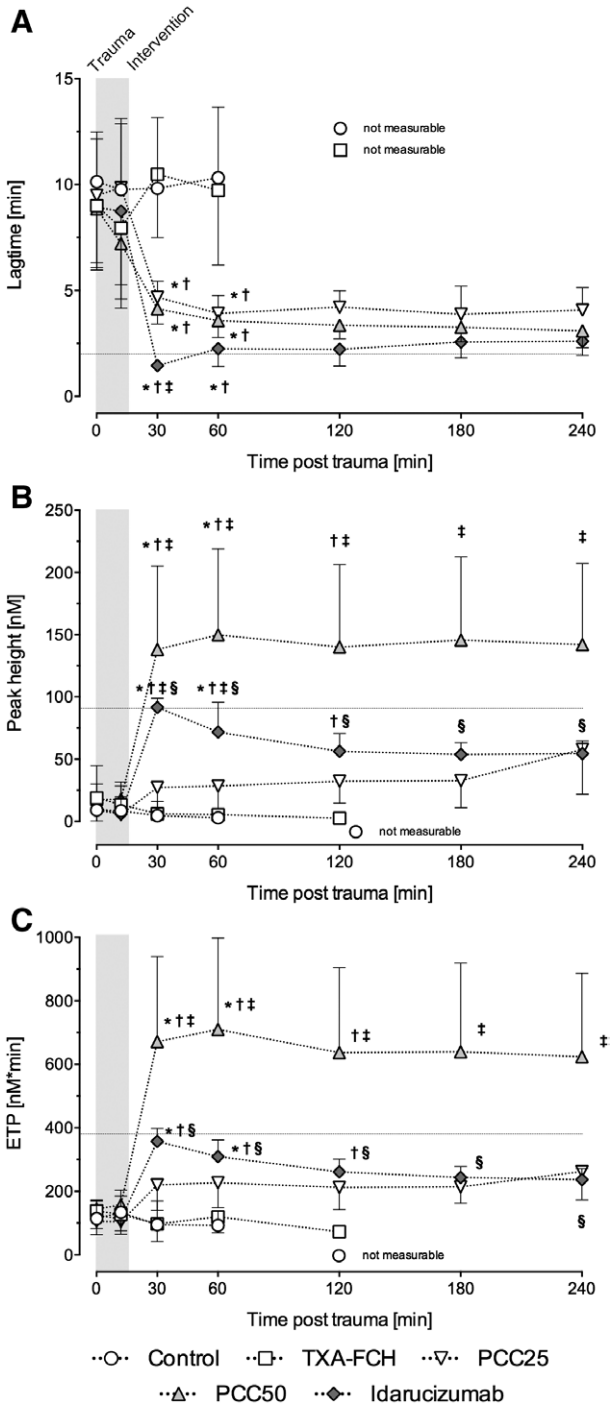

Fig. 2. Thrombin generation. Lag time (*A*), peak height (*B*), and endogenous thrombin potential (ETP; *C*) are shown. *Horizontal dotted lines* indicate baseline values before anticoagulation. Data are shown as mean ± SD; in each group, n = 9 animals initially. In control and tranexamic acid (TXA) plus human fibrinogen concentrate (FCH) animals (TXA–FCH), no thrombin generation could be detected later than 60 min posttrauma. **P* < 0.05 *versus* control group; †*P* < 0.05 *versus* TXA–FCH group; ‡*P* < 0.05 *versus* prothrombin complex concentrate (PCC) 25 U/kg group (PCC25); §*P* < 0.05 *versus* PCC 50 U/kg group (PCC50). Between-group differences are presented hierarchically as follows: idarucizumab (IDA) (§‡†*) → PCC50 (‡†*) → PCC25 (†*) → TXA–FCH (*) → control.

concentration 625 ± 196 ng/ml, n = 6; $PCC25_{low}$, 337 ± 84 ng/ml, n = 3). Bleeding after therapy with PCC25 was lower in the $PCC25_{low}$ group than in the $PCC25_{high}$ group. Higher survival rates and greater improvements in coagulation parameters were also observed in the $PCC25_{low}$ group (see Supplemental Digital Content, fig. 1, http://links.lww.com/ALN/B529).

Substitution with Fibrinogen, Tranexamic Acid, and Prothrombin Complex Concentrate (50 U/kg). PCC50 animals recovered from trauma after hemostatic intervention and fluid resuscitation as shown by significant decreases in prothrombin time (table 1), as well as in EXTEM and INTEM clotting time (table 2). EXTEM and INTEM MCF were restored close to baseline levels and the plasma fibrinogen concentration, while decreasing over time, remained higher than in all other groups except idarucizumab (fig. 3). Directly after prothrombin complex concentrate application (30 min after trauma), thrombin generation increased (fig. 2). Peak height and endogenous thrombin potential remained significantly different in the PCC50 group *versus* all other groups, including PCC25, throughout the study. In addition, thrombin–antithrombin complex and fibrinopeptide A concentrations were significantly higher than in all other study groups ($P < 0.0001$; fig. 3). Significantly higher levels of D-dimers were only observed 240 min after trauma ($P < 0.002$ *vs.* PCC25 and IDA). As expected, plasma concentrations of dabigatran were similar in the PCC50 group to those in the control, TXA–FCH, and PCC25 groups (table 1).

Substitution with Fibrinogen, Tranexamic Acid, and Idarucizumab. Fifteen minutes after administration of idarucizumab, dabigatran activity was close to zero (table 1). Dabigatran levels in the IDA group then increased gradually, reaching a peak of 142 ng/ml at 180 min postinjury. Treatment with idarucizumab, tranexamic acid, and fibrinogen concentrate normalized plasma coagulation tests (prothrombin time and activated partial thromboplastin time), as well as EXTEM and INTEM parameters (table 2). In addition, thrombin generation was restored immediately to baseline values (fig. 2). Levels of thrombin–antithrombin complex and fibrinopeptide A were elevated after idarucizumab therapy (fig. 3), but to a lesser extent than with PCC50.

Histopathologic Analysis

The histopathologic examination of injured liver sections revealed homogeneous tissue damage and comparable lacerations in all animals. No thromboemboli or other remarkable pathologic changes were present in kidneys, lungs, heart, or nontraumatized liver tissue.

Discussion

This study demonstrates for the first time that treatment of dabigatran anticoagulation in experimental polytrauma with either idarucizumab or prothrombin complex concentrate (50 U/kg), in combination with tranexamic acid and

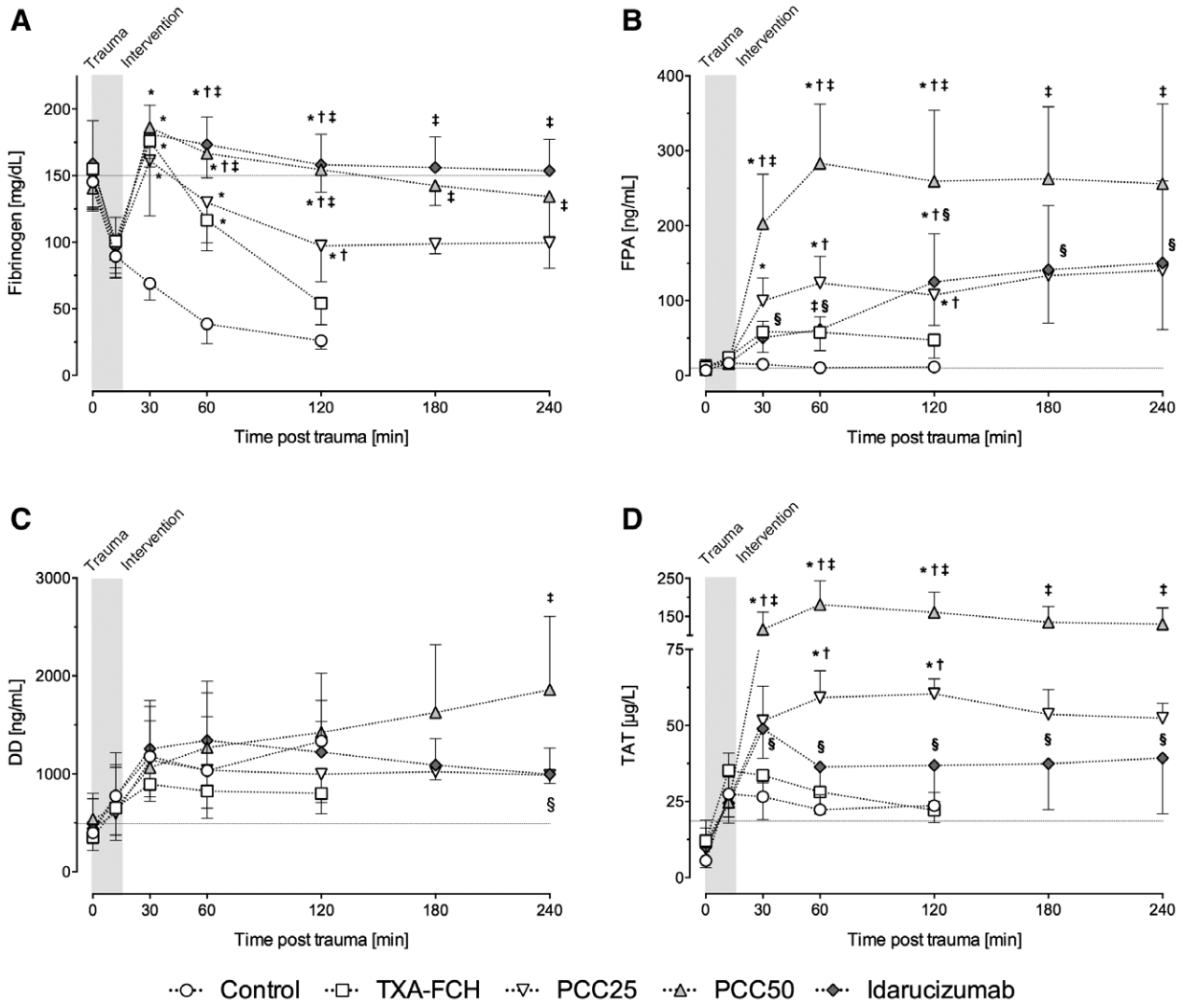

Fig. 3. Fibrinogen, fibrinopeptide A, D-dimer, and thrombin–antithrombin levels. Plasma fibrinogen levels (*A*) and levels of fibrinopeptide A (FPA; *B*), D-dimer (DD; *C*), and thrombin-antithrombin (TAT; *D*), are shown. *Horizontal dotted lines* indicate baseline values before anticoagulation. Data are shown as mean ± SD; in each group, n = 9 animals initially. **P* < 0.05 *versus* control group; †*P* < 0.05 *versus* tranexamic acid (TXA) plus human fibrinogen concentrate (FCH) group (TXA–FCH); ‡*P* < 0.05 *versus* prothrombin complex concentrate (PCC) 25 U/kg group (PCC25); §*P* < 0.05 *versus* PCC U/kg group (PCC50). Between-group differences are presented hierarchically as follows: idarucizumab (IDA) (§‡†*) → PCC50 (‡†*) → PCC25 (†*) → TXA–FCH (*) → control.

fibrinogen concentrate, is similarly effective in reducing blood loss. Idarucizumab binds and inactivates dabigatran, thereby restoring thrombin generation. In contrast, prothrombin complex concentrate overcomes dabigatran activity by increasing the amount of prothrombin in the plasma until it exceeds the level of dabigatran, and in our study, the 50 U/kg dose increased thrombin generation above baseline (measured before administration of dabigatran). Low-dose prothrombin complex concentrate (25 U/kg) did not increase thrombin generation above baseline and was also less effective in reducing blood loss. Thromboembolic events were not observed in animals treated with idarucizumab or prothrombin complex concentrate when combined with tranexamic acid and fibrinogen concentrate during the 4-h observation time.

In our model, the causes of coagulopathy included consumption and dilution of coagulation factors and platelets and impaired thrombin generation. The mortality rate was 100% in control animals. Tranexamic acid and fibrinogen concentrate were ineffective in restoring hemostasis. Increased fibrinolysis, reduced plasma levels of fibrinogen, and reduced clot strength are hypothesized to be important contributors to trauma-induced coagulopathy.[32–34] Although tranexamic acid and fibrinogen concentrate may be effective in treating these aspects, they do not enhance thrombin generation in the presence of dabigatran.

The addition of either idarucizumab or prothrombin complex concentrate to tranexamic acid and fibrinogen concentrate was effective in restoring hemostasis and reducing blood loss, enabling animals to survive. Idarucizumab restored thrombin

generation potential without exceeding the baseline level seen before anticoagulation. In addition, D-dimer levels showed that idarucizumab did not increase fibrinolysis as compared to the PCC50 group. Previous animal studies of dabigatran reversal have reported similar results with idarucizumab,[12,30] and clinical studies have shown a lack of procoagulant effects.[35,36]

PCC50 differed from idarucizumab in that thrombin generation potential (as measured by endogenous thrombin potential and peak height) and propagation of coagulation were increased above levels seen before anticoagulation. All procoagulant markers, including thrombin–antithrombin complex levels, were increased in the PCC50 group. As expected in relation to the mechanism of action, plasma dabigatran levels were unchanged in the presence of prothrombin complex concentrate. PCC25 did not increase thrombin generation potential (endogenous thrombin potential and peak height) above levels seen before anticoagulation, but this treatment was not fully effective in reversing the anticoagulant effects of dabigatran. A subanalysis of this group showed that the effectiveness of low-dose prothrombin complex concentrate mainly depends on the level of anticoagulation: PCC25 appeared to be effective in animals with low concentrations of dabigatran. Thrombin generation may be increased as a physiologic response to trauma,[37] and this may exacerbate the risk of thromboembolic complications with prothrombin complex concentrate. In trauma patients treated with prothrombin complex concentrate, a prothrombotic state has been reported to last for several days postoperatively.[18] Our study did not show thromboembolic complications with prothrombin complex concentrate plus tranexamic acid and fibrinogen concentrate, although the follow-up time was limited (4 h).

Idarucizumab restores hemostasis by binding dabigatran and eliminating it from the circulation (renally as a complex). The clinical dose of idarucizumab (5 g) is, for most patients, higher than the 60 mg/kg dose used in the current study. In addition, plasma levels of dabigatran in clinical practice are lower than those achieved in the current study (*e.g.*, in the Reversal Effects of Idarucizumab on Active Dabigatran clinical study, median plasma dabigatran levels between 100 and 150 ng/ml were reported).[36] This study was intended to provide consistent, reproducible bleeding and to simulate "worst case" scenarios. Two hours after idarucizumab administration, plasma concentrations of dabigatran rebounded. This can be explained by the equilibrium of dabigatran molecules between the tissues and the blood compartment. Binding of the molecules in plasma to idarucizumab triggers a transfer of molecules from the tissues to plasma. This process is not instant and, if idarucizumab molecules in the plasma are already bound to dabigatran, the molecules arriving from the tissues remain free, causing a rise (rebound) in the plasma level of dabigatran. Each molecule of idarucizumab binds one molecule of dabigatran.[35] Therefore, for full reversal of the anticoagulant effects of dabigatran, the administered dose of idarucizumab needs to be equimolar with the total quantity of dabigatran, in both blood and tissues.

Our results may be compared with a previous study using the same animal model, where prothrombin complex concentrate (25, 50, or 100 U/kg) was administered alone as hemostatic therapy.[10] Lower blood loss and mortality in the current study suggests that co-administration of tranexamic acid and fibrinogen concentrate enhances the effectiveness of prothrombin complex concentrate. Comparison with data from another animal study of dabigatran anticoagulation and trauma, where idarucizumab 60 mg/kg was monotherapy,[30] suggests that this product is similarly effective when administered either alone or with tranexamic acid and fibrinogen concentrate. Nevertheless, in human trauma patients, multimodal therapy may be required.

In clinical practice, idarucizumab is the preferred option for reversing dabigatran anticoagulation. However, in some cases it may not be clear whether anticoagulation is related to dabigatran or a different anticoagulant. Unlike idarucizumab, prothrombin complex concentrate may be effective for reversal of anticoagulation with a vitamin K antagonist or a factor Xa inhibitor.[38–40] Thus, prothrombin complex concentrate might be a valuable first-line approach to restoring hemostasis in selected clinical circumstances. However, prothrombin complex concentrates are not currently licensed for the reversal of non-vitamin K oral anticoagulants. Although no thromboembolic events were observed in this study, we would advocate a cautious approach if choosing to use prothrombin complex concentrate for treatment of dabigatran or factor Xa anticoagulation. There are differences between prothrombin complex concentrates in their levels of anticoagulants (*e.g.*, protein C, protein S, heparin) and these have been shown *in vitro* to affect the degree to which thrombin generation potential is increased.[41] However, it has not been confirmed whether these findings translate into differences between the available prothrombin complex concentrates regarding clinical risk of thromboembolic complications.

There are several potential limitations to this study, including its clinical applicability. Humans and pigs are different species, meaning there could be differences in coagulation status. Our study was performed in young, healthy animals, whereas in humans, anticoagulation therapy is prescribed to patients with hypercoagulability or a risk of thromboembolic events; such patients are usually elderly with many comorbidities and concomitant medications such as antiplatelet therapy. In addition, trauma patients exhibit physiologic responses to pain/inflammation. Such factors are not represented in our animal model. Due to the limited observation period of 4 h, prediction of the longer-term postoperative effects of prothrombin complex concentrate is not possible.

Plasma concentrations of dabigatran in the study animals were intentionally higher than those usually seen clinically. Low-dose prothrombin complex concentrate (25 U/kg) might have been more effective in animals with plasma dabigatran concentrations that are encountered clinically (100 to 150 ng/ml). In the subanalysis of results from the PCC25 group, we showed that the efficacy of prothrombin complex concentrate

is dependent on the level of anticoagulation. Selection of the optimal dose of prothrombin complex concentrate for dabigatran reversal is challenging in the absence of a point of care coagulation measurement that quantifies dabigatran.

Conclusions

Idarucizumab is more favorable than prothrombin complex concentrate for emergency reversal of the anticoagulant effects of dabigatran after trauma because its mode of action circumvents the risk of an overcorrection of thrombin generation. In clinical practice, determining an appropriate dose may be less challenging with idarucizumab than with prothrombin complex concentrate. However, this study shows that, in the context of multimodal therapy, high-dose prothrombin complex concentrate is similarly effective to idarucizumab for dabigatran reversal. The findings also show that prothrombin complex concentrate may be more effective as part of a multimodal approach than as monotherapy. Although prothrombin complex concentrates are not licensed for the reversal of non-vitamin K oral anticoagulants, they could be valuable when idarucizumab is unavailable or when there is uncertainty whether the patient has received dabigatran or a different oral anticoagulant.

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Competing Interests

Dr. Honickel has received travel support from Boehringer Ingelheim (Ingelheim, Germany). Dr. Rossaint has received honoraria for lectures and consultancy from CSL Behring (Marburg, Germany), Boehringer Ingelheim, and Novo Nordisk (Bagsvaerd, Denmark). Dr. ten Cate has received research funding from CSL Behring, Bayer (Leverkusen, Germany), Philips (Amsterdam, Netherlands), Pfizer (Berlin, Germany), and Boehringer Ingelheim, and honoraria for lectures and consultancy from Bayer, Leo Pharma (Neu-Isenburg, Germany), Boehringer, and Pfizer. Dr. ten Cate is a consultant to Stago (Dusseldorf, Germany) and a fellow of the Gutenberg Research Foundation, Center for Thrombosis and Haemostasis (Mainz, Germany). Dr. Grottke has received research funding from Bayer, Biotest (Dreieich, Germany), Boehringer Ingelheim, CSL Behring, Novo Nordisk, and Nycomed (Zurich, Switzerland). Dr. Grottke has also received honoraria for lectures and consultancy support from Baxalta (Unterschleißheim, Germany), Bayer Healthcare, Boehringer Ingelheim, CSL Behring, Octapharma (Lachen, Switzerland), Pfizer, Portola (San Francisco, California), and Sanofi (Berlin, Germany).

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