Brief Communications

High-dose aprotinin effectively reduces blood loss during on-pump coronary artery bypass grafting with bivalirudin anticoagulation

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Bivalirudin is a short-acting direct thrombin inhibitor that is increasingly used for anticoagulation during cardiac surgery in patients with heparin-induced thrombocytopenia (HIT).[1] During cardiopulmonary bypass (CPB) with heparin anticoagulation, aprotinin reduces hemostatic activation, inflammatory response, perioperative blood loss, and transfusion requirements. The current investigation was performed to assess the effects of aprotinin when bivalirudin is used for anticoagulation during CPB.

Materials and Methods

After approval by the German Ministry for Drug Safety and the local ethics committee and informed consent was obtained, 14 patients scheduled for first-time elective coronary artery bypass grafting (CABG) were enrolled in this prospective single-center investigation. Patients were randomized to 2 groups with 7 patients each: 1 group with bivalirudin anticoagulation only and 1 group with bivalirudin and aprotinin. All patients had normal renal function, a left ventricular ejection fraction of more than 30%, and antiplatelet therapy discontinued 5 days before surgery. Bivalirudin dosing and CPB management were performed as described before using closed CPB systems without cardiotomy suction.[2] Aprotinin was given according to a high-dose protocol with 2×10^6 kallikrein inhibiting units (KIU) as patient bolus, 2×10^6 KIU in the CPB priming solution, and continuous infusion of 0.5×10^6 KIU during CPB. Packed red blood cell concentrates were transfused when the hemoglobin level was less than 8 g/dL. The transfusion of fresh-frozen plasma and platelets was based on the physicians' decision. Samples for measurement of bivalirudin concentrations were obtained after the bolus was given and at intervals of 15 minutes during CPB, at intervals of 5 minutes until 1 hour after CPB, and at intervals of 15 minutes during the following hour. Bivalirudin concentrations were analyzed with high-performance liquid chromatography. Samples for assessment of markers of hemostatic activation (fibrinopeptide A and prothrombin fragment 1+2) and inflammation (interleukin 6 and myeloperoxidase) were obtained 5 minutes after the bivalirudin bolus was given (before initiation of CPB) and after termination of the bivalirudin infusion, shortly before termination of CPB. Samples were analyzed with standard enzyme-linked immune assays. Statistical analysis was performed using the Student *t*, Wilcoxon rank-sum, and paired Wilcoxon signed-rank tests.

Results

There were no differences regarding patients' demographic data, duration of CPB, or surgery (Table 1). The clinical course of all patients was uneventful. In control patients treated only with bivalirudin, there was a moderate increase in markers of hemostatic activation and inflammatory response during CPB. The administration of high-dose aprotinin did not influence bivalirudin pharmacokinetics, hemostatic activation, and inflammatory response, but there was a significant reduction of perioperative blood loss and a marked trend toward lower transfusion requirements (Table 1; Figure 1).

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
HIT = heparin-induced thrombocytopenia
KIU = kallikrein inhibiting unit

Discussion

The elimination of bivalirudin is mainly achieved by proteolytic cleavage. Because aprotinin is a proteinase inhibitor, concerns may be raised that high concentrations of this agent may prolong bivalirudin half-life and thereby increase the risk of hemorrhage. In a previous pilot investigation using a different protocol for bivalirudin and a half-dose aprotinin regimen, no impact of aprotinin on bivalirudin pharmacokinetics, blood loss, and transfusion requirements was noted.[3] Our current data show that a high-dose aprotinin protocol does not affect the pharmacology of bivalirudin. Moreover, the administration of aprotinin does not attenuate the moderate hemostatic activation and inflammatory response observed during bivalirudin anticoagulation of CPB. However, even in this small number of patients, the administration of aprotinin according to the high-dose protocol resulted in a highly significant decrease in perioperative blood loss and a marked trend toward a reduction of transfusions.

Aprotinin is one of the most effective drugs to reduce perioperative blood loss and transfusion requirements in patients undergoing CPB procedures with heparin anticoagulation. Recent studies associated the use of aprotinin with increased myocardial infarction, renal failure, and 5-year mortality when given during CPB with heparin anticoagulation and protamine reversal in patients undergoing elective CABG.[4,5] These results may promote the more cautious use of aprotinin, particularly in low-risk patients undergoing CABG. However, although the current investigation was not powered to assess patient outcomes in this regard, the observed reduction of blood loss and transfusions in our patients undergoing on-pump CABG with bivalirudin anticoagulation remains impressive. The effects of drugs influencing the hemostatic system observed in patients without HIT cannot automatically be translated to patients with HIT. Nevertheless, in view of the current data, we believe that in the high-risk population of patients with HIT,

TABLE 1. Clinical and laboratory data

	Bivalirudin (n = 7)	Bivalirudin + aprotinin (n = 7)	*P*
Baseline characteristics			
Age	63.0 ± 7.0	61.7 ± 9.1	.70
Gender, male %	85.7	85.7	1.0
Weight (kg)	88.7 ± 15.0	89.0 ± 14.9	.85
CPB + surgery			
Time on CPB (min)	86.4 ± 21.4	93.0 ± 28.2	.57
Duration of surgery (min)	213.9 ± 38.4	214.7 ± 54.8	.85
Blood loss + transfusions			
Mean blood loss 2 h postsurgery (mL)	454 ± 304	96 ± 37	.002
Mean blood loss 12 h postsurgery (mL)	959 ± 472	274 ± 53	.002
Any transfusions (%)	71.4	42.9	.59
PRBC (%)	57.1	28.6	.59
Mean no. of units in patients with PRBC	3.3 ± 2.6	2 ± 0	.62
Inflammation + hemostatic activation			
MPO (pM) pre-CPB	66.8 ± 136.7	69.4 ± 153.0	.65
MPO (pM) post-CPB	63.5 ± 88.4	76.7 ± 133	.95
Pre vs post-CPB *P* value (within group)	.56	.237	
IL6 (pg/mL) pre-CPB	13.0 ± 4.7	15.9 ± 11.4	.85
IL6 (pg/mL) post-CPB	72.1 ± 49.4	83.6 ± 42.1	.57
Pre vs post-CPB *P* value (within group)	.018	.028	
FPA (ng/mL) pre-CPB	20.6 ± 19.6	14.2 ± 8.1	.85
FPA (ng/mL) post-CPB	26.0 ± 16.6	32.6 ± 19.6	.41
Pre vs post-CPB *P* value (within group)	.091	.063	
PF 1+2 (pM) pre-CPB	476 ± 264	222 ± 54	.025
PF 1+2 (pM) post-CPB	512 ± 251	418 ± 211	.37
Pre vs post-CPB *P* value (within group)	.128	.043	

CPB, Cardiopulmonary bypass; *PRBC,* packed red blood cell concentrates; *MPO,* myeloperoxidase; *IL,* interleukin; *FPA,* fibrinopeptide A; *PF 1+2,* prothrombin fragment 1+2.

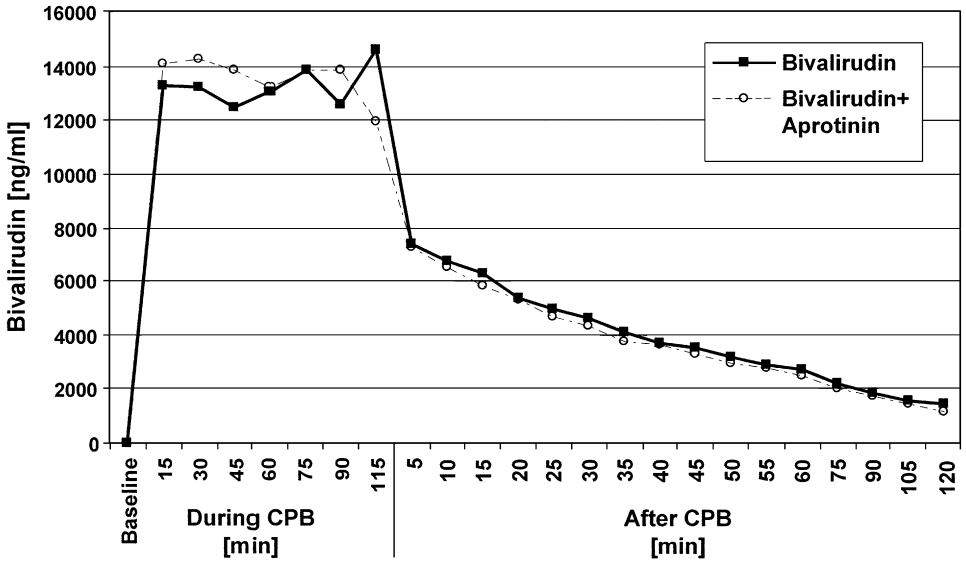

Figure 1. Group 1 = bivalirudin; Group II = bivalirudin + aprotinin.

high-dose aprotinin may be considered as an adjunctive agent during CPB anticoagulation with bivalirudin. This applies particularly to complex procedures with a high risk of increased perioperative bleeding.

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