Use of argatroban: Experiences in continuous renal replacement therapy in critically ill patients after cardiac surgery

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Objectives: Acute kidney injury requiring renal replacement therapy (RRT) is a common complication after cardiac surgery, complicated by suspected or proven heparin-induced thrombocytopenia (type II). The present study evaluated the use of argatroban as an anticoagulant during continuous RRT in the early period after cardiac surgery. Argatroban was compared with unfractionated heparin (UH) with respect to bleeding complications and the effectiveness of anticoagulation.

Methods: Patients requiring RRT after cardiac surgery from March 2007 to June 2009 were identified. The effectiveness of anticoagulation was measured indirectly by the duration of dialysis filter use. Bleeding was defined as clinical signs of blood loss or the need for transfusion.

Results: Of 94 patients, 41 received argatroban, 27 UH, and 26 required conversion from UH to argatroban. In all 3 subgroups, RRT was begun within a median postoperative period of 2.0 days. Similar levels of anticoagulation were achieved with the duration of the circuit and filter changed an average of 1.1 times daily during RRT. Liver function was comparable in all patients. Neither clinically relevant signs of bleeding nor significant differences in the hemoglobin levels or a requirement for transfusion were noted. However, the Simplified Acute Physiology Score II values during dialysis and mortality were significantly greater in the patients initially receiving argatroban compared with those who received UH alone (54 ± 2 vs 43 ± 3, $P < .001$; 71% vs 44%, $P = .04$).

Conclusions: Argatroban can provide effective anticoagulation in postoperative cardiac patients receiving continuous RRT. Close monitoring and dose titration resulted in a comparable risk of bleeding for anticoagulation with both argatroban and heparin, regardless of the disease severity or impaired hepatic function. (J Thorac Cardiovasc Surg 2014;147:1918-24)

Acute kidney injury (AKI) is a common complication after cardiac surgery. Depending on the definition of AKI, the incidence has varied from 0.3% to 29.7%, with a need for renal replacement therapy (RRT) occurring in approximately 5% of cases.[1-3]

Unfractionated heparin (UH) has remained the anticoagulant of choice during RRT, because it is inexpensive, ubiquitously available, simple to dose and monitor, and has a known antidote in cases of bleeding.[4] However, heparin is contraindicated in certain situations, in particular, if heparin-induced thrombocytopenia (HIT) type II (HIT II)

is suspected or proved. HIT is an important and increasingly recognized antibody-mediated complication of heparin therapy occurring in approximately 0.5% to 5% of patients receiving heparin for ≥ 5 days.[5] Patients undergoing cardiac surgery are at particular risk. Everett and colleagues[6] reported that the postoperative prevalence of heparin/platelet factor 4 antibodies was as great as 22.4% and that thromboembolic events occurred in 8.8% of patients with negative antibodies. This requires an alternative method of anticoagulation (eg, argatroban).[7,8] Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine,[9] with elimination principally via the hepatic system,[10] avoiding dose adjustment concerns in patients with renal insufficiency. Furthermore, the development of antibodies or cross-reactivity resulting in HIT II has not been described during argatroban therapy.[11] Concerns exist, however, regarding the critically ill, in particular those with hepatic insufficiency in whom the half-life for elimination is increased, rendering monitoring and dose adjustment difficult.[8,12] This could increase the potential risk of severe bleeding complications.

In critically ill patients with AKI requiring RRT, the risk of bleeding complications within the early postoperative period increases owing to the anticoagulation required to

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prevent blood clotting in the extracorporeal dialysis circuit. Moreover, in cases of continuous RRT, anticoagulant accumulation can occur over time. Data on the use of argatroban within this specific patient population are sparse.[13-15] The aim of the present study was to evaluate the use of argatroban as an anticoagulant during continuous RRT for critically ill patients with AKI requiring RRT during the early period after cardiac surgery and compare it with the standard practice anticoagulation using heparin.

METHODS
Patients

All cases of RRT performed from March 2007 to June 2009 within an intensive care setting at the University Hospital of Saarland were retrospectively analyzed. The institutional review board (ethical committee of the Saarland, Germany, 233/11) approved the present study.

Within the study period, 104 patients required RRT in intensive care unit after cardiac surgery. Ten patients were excluded from the analysis because their anticoagulation regimen for continuous RRT required conversion on several occasions from heparin to argatroban or citrate. Data were collected by retrospective medical chart review for all patients undergoing continuous RRT. RRT was initiated in cases of AKI with blood urea nitrogen levels >100 mg/dL or complications such as volume overload or hyperkalemia became life-threatening and could not be corrected by conservative treatment. Postoperative AKI was defined on the basis of the Acute Kidney Injury Network criteria.[16] All patients received continuous venovenous hemodialysis with titration of either UH or argatroban for anticoagulation. Argatroban was given in cases of proven or clinically suspected HIT II.[17] Clinical suspicion of HIT was determined by a persistently low or rapid decline in the platelet count or evidence of thrombosis or embolism as suggested by Lo and colleagues.[18]

Study Groups

Three subgroups were defined: group 1, patients receiving argatroban (n = 41); group 2, patients receiving heparin throughout the entire observation period (n = 27); and group 3, patients requiring conversion from UH to argatroban (n = 26). Conversion to argatroban was in line with current recommendations suggesting lower dose argatroban for critically ill patients, in particular patients with impaired hepatic function or after cardiac surgery.[8,15,19] The initial argatroban dose was 0.25 μg/kg/min. The subsequent dosage was titrated according to the activated partial thromboplastin time (60-90 seconds) measured within the extracorporeal circuit. Similarly, anticoagulation with UH was achieved by an initial bolus and subsequent continuous infusion to maintain the activated partial thromboplastin time at 60 to 90 seconds.

Treatment and Measurements

The effectiveness of anticoagulation was measured indirectly by the duration of dialysis filter use. Because the filters were changed routinely

every 24 hours, the requirement for >1 filter daily indicated ineffective anticoagulation resulting in filter clotting.

Bleeding during anticoagulant therapy was defined as clinical bleeding signs (eg, postoperative wound bleeding or an increased postoperative drain volume) or the need for transfusion. The need for transfusion of erythrocytes was defined by hemoglobin < 9.5 g/dL, independent of the presence of signs of bleeding. Total erythrocyte transfusion requirements during the postoperative dialysis period in intensive care were measured and divided by the days of RRT, described as the erythrocyte concentrate/day of RRT. The need for platelet transfusion was defined as thrombocytopenia < 20,000/μL without active bleeding or < 50,000/μL with signs of active bleeding. The total number of platelet transfusions during the dialysis period in intensive care was measured and divided by the days of RRT, depicted as the number of platelet transfusions/day of RRT. Additional parameters considered included morbidity (Simplified Acute Physiology Score [SAPS] II) and outcomes (length of intensive care and hospital stay, duration of artificial ventilation, and mortality). The biochemical values were obtained from routine blood samples analyzed within an onsite clinical laboratory.

Statistical Analysis

All data are presented as the mean ± standard error of the mean. Data analysis was performed using SPSS Statistics, version 19 (IBM, Ehningen, Germany). An initial comparison between the groups regarding the dichotomous variables was performed using chi-square tests. Student t tests were performed for continuous variables to compare the differences among the groups (Welch's t tests in the case of inhomogeneous variances). Two-sided P values were computed.

RESULTS
Patients

Of the 94 patients, 41 (43.6%) received argatroban, 27 (28.7%) received UH, and 26 (27.7%) were converted from UH to argatroban. In all 3 subgroups, dialysis was begun within a median postoperative period of 2.0 days. At the initiation of RRT, no significant differences were noted in the distribution of gender, age, EuroSCORE II, or SAPS II scores (Table 1) among the 3 groups.

Biochemical Markers at Initiation of Hemodialysis

The values for biochemical markers obtained at admission and at the initiation of RRT did not differ significantly between the argatroban and UH groups, inclusive of platelet count, markers of renal function (serum urea or creatinine), and markers of hepatic function (bilirubin, cholinesterase, and albumin; Table 1). When RRT was started postoperatively, the hemoglobin level was comparable but significantly greater statistically in the patients treated with argatroban (10.8 g/dL) than in those receiving UH (10.1 g/dL) exclusively. Overall, 3 patients had pre-existing liver disease (2 with Child A, 1 with Child B). None of these 3 patients had received argatroban.

Results During Hemodialysis

Comparing anticoagulation with argatroban and UH, no significant differences in hemoglobin levels were noted during the first 3 days of RRT (Figure 1). Furthermore,

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