Anticoagulation for Critically Ill Cardiac Surgery Patients: Is Primary Bivalirudin the Next Step?

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Objective: **Anticoagulation with unfractionated heparin (UFH) in critically ill cardiac surgery patients has several limitations, including the risk of heparin-induced thrombocytopenia. The use of a direct thrombin inhibitor, such as bivalirudin, might either treat this complication or completely eliminate it. The aim of the present study was to analyze the use of bivalirudin in this setting, as either a secondary drug switching from heparin or as the primary anticoagulant, and to evaluate clinical outcomes.**

Design: **Propensity-matching retrospective analysis.**

Setting: **A cardiac surgery intensive care unit.**

Participants: **One hundred propensity-matched patients who received heparin or bivalirudin.**

Interventions: **Bivalirudin was administered as a first-line or second-line drug after heparin discontinuation in case of thrombocytopenia and suspicion of heparin-induced thrombocytopenia. Twenty-six patients (52%) received bivalirudin as a primary anticoagulant, while 24 patients (48%) received bivalirudin after switching from heparin.**

Measurements and Main Results: **Bivalirudin treatment was associated with a reduction of major bleeding ($p = 0.05$) compared with the control group. Interestingly, in an intention-to-treat analysis, patients receiving primary bivalirudin showed significant reductions in minor bleeding ($p = 0.04$), and mortality ($p = 0.01$) compared with the secondary bivalirudin group and, similarly, compared with the rest of the study population (UFH and secondary bivalirudin patients, $p = 0.01$ and $p = 0.05$, respectively). Predictors of hospital mortality by multivariate analysis included urgent admission (odds ratio [OR] = 2.7; 95 confidence interval [CI], 1.03-7.2; $p = 0.04$), ; septic shock (OR = 8.0; 95 CI, 2.26-28.7; $p < 0.005$) and primary therapy with UFH (OR = 19.2; 95 CI, 2.2-163.9; $p = 0.007$).**

Conclusions: **Novel anticoagulant strategies might play a crucial role in critically ill cardiac surgery patients. In a propensity-matched population, results of the present study showed that primary bivalirudin anticoagulation may reduce bleeding complications and mortality.**

KEY WORDS: bivalirudin, heparin, cardiac surgery, mortality, heparin-induced thrombocytopenia

PERIOPERATIVE ANTICOAGULATION after cardiac surgery is performed routinely with unfractionated heparin (UFH). However, UFH-based anticoagulation has several limitations, including a variable anticoagulant response, the inability to effectively inhibit thrombin bound to fibrin, platelet activation, and, more importantly, the risk of heparin-induced thrombocytopenia (HIT).[1–3]

HIT is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor 4 complex; clinical effects include development of severe thrombocytopenia and, eventually, venous and arterial thrombosis.

Bivalirudin is a direct thrombin inhibitor that acts on both soluble and fibrin-bound thrombin. It has a more predictable anticoagulant effect compared with UFH due to its lack of binding to other plasma proteins. Moreover, it is characterized by an antiplatelet effect due to inhibition of thrombin's platelet-activating properties and the absence of immune-mediated thrombocytopenia.[4] It has been investigated extensively as periprocedural anticoagulation during percutaneous coronary intervention (PCI), with positive effects on mortality, major adverse and cerebrovascular events, and bleeding.[5–11] Therefore, the rationale for the use of bivalirudin in critically ill cardiac patients is strong.

The aim of the present study was to compare anticoagulation with UFH and bivalirudin in critically ill cardiac surgery patients.

METHODS

Data from 112 critically ill patients who required anticoagulation with UFH or bivalirudin in the cardiac surgical intensive care unit (ICU) of an Italian university hospital between January 2009 and January 2012 were retrospectively analyzed. The study included patients with complicated ICU stay (eg, at least 1 major organ failure requiring supportive or replacement therapy) after scheduled or urgent cardiac surgery or interventional cardiology procedures requiring multiple organ support or extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD) implantation.

The initial anticoagulation strategy in the study period was based on UFH. HIT was presumed if the platelet count was less than 100×10^9/L or decreased more than 50% from the baseline, thus triggering the performance of an immunologic test (ELISA). If the results were questionable, a heparin-induced platelet aggregation assay also was performed. When HIT was presumed, all sources of heparin were removed, and bivalirudin (Angiox, The Medicines Company, Parsippany, NJ) was administered. Afterward, clinical practice shifted to the direct use of bivalirudin as the primary anticoagulant in this setting.

UFH and bivalirudin starting doses were 3 IU/kg/hour and 0.025 mg/kg/hour, respectively, without bolus. In patients with glomerular filtration rate (GFR) <30 mL/min, bivalirudin starting dose was halved. Anticoagulation was monitored by activated partial thromboplastin time (aPTT), repeated every 8 hours, targeted between 45 and 60 seconds. If necessary, drug infusion was increased or decreased by steps never exceeding 15% of the previous dosage. If a supramaximal aPTT value was recorded (that is, an aPTT longer than

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80 seconds), drug infusion was discontinued for 2 hours, and then started again at a dose 15% lower.

Additionally, aspirin was administered as clinically appropriate. Warfarin was started only when the platelet count had recovered and if clinically required (patient orally fed, no pericardial or pleural effusions, and mobilized).

Allogeneic blood products were administered according to a specific protocol. Packed red cells (PRC) were transfused to maintain a hemoglobin value of ~10 g/dL. Fresh frozen plasma (FFP) was used for the treatment of active bleeding. Platelet concentrates were used in case of active bleeding and platelet count $<50 \times 10^9$/L.

Data extracted from each patient chart included demographic and clinical characteristics, complete information on the type of procedure performed, previous UFH exposure, HIT test results (immunologic and/or functional assays), UFH/bivalirudin dosing patterns, anticoagulant response, thromboembolic and bleeding complications, and survival.

Patients were divided into 2 groups: Those treated with UFH (group H), and those treated with bivalirudin (group B). Group B included patients who received bivalirudin as a primary anticoagulant (primary bivalirudin, PB), and those who received bivalirudin after switching from UFH (secondary bivalirudin, SB).

Platelets count (PLT), aPTT, international normalized ratio, and antithrombin (AT) activity were recorded immediately before starting the anticoagulation and every 12 hours during treatment. PLT at the end of anticoagulation therapy with UFH/bivalirudin and at discharge from the ICU also were recorded.

Bleeding was divided into major and minor bleeding. Major bleeding included all cases of intracranial, intraocular, retropharyngeal, and retroperitoneal bleeding, persisting hemorrhage requiring either radiologic intervention or surgical revision, a decrease in serum hemoglobin >3 g/dL, and bleeding with the need of transfusion of at least 2 PRC units. Minor bleeding included all cases of overt bleeding not meeting criteria for major bleeding. Thromboembolic complications were defined as DVT, myocardial infarction, embolic cerebrovascular accident, PE, limb ischemia, or any clinically relevant thrombosis.

All data were extracted from clinical record charts. Data are presented as mean ± SD, n (%), or for non-normally distributed variables as median (interquartile range). The Stata 11 software (College Station, TX) was used. Statistical analysis included the two-tailed paired t test for normally distributed variables or the Kruskal-Wallis for nonparametric variables. Chi square test or Fisher's exact test was used for the comparison of categoric variables, as appropriate. A two-tailed p value <0.05 was considered significant. Propensity score matching analysis was used to match baseline characteristics between the 2 groups. The following variables were included: Age, gender, body mass index (BMI), chronic renal failure, bleeding diathesis, previous PCI, urgent admission, and ECMO or VAD implantation.

For multivariate analysis, the binary logistic regression model was applied. The initial selection of the variables entered into the model was based on univariate analysis significance. The results of multivariate analysis are presented as the hazard ratio with 95% confidence interval.

The study was approved by the local ethics committee. The need for informed consent was waived for this retrospective analysis of data.

RESULTS

After propensity score matching, 100 patients were analyzed (group B = 50 patients; group H = 50 patients), and 12 patients were excluded. Patients' characteristics and surgical data are reported in Table 1.

The median duration of anticoagulation was 6 (5-14) days in group B and 6 (4-9) days in group H. Mean baseline PLT at the beginning of treatment was significantly lower in patients receiving bivalirudin compared with the heparin group ($71.4 \pm 58.2 \times 10^9$/L *v* $127.8 \pm 73.4 \times 10^9$/L, p < 0.005). Mean baseline aPTT in group B and group H was 37.3 ± 9.0 seconds and 34.0 ± 6.2 seconds, respectively (p = 0.03); aPTT at 24 hours after the beginning of anticoagulation was in the therapeutic range in 16 (32%) patients in group B and in 17 (34%) patients in group H. Two patients in group B had 1 episode of aPTT > 80 seconds; in group H, 19 episodes of supramaximal aPTT were registered in 10 patients.

Table 1. Patients' Demographic and Clinical Characteristics

Characteristics	B (n = 50)	H (n = 50)	p Value
Age (mean ± SD)	62.9 ± 14.6	59.3 ± 14.7	0.22
Male, n (%)	35 (70)	36 (72)	0.50
BMI (mean ± SD)	25.4 ± 4.0	25.7 ± 5.1	0.7
Previous PCI, n (%)	9 (18)	11 (22)	0.4
Chronic renal failure, n (%)	8 (16)	9 (18)	0.79
Bleeding diathesis, n (%)	0	0	0
Reintervention, n (%)	9 (18)	4 (8)	0.23
Urgent admission, n (%)	22 (44)	24 (48)	0.69
Surgery, n (%)	38 (76)	32 (64)	0.19
IABP, n (%)	32 (64)	24 (48)	0.1
ECMO, n (%)	21 (42)	20 (40)	0.83
VAD, n (%)	6 (12)	6 (12)	1.00
HIT, n (%)	18 (36)	0	0.0
CVVH, n (%)	26 (52)	21 (42)	0.31
DIC, n (%)	2 (4)	5 (10)	0.43
Associated antiplatelet therapy, n (%)	7 (14)	14 (28)	0.08

Abbreviations: B, bivalirudin group; BMI, body mass index; CVVH, continuous veno-venous hemofiltration; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; H, unfractionated heparin group; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; VAD, ventricular assist device.

Clinical outcomes are shown in Table 2. Major bleeding episodes were more frequent in group H than in group B: 10 (20%) episodes of major bleeding in group H versus 3 (6%) episodes in group B (p < 0.05). Minor bleeding was not statistically different between the 2 groups: 24 (48%) episodes of minor bleeding in group H versus 16 (32%) in group B (p = 0.1). In group B, 8 (16%) cases of thromboembolic events were recorded, and in group H, 7 (14%) cases of thromboembolic events were recorded (p = 0.78). Tranfusion requirements during ICU stay are reported in Table 2.

ICU stay was significantly longer in group B (17 days [9-27 d] compared with group H (8.5 days [6-15 d], p < 0.005). No statistically significant difference in hospital mortality was observed (36% in group B *v* 42% in group H, p = 0.54).

Data were further analyzed in the bivalirudin group according to an intention-to-treat analysis (Tables 3 and 4). Twenty-four patients (48%) in group B received bivalirudin after switching from heparin (SB), while 26 patients (52%) in group A received bivalirudin as a primary anticoagulant (PB).

Minor bleeding was significantly lower in patients receiving primary bivalirudin than in patients receiving bivalirudin after switching from UFH (19.2% *v* 45.8%; p = 0.04), but no statistically significant reduction in major bleeding in cases of primary bivalirudin therapy (3.8%) versus secondary