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ORIGINAL ARTICLE

Comparison of Safety and Efficacy of Unfractionated Heparin Versus Bivalirudin in Patients Undergoing Percutaneous Coronary Intervention

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Q4 **Background** Anti-platelet and anti-coagulant adjunctive therapies are associated with a clinically significant increased risk of major bleeding. We retrospectively assessed in hospital major adverse clinical events (MACE) and major bleeding in patients undergoing percutaneous coronary intervention (PCI) who received either unfractionated heparin (UFH) or bivalirudin.

Method Consecutive patients undergoing PCI for acute coronary syndrome (ACS) at Fremantle Hospital from August 2008 to December 2013 were identified. Patients received dual antiplatelet therapy (DAPT), with either UFH (50–100IU/kg) or bivalirudin (bolus 0.75 mg/kg and infusion 1.75 mg/kg/hr). Adjunctive glycoprotein IIbIIIa (GPIIbIIIa) antagonist use was at the operator's discretion. In hospital events were identified from case notes and PCI database review.

Results Of 3371 patients identified, 1740 received UFH and 1631 received bivalirudin. The two groups were similar with respect to age, 62.5 SD 12.1 yrs vs. 62.8 SD 12.2 yrs, (p = 0.575) female gender, 24% vs. 26% (p = 0.10), current smokers, 66% vs. 70% (p = 0.53), diabetes, 25% vs. 26% (p = 0.62) and the use of DAPT (p = ns). Presentation with ST-segment–elevation myocardial infarction (STEMI) was significantly higher in the UFH group (28% vs. 19%, p<0.001).
The use of transfemoral arterial access was similar (93% UFH vs. 92% bivalirudin) (p = 0.41). More patients received GPIIbIIIa antagonist in the UFH group (30% vs. 3%; p < 0.001). There was no difference in pre-discharge acute stent thrombosis (< 24 hours) occurring in 1.0% with UFH vs. 0.5% with bivalirudin (p = 0.20). The equipoise on the outcomes of stent thrombosis persisted after multivariate adjustment for difference in rates of STEMI. In hospital BARC1-3 major bleeding occurred in 3.7% in the UFH group vs. 2.9% in the bivalirudin group (p = 0.20).

Conclusion Unfractionated heparin compared with bivalirudin was not associated with a higher incidence of in hospital MACE or major bleeding in a cohort with overall high rates of transfemoral access, despite significantly higher use of GPIIbIIIa antagonists in the UFH group.

Keywords Unfractionated heparin • Percutaneous coronary intervention • Major adverse cardiac events • Bare metal stent • Drug-eluting stent • Dual anti-platelet therapy

Abbreviations: ACS, Nnstable angina (USA); BMS, Bare metal stent; DAPT, Dual anti-platelet therapy; DES, Drug-eluting stent; MACE, major adverse cardiac events; NSTEMI, Non–ST-segment–elevation myocardial infarction; PCI, Percutaneous intervention; STEMI, ST-segment–elevation myocardial infarction; UFH, Unfractionated heparin

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Background

Anticoagulant and anti-platelet therapy remains a cornerstone of management of acute coronary syndrome [ACS; unstable angina (USA), non–ST-segment–elevation myocardial infarction (NSTEMI), and ST-segment–elevation myocardial infarction (STEMI)] and is endorsed by practice guidelines. Unfractionated heparin (UFH), low molecular weight heparin (LMWH), and bivalirudin have all received class Ic/Ib [1] recommendations for various clinical presentations of ACS. Bivalirudin use is associated with decreased bleeding in randomised controlled trials [2,3] when compared to control strategies using UFH plus glycoprotein IIb IIIa (GPIIbIIIa) antagonist. Wide adoption of bivalirudin has been tempered by an excess risk of stent thrombosis [3,4].Furthermore, the routine use of GPIIbIIIa antagonist is no longer recommended in combination with UFH, due to an unclear benefit in the era of modern ADP receptor antagonists and an associated significant increase in bleeding risk [5–8]. Lower rates of GPIIbIIIa antagonist use in current clinical practice suggest that the control groups in the bivalirudin RCTs are historical and may deviate from current clinical practice. The recent HEAT PPCI [4]and BRAVE 4 [9] studies have suggested that UFH with bailout only use of GPIIbIIIa antagonist may be an equivalent and cheaper alternative to bivalirudin. Thus, greater appreciation of real-world practice patterns of anticoagulant and antiplatelet therapy and the associated risk of bleeding is important.

Method

All patients with ACS treated with PCI at Fremantle Hospital from August 2008 to December 2013 were eligible and were retrospectively identified from the Cardiac Catheter laboratory database. During this period, all cases were routinely entered into the database by a dedicated data custodian. At the time of hospital discharge or following in hospital death, case notes were reviewed by the data custodian and medical staff to identify any procedure-related complications and to document outcomes.

According to regional and hospital protocol, all ACS patients were pre-treated on admission to hospital with dual antiplatelet therapy (aspirin with clopidogrel/ticagrelor or prasugrel). Patients who presented with STEMI were routinely given a bolus of 5000IU UFH and loaded with DAPT (aspirin with clopidogrel or ticagrelor) at the first medical contact. At the time of PCI, following our centre protocols, intravenous UFH (50–100 unit per kg) was administered to achieve adequate activated coagulation time 250–300 sec prior to coronary intervention or bivalirudin (bolus 0.75 mg/kg and infusion 1.75 mg/kg/hr, until the end of the procedure only). Adjunctive glycoprotein IIb IIIa antagonist use was left at the discretion of the interventional cardiologist. All patients underwent pre- and post-intervention ECG with plasma CK and troponin levels measured the following day to detect new ischaemic events. In hospital major bleeding and acute stent thrombosis (<24 hours) events were identified from case notes and PCI database review.

Study Endpoints

The primary endpoint for the study was in hospital incidence of MACE defined as the composite of all-cause mortality, myocardial infarction, stroke, and acute stent thrombosis. Secondary endpoints were BARC major bleeding rates.

Definitions

Procedural Success was defined as <20% residual stenosis and TIMI 3 flow in the obstructed vessel without further complication. Myocardial infarction was defined according to the Third Universal Definition of MI [10]. Stent thrombosis was defined as angiographically documented stent thrombosis [11]. Major bleeding was defined according to BARC criteria [12].

Statistical Methods

Data are presented as the mean ± standard deviation (SD) for continuous variables and n (%) for categorical variable. Non-parametric continuous variables with significant Kolmogorov-Smirnov test were logarithmically transformed prior to analysis. Student's t-test was used to compare normally distributed continuous variables and chi squared test for categorical variables. Statistical significance was defined as a two-sided $p < 0.05$. Binary logistic regression was performed to ascertain the effect of anticoagulant (heparin/bivalirudin) and ACS presentation (STEMI vs. NSTEMI/USA) on the outcome of stent thrombosis. SPSS Statistics package version 22 (IBM Corporation, New York) was used for all data analyses.

Results

Demographic and Procedural Characteristics

Of 3371 patients identified, 1740 received UFH and 1631 received bivalirudin. Demographic results are given in Table 1 and there was no significant difference between the two groups. Presentation with STEMI was significantly higher in the UFH group (28% vs. 19%, $p < 0.001$). NSTEMI/USA occurred 51% vs. 58% and elective PCI was performed in 19% vs. 23% in UFH vs. bivalirudin groups (p = ns for all). Procedural data are given in Table 2. In addition to aspirin, 85% of patients received clopidogrel, 8% ticagrelor and 4% prasugrel in both groups (p = ns for all comparisons). More

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