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Safety of eptifibatide when added to bivalirudin during ST-segment elevation myocardial infarction ☆

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ABSTRACT

Background: Patients presenting with ST-segment elevation myocardial infarction (STEMI) represent a high-risk group for in-hospital adverse events and bleeding. The safety and outcomes of eptifibatide in addition to bivalirudin in this population have not been determined.

Methods: Over an 11-year period, we identified 1849 STEMI patients undergoing primary percutaneous coronary intervention (PCI), of which 1639 received bivalirudin monotherapy compared with 210 patients who received both bivalirudin and provisional eptifibatide. Safety of combination therapy was assessed by the occurrence of thrombolysis in myocardial infarction (TIMI) major bleeding. In-hospital event rates of death, Q-wave myocardial infarction (MI), and acute stent thrombosis were evaluated for efficacy. Multivariate analysis was used to adjust for significant differences between groups.

Results: Patients treated with bivalirudin plus eptifibatide, when compared with patients with bivalirudin monotherapy, had increased rates of cardiogenic shock (15.7% vs. 9.4%), aspiration thrombectomy (48.5% vs. 23.7%), pre-TIMI flow ≤1 (63.5% vs. 40%), and higher peak troponin I (93.65 ± 92.7 vs. 49.16 ± 81.59; all $p < 0.01$). These, however, were not associated with differences in the primary end point after adjusting for significant baseline and procedural characteristics (OR: 1.63; 95% CI, 0.90–2.96, $p = 0.12$). Importantly, TIMI major bleeding was not significantly different between groups (OR 1.78; 95% CI, 0.79–2.95, $p = 0.20$).

Conclusion: The addition of eptifibatide to bivalirudin during primary PCI reflects a high-risk STEMI population. This therapy results in similar in-hospital outcomes without an increase in major bleeding. Therefore, when required, combination therapy may be considered in this population.

1. Introduction

Acute coronary syndrome typically occurs as the result of a ruptured atherosclerotic plaque. Prompt coronary reperfusion after acute ST-segment elevation myocardial infarction (STEMI) improves patient outcomes; and primary percutaneous intervention (PCI) remains the most effective reperfusion modality for patients presenting with acute STEMI [1]. At the heart of the issue remains the battle between the injured vessels' attempt at repair, which includes platelet aggregation and thrombus formation, and the clinician's attempt at inhibiting this process. The use of both antiplatelet and antithrombotic agents, in combination with primary PCI during the peri-procedural time, is imperative for both short- and long-term vessel patency. This comes at a cost, however. Among patients undergoing primary PCI for acute STEMI, glycoprotein IIb/IIIa inhibitors (GPI) given peripherally improve patient outcomes, although the majority of these data comes from randomized controlled trials performed prior to the routine use of P2Y12 inhibitors as part of dual antiplatelet therapy [2–5]. Furthermore, these agents are associated with increased rates of major bleeding.

In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, while bivalirudin was found to significantly reduce major bleeding compared to eptifibatide plus unfractionated heparin, a 1% absolute increase in acute (<24 hours) stent thrombosis was seen [6]. More recently, the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) [7] and How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) [8] trials again showed a similar increased risk of stent thrombosis with bivalirudin use compared with GPI. The objective of the current analysis is to assess in-hospital safety and ischemic cardiovascular outcomes in patients who receive bivalirudin plus eptifibatide during treatment for acute STEMI in combination with primary PCI.

Abbreviation: GPI(s), glycoprotein IIb/IIIA inhibitor(s).

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2. Methods

2.1. Patient population

We performed a retrospective analysis using data from the MedStar Cardiovascular Research Network's data warehouse (MedStar Washington Hospital Center, Washington, DC) from December 2002 to June 2013 and identified 1849 patients who underwent primary PCI for STEMI. We evaluated the clinical and procedural characteristics, as well as in-hospital outcomes and bleeding events, in patients based upon procedural anticoagulation: bivalirudin monotherapy (n = 1639) versus bivalirudin with provisional eptifibatide (n = 210). Patients who received thrombolytic therapy or GPI prior to cardiac catheterization were excluded. Data collection was performed by trained research personnel by way of chart review. These data were subsequently entered into the registry by dedicated data center personnel. Both data collection and data entry personnel were unaware of the study's objective.

In-hospital outcomes were available on all patients and were assessed by electronic health records. The basis for each clinical event was adjudicated by independent physicians not involved in the clinical procedure. All patients provided written, informed consent for PCI and the institutional review board at MedStar Washington Hospital Center approved the study. PCI was performed according to standard clinical practice, while interventional strategy and choice of pharmacological therapy was at the discretion of the operator. Patients were pretreated with aspirin 325 mg and received either a 300- or 600-mg loading dose of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor prior to PCI. Choice of anticoagulant was based on operator's preference as dictated by the clinical scenario. When bivalirudin was used, an activated clotting time of >250 seconds was achieved. It is our laboratory's practice to discontinue bivalirudin at the end of the case, prior to the patient leaving the laboratory. GPI were also administered at the physician's discretion according to guidelines.

2.2. Outcomes

Composite ischemic end points of in-hospital death, Q-wave myocardial infarction (MI) and acute stent thrombosis were assessed for primary outcome analysis. Safety end points of major bleeding were assessed by in-hospital non-coronary artery bypass grafting thrombolysis in myocardial infarction (TIMI) major bleeding as well as vascular access site complications. We also used the CathPCI registry version 4.0 definition to identify whether the addition of eptifibatide better predicts bleeding according to the National Cardiovascular Database Registry risk model [9]. End points analyzed include in-hospital death, cardiac death, Q-wave MI, acute and subacute stent thrombosis, cerebrovascular accident, and transient ischemic.

Death was defined as all-cause mortality. Q-wave MI was defined as an increase of creatine kinase-MB twice the upper limit of normal with the development of a new Q-wave, deeper than ≥1 mm in ≥2 contiguous leads. Cerebrovascular accident was defined as the loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting ≥24 hours or leading to death. Transient ischemic attack was defined as a focal neurologic deficit that resolved spontaneously without evidence of a residual deficit at 24 hours. Stent thrombosis was determined using the Academic Research Consortium definitions and included both "definite" and "probable" [10]. Acute stent thrombosis was defined as thrombosis occurring ≤24 hours after stent placement. Angiographic success was defined as post-procedural stenosis ≤30% and TIMI 3 flow. Bleeding complications were defined using TIMI major and minor criteria [11], along with individual vascular access site related complications: groin hematoma ≥2 × 4 cm or requiring transfusion, packed red blood cell transfusion, retroperitoneal bleed, arteriovenous fistula, pseudoaneurysm, intracranial hemorrhage and gastrointestinal bleed.

2.3. Statistical analysis

A dedicated data coordinating center (Data Center, MedStar Health Research Institute, Washington, DC) performed all data management and analyses. SAS 9.2 (SAS Institute, Cary, NC) was used. Continuous variables are presented as mean ± SD and are compared using Student's *t* test. Categorical variables are expressed as absolute numbers and percentages and are compared using the chi-square test or the Fisher exact test, as appropriate. To adjust for significant baseline demographics, clinical and procedural characteristics, a logistic regression analysis was performed. Variables were selected on the basis of overall clinical relevance and included age, systemic hypertension, diabetes mellitus, cardiogenic shock, target coronary vessel, rotational atherectomy, aspiration thrombectomy, direct stenting, type C lesion, dissection, pre-procedural TIMI flow ≤1, and troponin I maximum.

After univariate analysis, variables with a p value of <0.1 were included into the multivariate analysis for analysis of the study end points, a composite ischemic end point of in-hospital death, Q-wave MI, or acute stent thrombosis, as well as the safety endpoint of TIMI major bleeding. Factors incorporated into the final model included age, systemic hypertension, history of diabetes mellitus, cardiogenic shock, rotational atherectomy, type C lesion, pre-procedural TIMI flow ≤1, and eptifibatide use.

Statistical significance was set at a p value <0.05. To evaluate eptifibatide's influence on prediction of bleeding, we compared our cohort's risk of bleeding via the well recognized and validated National Cardiovascular Database Registry risk model [9] with and without eptifibatide. Separate receiver operating characteristic curves were generated for both conditions, then combined and p values generated from chi-square analysis to test whether eptifibatide improves the models accuracy to predict bleeding.

3. Results

3.1. Patient population

We identified 1849 patients who underwent primary PCI for acute STEMI who met the inclusion criteria. These 1849 patients form the study population. All patients received bivalirudin, while 210 patients also received provisional eptifibatide. Thus, the current population consists of 1639 patients who received bivalirudin monotherapy as well as 210 patients who received both bivalirudin and eptifibatide. Patients' baseline characteristics are summarized in Table 1. It should be noted that those patients who received both bivalirudin and eptifibatide were younger and had less systemic hypertension, but were more likely to have cardiogenic shock upon presentation (15.7% vs. 9.4% p = 0.004).

3.2. Procedural characteristics

Angiographic and procedural characteristics are presented in Table 2. A total of 2683 lesions were treated. Angiographic success was similar between bivalirudin monotherapy (97.8%) and bivalirudin plus eptifibatide (98.7%). Choice of thienopyridine loading agent was fairly similar, with the exception of prasugrel, which was given more frequently in the bivalirudin plus eptifibatide arm (8.4% vs. 4.8%, p = 0.01). Interventions to the left anterior descending coronary artery were similar between groups. The use of intravascular ultrasound and a direct stenting method occurred with greater frequency in the bivalirudin monotherapy group. This group also had a greater number of stents implanted. Use of rotational atherectomy was greater in the bivalirudin monotherapy group (1.9% vs. 0%), while aspiration thrombectomy occurred more often in the combination therapy arm (48.5% vs. 23.7%; p = 0.013) as did treatment of type C lesions (50.5% vs. 42.4%; p = 0.007). Pre-procedural TIMI flow ≤1 was present more often during combination therapy than with bivalirudin monotherapy