Comparison of Bolus Only With Bolus Plus Infusion of Bivalirudin in Patients Undergoing Elective Percutaneous Coronary Intervention: A Retrospective Observational Study

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Abstract
Background: Anticoagulation therapy during percutaneous coronary intervention (PCI) has been the focus of numerous clinical trials. Low-anticoagulant doses have been successfully used in patients undergoing elective PCI, a situation with low-thrombogenic milieu. Objective: The purpose of the study was to evaluate the safety and efficacy of shorter duration of treatment with bivalirudin in patients undergoing elective PCI and receiving optimal antiplatelet therapy. Methods: We compared patients undergoing PCI who received aspirin and clopidogrel loading dose in addition to either conventional bivalirudin dosing (intravenous [IV] bolus of 0.75 + 1.75 mg/kg per h for the duration of PCI; n = 197) or a reduced bivalirudin dose (IV bolus of 0.75 mg/kg; n = 200). Results: Procedural success was obtained in 100% of cases. The primary end point (in-hospital death, acute myocardial infarction, or need for urgent target vessel revascularization) did not differ between both the groups (6 patients [3%] in the conventional dose group vs 5 patients [2.5%] in the reduced dose group). Major bleeding occurred in 1 patient in the conventional dose group (P = nonsignificant [NS]). Minor bleeding occurred in 4 patients (2%) in the conventional dose group vs 5 patients (2.5%) in the reduced dose group (P = NS) and was mainly due to bleeding at entry site. Conclusion: In patients undergoing elective PCI, using bivalirudin as a bolus only dosing may be as effective and less costly when compared with bolus followed by an infusion for the duration of the intervention. A larger study is needed to confirm our findings.

Keywords
bivalirudin, percutaneous coronary intervention, antithrombotic

Introduction
Percutaneous coronary intervention (PCI) results in plaque rupture that increases the risk of thrombosis and ischemic complications. PCI has dramatically improved because of innovation in techniques, stents, and antiplatelet agents, but optimal adjunctive antithrombotic treatment remains uncertain. The central role of thrombin in thrombosis arising from plaque rupture makes thrombin an essential target for pharmacotherapy. Bivalirudin (Angiomax®) is a direct thrombin inhibitor that has been extensively investigated in the prevention of thrombosis during and shortly after PCI.¹-⁷ In PCI, bivalirudin has provided similar antithrombotic protection as unfractionated heparin (UH) with glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors with significantly less major.¹,⁴,⁶,⁷ The American College of Cardiology and American Heart Association guidelines gave bivalirudin a class I recommendation in PCI.⁸

Important theoretical advantages of bivalirudin over UH are the lack of platelet-activating effect and lack of rebound effect characterized by increased thrombosis activity and myocardial infarction (MI).⁹,¹⁰ A consistent finding across multiple clinical studies of bivalirudin is the reduction in the rates of bleeding without the loss of antithrombotic efficacy. Potential cost benefits from the extensive use of bivalirudin include the reduction in the use of GPIIb/IIIa inhibitors and rates of bleeding. A further reduction in the cost can be achieved if an expensive prolonged infusion could be avoided in low-risk patients undergoing PCI. Bivalirudin comes in a 250-mg vial with an average cost of $572 per vial.

More recent studies have asked whether anticoagulation is necessary for low-risk elective PCI, when aggressive upstream antiplatelet therapy is already in use.¹¹-¹³ One study has claimed that only minute doses of UH are needed during

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uncomplicated stent placement. We hypothesized that in low-risk patients already receiving optimal antiplatelet therapy prior to elective PCI, a bolus dose of 0.75 mg/kg bivalirudin would be therapeutically equivalent to the same bolus dose followed by an infusion of 1.75 mg/kg per h for the duration of the PCI procedure. In this retrospective observational analysis of major adverse cardiovascular events (MACEs) in patients undergoing elective PCI, we compared the efficacy and safety of bivalirudin bolus plus infusion against bolus only.

**Methods**

From our database at Huntsville Hospital, an 881-bed regional referral center located in North Alabama, we retrospectively identified low-risk patients undergoing elective PCI and compared 2 groups of patients, 1 group received conventional bivalirudin dosing (IV bolus of 0.75 + 1.75 mg/kg per h for the duration of PCI) and another group received reduced bivalirudin dose (IV bolus of 0.75 mg/kg). The use of the reduced bivalirudin dose was left to the discretion of the operator. All patients received 325 mg of aspirin and 300 to 600 mg of clopidogrel at least 2 hours before the procedure. During PCI, either abciximab or eptifibatide were given for procedural complications, such as thrombus, distal embolization, slow flow, or prolonged myocardial ischemia. Coronary stenting with either bare-metal or drug-eluting stents, according to the choice of the physician, was the preferred method of PCI. We excluded patients who had acute coronary syndrome (ACS).

The primary end point was a composite of death, acute MI, or need for urgent target vessel revascularization occurring during hospitalization. MI was defined as new Q waves on electrocardiogram or creatine kinase (CK) or Creatine Kinase Myocardial Band (CK-MB) elevation ≥3 times the upper limit of normal. In addition, we assessed length of hospitalization post-PCI and incidence of noncoronary artery bypass graft bleeding. Major bleeding was defined as a drop in hemoglobin level to >4 g/dL, overt bleeding with a drop in hemoglobin level to >3 g/dL, a blood transfusion of ≥2 units or retroperitoneal, intracranial, or intracranial hemorrhage. Minor bleeding was defined as overt bleeding not meting criteria for major bleeding. Procedural success was considered a <30% residual stenosis and achieving a thrombolysis in MI (TIMI) flow grade of 3.

**Statistical Analysis**

All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) software. Chi-square tests were performed to evaluate the statistical association between the patients who were given the conventional bivalirudin regimen compared with the reduced regimen and the reported primary end points or other related categorical variables. The t test were performed for continuous variables. Results were statistically significant when \( P \leq .05 \).

**Results**

Table 1 lists the baseline characteristics. A total of 197 patients received conventional bivalirudin dose (group 1), while 200 patients received the reduced bivalirudin dose (group 2). Both the groups were well matched in all baseline characteristics except for the use of GPIIb/IIa inhibitors. Eptifibatide and abciximab, whose infusion was started in the catherization
laboratory, were used in 26% of patients in the conventional dose group and 38% of patients in the reduced dose group ($P = .025$).

Procedural success was 100% in both the groups. The primary end point of the study did not differ between both the groups (6 patients [3%] in the conventional dose group vs 5 patients [2.5%] in the reduced dose group; Table 2). There was no significant difference in the rate of periprocedural MI among patients treated with the conventional dose versus the reduced dose bivalirudin (5 patients, 2.5% vs 3 patients, 1.5%; $P = \text{NS}$). None of the patients died in the conventional dose group, while 2 patients died in the reduced dose group ($P = \text{NS}$). One patient underwent urgent target vessel revascularization in the conventional dose group while none in the reduced dose group ($P = \text{NS}$). Major bleeding occurred in 1 patient in the conventional dose group while none occurred in the reduced dose group ($P = \text{NS}$) and was due to intracranial hemorrhage. Minor bleeding occurred in 4 patients (2%) in the conventional dose group versus 5 patients (2.5%) in the reduced dose group ($P = \text{NS}$) and was mainly due to bleeding at entry site. Hospital stay did not differ significantly between both the groups (Table 3).

Discussion

PCI is the most commonly performed invasive therapeutic cardiac procedure and plays an important role in the treatment of ischemic heart disease. Procedural anticoagulation therapy has been the focus of numerous clinical trials. The REPLACE-2 trial (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) was conducted in the setting of coronary stenting in a lower risk elective population. The study randomized 6010 patients undergoing urgent or elective PCI to either UH plus planned GPIIb/IIIa inhibitors or to bivalirudin with provisional use of GPIIb/IIa given only for procedural complications.4 The primary end point was a 30-day incidence of death, MI, urgent repeat revascularization, or in-hospital major bleeding. Bivalirudin with provisional GPIIb/IIa inhibitors was found to be statistically noninferior to UH plus planned GPIIb/IIa blockade and was associated with less bleeding. Some clinical trials have suggested that in simple and elective procedures, the use of anticoagulation is not crucial, while some studies suggested that low-dose anticoagulant therapy is as effective as full dose.11-15

Our study analyzed the outcomes in low-risk patients who had been treated with 325 mg aspirin and a loading dose of 300 to 600 mg clopidogrel at least 2 hours before undergoing elective PCI. The GPIIb/IIa was used for procedural complications. All patients received clopidogrel at a loading dose of at least 300 mg prior to the procedure in order to achieve a high degree of platelet inhibition by the time the coronary intervention was performed.16,17 We compared the conventional bivalirudin dose with a reduced dose where the continuous infusion was omitted. Our study did not find the differences between the regimens in terms of in-hospital death, MI, or urgent revascularization, nor in the individual end point components. In addition, no differences were found between the 2 groups in major and minor bleeding, vascular entry site complications, and length of hospital stay after PCI. It is noteworthy that 2 patients died in the bolus only group while none in the bolus + infusion group, which was not statistically significant. However, a larger sample size is needed to rule out any potential difference related to death.

We expected the reduced dose arm to experience a lower incidence of bleeding. However, the similar rate of bleeding between both the groups could be explained by the small sample size or the more frequent use of GPIIb/IIa inhibitors in the reduced dose arm (26% vs 38%).

The results of this study are consistent with those of lower anticoagulant dosing in low-risk patients undergoing PCI. Godon et al used a single bolus dose of UH of 30 U/kg in 418 patients undergoing PCI, excluding those with recent MI or left main stem disease and concluded that the use of this low-dose UH appears to be safe and effective, allows faster mobilization, and earlier hospital discharge.14 In addition, Choussant et al examined a reduced dose (0.5 mg/kg) of enoxaparin in elective PCI patients and concluded that the dose appears to be safe and effective.15 Bivalirudin has a half-life of 25 minutes.18

The study has several limitations. First, it is monocentric, not randomized, retrospective, and is of a small sample size. Second, we did not follow patients after hospital discharge to assess the incidence of MACE. Finally, more patients in the reduced dose group received GPIIb/IIa inhibitors.

It has to be noted that all of our patients underwent elective PCI to treat chronic artery disease, and hence, the results of this study may not be applicable to patients with ACS, a situation with high thrombogenic milieu.

Conclusion

In patients undergoing elective PCI, using bivalirudin as a bolus only dosing may be as effective and less costly when compared with bolus followed by an infusion for the duration of the intervention. A larger study is needed to confirm our findings.

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