Preoperative Use of Enoxaparin Compared With Unfractionated Heparin Increases the Incidence of Re-Exploration for Postoperative Bleeding After Open-Heart Surgery in Patients Who Present With an Acute Coronary Syndrome

Clinical Investigation and Reports

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Background—Enoxaparin has become an attractive therapy for use during acute coronary syndrome (ACS) because of its potential superior efficacy over unfractionated heparin (UFH), its longer activity, and its subcutaneous route of administration. However, because a significant number of patients presenting with ACS may be sent directly to open heart surgery while still on anticoagulation, it is important to understand any potential bleeding risks that may be associated with the use of enoxaparin under these circumstances.

Methods—From 1998 to 2001, 1159 consecutive patients presenting with an acute coronary syndrome who received either UFH (n=1008) or enoxaparin (n=151) before proceeding to open heart surgery for urgent therapy during the same hospitalization were included in this study. Incidence of perioperative bleeding as evidenced by the units of blood products (packed red blood cells or platelets) transfused or the need for surgical re-exploration for postoperative bleeding was recorded.

Results—Average age was 65±11 and 67±11 years for patients receiving UFH and enoxaparin, respectively (P=0.005). Seventy-five percent of those receiving UFH and 64% of those receiving enoxaparin (P<0.005) were males. After discharge, the incidence of rehospitalization for hemorrhage requiring return to surgery for re-exploration was 7.9% in the enoxaparin group and 3.7% in the UFH group (adjusted hazard ratio=2.6, P=0.03). The use of blood products did not differ between groups (UFH=2.7±6.5 U and enoxaparin=2.3±4.5 U; P=NS).

Conclusion—The preoperative use of enoxaparin compared with UFH in patients presenting with an ACS who undergo open-heart surgery during the same hospitalization is associated with a significantly increased incidence of re-exploration for postoperative bleeding. Further study is needed to understand the mechanism of this phenomenon and to develop appropriate guidelines to address this potentially important issue. (Circulation. 2002;106[suppl I]:I-19-I-22.)

Key Words: acute coronary syndrome ■ enoxaparin ■ coronary artery bypass graft surgery ■ re-exploration ■ hemorrhage

Despite major advances in the treatment of ischemic heart disease and the acute coronary syndromes (ACS), it is still the leading cause of death in the industrialized world.1 Numerous studies of ACS have demonstrated that the use of antithrombotic therapy is effective in preventing worsening ischemia, myocardial infarction, and death.2-3 As a result, its use has become the standard of care in the stabilization process of patients who present with ACS.4 For many years, unfractionated heparin (UFH) has been the standard of care as the major antithrombotic agent used in the treatment of ACS.5 However, because of its unpredictable anticoagulant effect, requiring frequent testing to adjust the dose,6 a tendency to produce rebound ischemic reactivation with discontinuation,7 and risk of heparin-induced thrombocytopenia,8 UFH has not been considered an ideal agent. Low-molecular-weight heparins (LMWHs) offer a number of practical and clinical advantages over UFH, such as higher bioavailability and administration by subcutaneous injection.9 Besides these convenience issues, 2 recent studies with 1 of the LMWHs, enoxaparin, have independently shown that this agent is more effective than UFH in preventing coronary events inpatients with ACS.10,11 This clinical benefit was also shown to last for

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at least 1 year. However, this superior clinical efficacy came at the cost of an increase in the rates of minor hemorrhage. Specifically, in the ESSENCE and TIMI-11b studies, the pooled incidence of major hemorrhagic complications during short-term treatment was 1.3% in the enoxaparin group and 1.1% in the UFH group (P=0.35). The incidence of minor hemorrhages during the short-term phase was 10% and 4.3%, respectively (P<0.001).13

Because of its improved efficacy and the absence of any statistically significant increase in major hemorrhage, LMWH has been given a Class I indication within the National ACS Management Guidelines. However, the effect of the use of LMWH on ACS patients proceeding directly to open-heart surgery for coronary artery bypass grafting is not well known. Because of its longer half-life, its greater incidence of minor bleeding, and its inability to be completely reversed with protamine, the possibility exists that more postoperative bleeding complications might result. This question may become important as more patients with ACS begin to receive LMWH. Therefore, the objective of this study was to evaluate the incidence of bleeding complications in patients presenting with an ACS who receive preoperative antithrombotic therapy of UFH or LMWH within 48 hours of proceeding to open-heart surgery.

Methods

Study Population
Between January 1998 and March 2001, all consecutive patients undergoing open-heart surgery at LDS Hospital who met the inclusion and exclusion criteria were enrolled in the study. Inclusion criteria included the following: (1) the patient presented with a diagnosis of unstable angina or non-Q-wave myocardial infarction and (2) the patient received antithrombotic therapy with either UFH or enoxaparin within 48 hours before proceeding to surgery. Exclusion criteria included the following: (1) the patient received no antithrombotic therapy (UFH or enoxaparin) within 48 hours of the surgical procedure and (2) follow-up clinical data were not available. This retrospective study was performed under the approval of the hospital’s institutional investigational review board. UFH was stopped before the patient entered the surgical suite, with no neutralization therapy performed. All patients received 300 to 400 U/kg of UFH perisurgery or until the activated coagulation time (ACT, seconds) exceeded 480. Subsequent reversal of UFH was accomplished with protamine (1 mg per 100 U of periorative UFH received) with additional doses administered until the ACT was normalized after bypass cannulae were removed.

Follow-Up Protocol
Patients were followed from the time of the initial operative procedure until discharge. Baseline characteristics were collected in a cardiovascular database and included the following: age, sex, surgical procedure performed (coronary bypass grafting, valvular procedure, or both), preoperative (within 48 hours) usage of oral antiplatelet agents (aspirin, clopidogrel/ticlopidine), preoperative usage of intravenous glycoprotein IIb/IIIa inhibitors (abciximab, epifibatide, or tirofiban), time between the last enoxaparin administration and proceeding to surgery, and length of the surgical procedure. Primary study end points related to perioperative bleeding and included (1) incidence and amount of blood products (packed red blood cells or platelets) transfused and (2) surgical re-exploration for postoperative bleeding. Need for re-exploration as a result of postoperative bleeding was determined by the attending thoracic surgeon. In general, patients returned to surgery because of the development of uncontrollable chest tube drainage or hemodynamic instability from cardiac tamponade or graft-site compromise diagnosed by echocardiography. Distinction between intraoperative and postoperative transfusion of blood products was not made. Timing of surgical re-exploration after the initial operative procedure was recorded. Blood product transfusion and surgical re-exploration were treated as 2 separate clinical end points. A secondary clinical end point of in-hospital postprocedural death was also collected.

Statistical Considerations
Differences in use of blood products between the UFH and enoxaparin groups were evaluated by the Mann-Whitney U statistic, and differences in the incidence of return to surgery between those groups were evaluated by the chi-square statistic. Comparisons of other characteristics among the 2 treatment types were performed by the Mann-Whitney test for continuous variables and the chi-square test for categorical variables.

Cox regression analysis was used to model the prediction of return to surgery based on treatment type while controlling for patient age, sex, type of surgery, need for blood products, and preoperative use of other antiplatelet agents. Hazard estimates were computed graphically. Similar analyses were performed for death and for a dichotomous outcome of need for any blood product or not. Two-tailed probability values were used with P=0.05 designated as the threshold for statistical significance.

Results
Patient characteristics are outlined in Table 1. The last dose of enoxaparin was administered at an average of 14.7 hours before surgery (range 3 to 40 hours). Some significant differences were noted between the group receiving UFH and the group receiving enoxaparin. Patients receiving enoxaparin were older and more likely to be women. They were also more likely to be receiving a valve procedure, either with coronary artery bypass grafting or without. There was no difference between the groups regarding the preoperative usage of aspirin. The preoperative use of clopidogrel/ticlopidine and glycoprotein IIb/IIIa inhibitors was low and did not differ between groups.

The incidence of perioperative transfusion of blood products is shown in Table 2. No difference between groups was noted in the average number of units of packed red blood cells or platelets transfused. Additionally, no difference was noted between groups in the total numbers of patients requiring any

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (males)</td>
</tr>
<tr>
<td>Preoperative antiplatelet therapy</td>
</tr>
<tr>
<td>Aspirin</td>
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<tr>
<td>Clopidogrel/ticlopidine</td>
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<td>IIb/IIIa inhibitors</td>
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<td>Surgical procedure performed</td>
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<tr>
<td>CABG</td>
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<tr>
<td>Valve</td>
</tr>
<tr>
<td>Both</td>
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<tr>
<td>Length of surgical procedure</td>
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CABG=coronary artery bypass graft; NA=not applicable; NS=not significant; UFH=unfractionated heparin.
TABLE 2. Preoperative Use of Transfused Blood Products

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UFH</th>
<th>Enoxaparin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBCs</td>
<td>1.7±3.7 units</td>
<td>1.6±2.9 units</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.9±3.9 units</td>
<td>0.7±2.7 units</td>
<td>NS</td>
</tr>
<tr>
<td>All blood products</td>
<td>2.7±6.5 units</td>
<td>2.3±4.5 units</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=not significant; PRBCs=Packed red blood cells; UFH=unfractionated heparin.

blood product transfusion (enoxaparin=43%, UFH=44%, P:NS).

However, a significantly greater incidence of return to surgery for bleeding complications (chest tube drainage, cardiac tamponade, valve or graft site compromise diagnosed by the use of echocardiogram) was noted in the enoxaparin group compared with the UFH group (7.9% versus 3.7%, P=0.04). This difference remained significant after controlling for age, sex, type of surgery, need for blood products, and preoperative use of other antiplatelet agents (adjusted hazard ratio [HR]=2.6, CI=1.1 to 5.9, P=0.03). Interestingly, the adjusted HR for returning to surgery was higher in univariate because of greater confounding by glycoprotein IIb/IIIa use among UFH patients (for IIb/IIIa agents, HR=2.6, CI=0.8 to 8.9, P=12). Figure 1 shows the hazard curves for return to surgery for bleeding complications for the enoxaparin and UFH groups. No significant differences for in-hospital mortality were noted between the enoxaparin and UFH groups (5.3% versus 4.9%, P=NS).

Discussion

This study demonstrates that patients presenting with ACS and treated with antithrombotic therapy who proceed to open heart surgery within 48 hours after administration of LMWH or enoxaparin experience a significantly higher risk of postoperative bleeding complications (ie, chest tube drainage, cardiac tamponade) requiring surgical re-exploration. The mechanism of this increased risk is not certain, and the results are complicated by the fact that the increased risk of surgical re-exploration was not accompanied by an increased use of transfused blood products. However, a variety of potential explanations may be explored. First, the dosage of enoxaparin (generally 1 mg/kg subcutaneously twice per day) may induce a greater antithrombotic effect than a standard dose UFH.9 Indeed, this may explain its superior clinical efficacy. Additionally, at the standard recommended dose of enoxaparin, the activated partial thromboplastin time is relatively insensitive to its anticoagulant effect, thereby making it difficult to make individual adjustments to the dose. Second, the longer half-life of enoxaparin might increase its length of action to well beyond the completion of the surgery and result in increased risk of bleeding.9 Third, because of its relative resistance to neutralization by protamine, anticoagulation caused by the enoxaparin may not be appropriately reversed after surgery, resulting in an increased risk of bleeding.9 Regardless of the mechanism, a more than doubling of the risk of surgical re-exploration after open heart surgery is something of potentially significant clinical impact.

This finding, however, does not necessarily call into question the indication for the use of enoxaparin in ACS. Overall, relatively few patients with ACS actually proceed directly to open-heart surgery. Additionally, the absolute incidence of surgical re-exploration is still fairly low and does not appear to have an impact on overall in-hospital surgical mortality. Moreover, it is possible that the relatively simple act of converting the preoperative ACS patient from treatment with enoxaparin to UFH at least 48 hours before proceeding to open-heart surgery may successfully eliminate the observed bleeding risk associated with enoxaparin use in these patients.

Study Limitations

This study is limited by its retrospective nature and lack of randomization. Indeed, significant differences were noted in baseline characteristics between the 2 groups in relation to age, sex, and type of surgery performed. However, multivariate adjustment for type of surgery and type of blood products received increased, if anything, the strength of the study’s finding. The lack of correlation between blood product usage and an increased risk of surgical re-exploration may also be concerning. However, this may be explained by the presence of differing indications for surgical re-exploration than for product transfusion. Finally, this study is limited by its small size, although, to our knowledge, it is the largest series of patients treated with enoxaparin going to open heart surgery yet reported. Certainly more studies will be necessary to verify this initial finding.

Conclusion

The preoperative use of enoxaparin compared with unfractionated heparin inpatients presenting with an acute coronary syndrome who undergo open-heart surgery within 48 hours of receiving the agent is associated with a significantly increased incidence of re-exploration for postoperative bleed-
Further study is needed to understand the mechanism of this phenomenon and to develop appropriate guidelines to address this potentially very important issue.

References
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