Heparin After Percutaneous Intervention (HAPI): A Prospective Multicenter Randomized Trial of Three Heparin Regimens After Successful Coronary Intervention

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Royal Oak and Saginaw, Michigan; Little Rock, Arkansas; Oklahoma City, Oklahoma; Worcester, Massachusetts; Sydney, Australia

OBJECTIVES

The purpose of this study was to determine the incidence of bleeding, vascular, and ischemic complications using three different heparin regimens after successful intervention.

BACKGROUND

The ideal dose and duration of heparin infusion after successful coronary intervention is unknown.

METHODS

Patients were randomized to one of three heparin strategies after coronary intervention: Group 1 (n = 157 patients) received prolonged (12 to 24 h) heparin infusion followed by sheath removal; Group 2 (n = 120 patients) underwent early removal of sheaths, followed by reinstitution of heparin infusion for 12 to 18 h; Group 3 (n = 137 patients) did not receive any further heparin after intervention with early sheath removal. The primary end point of the study was the combined incidence of in-hospital bleeding and vascular events. Secondary end points included in-hospital ischemic events, length of stay, cost and one-month outcome.

RESULTS

After successful coronary intervention, 414 patients were randomized. Unstable angina or postinfarction angina was present in 83% of patients before intervention. The combined incidence of bleeding and vascular events was 21% in Group 1, 14% in Group 2 and 8% in Group 3 (p = 0.01). The overall incidence of in-hospital ischemic complications was 2.2%; there were no differences between groups. Length of hospital stay was shorter (p = 0.033) and adjusted hospital cost was lower (p < 0.001) for Group 3. At 30 days, the incidence of delayed cardiac and vascular events was similar for all three groups.

CONCLUSIONS

Heparin infusion after successful coronary intervention is associated with more minor bleeding and vascular injury, prolonged length of stay and increased cost. In-hospital and one-month ischemic events rarely occur after successful intervention, irrespective of heparin use. Routine postprocedure heparin is not recommended, even in patients who present with unstable ischemic syndromes. (J Am Coll Cardiol 1999;34:461–7) © 1999 by the American College of Cardiology

Before percutaneous coronary intervention, aspirin and heparin are routinely administered to reduce the risk of vessel occlusion (1–18). Despite widespread use of percutaneous transluminal coronary angioplasty (PTCA) for nearly 20 years, the ideal doses of both intra- and postprocedural heparin are unknown (1). A recent national survey on anticoagulation for PTCA reported the routine use of postprocedural heparin in 70% of procedures (9). Furthermore, although heparin is clearly indicated during the interventional procedure, the need for any postprocedural heparin has not been clearly established. Despite the results of a recent randomized trial (10), which demonstrated that, for elective PTCA and a good angiographic result, no further postprocedural heparin was necessary and early discharge was safe, this strategy has not been widely applied to patients with unstable ischemic syndromes because of concerns of postprocedural ischemic complications. Accordingly, the purpose of this study was to determine the incidence of bleeding, vascular and ischemic complications associated with three different postpro-
Methods

Patient population. Between May 1995 and June 1996, a total of 414 patients from six institutions were enrolled in this prospective randomized trial. Written informed consent was obtained from each patient according to protocols approved by the Human Studies Committee at each institution. All patients received aspirin (325 mg daily) at least 24 h before intervention. Patients were considered for enrollment in the study after successful balloon angioplasty, laser or atherectomy of a native coronary artery. Success was defined as final diameter stenosis <35% without flow-limiting dissection, using on-line visual estimates of stenosis severity. Patients with cardiogenic shock, myocardial infarction within five days, intracoronary stent implantation and need for chronic warfarin anticoagulation were excluded.

Heparin administration. After insertion of the femoral arterial sheath, patients were treated with intravenous (IV) heparin to maintain the activated clotting time (ACT) ≥150 s, followed by discharge within 8 to 12 h. Vascular sheaths were removed within five days, intracoronary stent implantation and need for chronic warfarin anticoagulation were excluded.

Definitions. Several definitions were used in this study: major bleeding was defined as any bleeding requiring a blood transfusion; major vascular events were defined as any vascular repair, arteriovenous (AV) fistula, pseudoaneurysm, femoral nerve injury or retroperitoneal hemorrhage; minor bleeding was defined as a decrease in hemoglobin concentration >3 g/dl, not requiring a blood transfusion; minor vascular injury was defined as a femoral hematoma >6 cm, not requiring transfusion or vascular repair. Major ischemic complications were defined as chest pain with new electrocardiogram (ECG) changes, Q-wave and non-Q-wave myocardial infarction, repeat PTCA, stent placement for acute abrupt closure and CABG during the same hospital stay. Myocardial infarction was defined as elevation in creatine kinase (CK) greater than 2 times normal, and elevation of MB isoform.

Statistical analysis. Continuous variables were analyzed by the Student t test, and categoric variables were analyzed by the chi-square or Fisher exact test. Group comparisons were performed by analysis of variance (ANOVA). Multivariate analysis was performed using the Cox proportional hazards regression model. Variables that proved to be significant on univariate analysis or were believed to have important prognostic value were entered into the multivariable model. A p-value <0.05 was considered statistically significant. Sample size calculation was based on the assumption that the incidence of bleeding and vascular complications for patients receiving prolonged heparin was 15%; a total of 1,650 patients (550 patients per arm) would be required (two-tailed t test) to demonstrate a 43% reduction to 8.5% (90% power, alpha = 0.05). Data were analyzed after entry of 100 and 400 patients to ensure safety, and interim reports were presented to the Human Investigations Committee. Because of significant differences in outcome during interim analysis, the study was prematurely terminated at the recommendation of the Human Investigations Committee.

Results

Patient population. The study population consisted of 414 patients. Patients in each group were similar with respect to
age, gender, height, weight, body surface area and prior history of diabetes and peripheral vascular occlusive disease; hypertension was more prevalent in Group 2 patients (Table 1). Clinical indications for revascularization included unstable angina in 69%, stable angina in 17% and postinfarction angina in 14% of patients (Table 1). Patients in this study represented a high-risk population, characterized by multivessel disease in nearly half of the patients (Table 2), and by the need for preprocedural IV heparin infusion in more than one-third of patients (Table 1).

**Angiographic characteristics.** Treatment groups were similar regarding left ventricular ejection fraction, extent of coronary artery disease and target vessel distribution (Table 2). The primary interventional device was PTCA alone in 88%; directional, mechanical or extractional atherectomy in 11%; and excimer laser angioplasty in 1%, using an average arterial sheath of 8.1 ± 0.5F.

**Bleeding and vascular events.** The combined incidence of bleeding and vascular events was significantly higher in patients who received prolonged heparin infusion compared with those who did not receive additional heparin (Fig. 1): 21% in Group 1, 14% in Group 2 and 8% in Group 3 (p < 0.01). The duration of postprocedural heparin infusion in hours for Group 1 was 14.3 ± 10.9 and for Group 2 was 12.9 ± 5.8. Major bleeding and major vascular injury occurred in 1% of patients, and there were no differences between groups. However, minor bleeding complications (defined as a decline in postprocedure hemoglobin >3 g/dl; p < 0.01) and minor vascular complications (femoral hematoma; p = 0.07) were more frequent in patients

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### Table 1. Baseline Characteristics of Patients Undergoing Successful Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 414)</th>
<th>Group 1 (n = 157)</th>
<th>Group 2 (n = 120)</th>
<th>Group 3 (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62 ± 11</td>
<td>62 ± 10</td>
<td>62 ± 11</td>
<td>61 ± 11</td>
</tr>
<tr>
<td>Female (%)</td>
<td>136 (33)</td>
<td>50 (32)</td>
<td>41 (34)</td>
<td>45 (33)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>94 (23)</td>
<td>35 (22)</td>
<td>29 (24)</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>33 (8)</td>
<td>16 (10)</td>
<td>8 (7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Hypertension (&gt;140/90) (%)</td>
<td>235 (57)</td>
<td>77 (49)</td>
<td>80 (67)*</td>
<td>78 (57)</td>
</tr>
<tr>
<td>Preprocedural heparin (%)</td>
<td>149 (36)</td>
<td>58 (37)</td>
<td>43 (36)</td>
<td>48 (35)</td>
</tr>
<tr>
<td>Angina type (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>71 (17)</td>
<td>27 (17)</td>
<td>23 (19)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Unstable</td>
<td>284 (69)</td>
<td>112 (88)</td>
<td>83 (69)</td>
<td>89 (65)</td>
</tr>
<tr>
<td>Post-MI</td>
<td>59 (14)</td>
<td>18 (12)</td>
<td>14 (12)</td>
<td>27 (20)</td>
</tr>
</tbody>
</table>

BSA = body surface area; MI = myocardial infarction. Group 1 = Continuous postprocedural heparin infusion; Group 2 = sheaths removed, reinstitution of postprocedural heparin; Group 3 = no heparin postprocedure. *p < 0.05.

### Table 2. Angiographic Characteristics of Patients Undergoing Successful Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 414)</th>
<th>Group 1 (n = 157)</th>
<th>Group 2 (n = 120)</th>
<th>Group 3 (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>53 ± 4</td>
<td>52 ± 4</td>
<td>54 ± 4</td>
<td>52 ± 4</td>
</tr>
<tr>
<td>Extent of CAD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel</td>
<td>224 (54)</td>
<td>87 (55)</td>
<td>60 (50)</td>
<td>77 (56)</td>
</tr>
<tr>
<td>Multivessel</td>
<td>190 (46)</td>
<td>70 (45)</td>
<td>60 (50)</td>
<td>60 (44)</td>
</tr>
<tr>
<td>Target vessel (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>LAD</td>
<td>180 (37)</td>
<td>72 (37)</td>
<td>45 (35)</td>
<td>63 (38)</td>
</tr>
<tr>
<td>LCX</td>
<td>159 (33)</td>
<td>61 (32)</td>
<td>44 (34)</td>
<td>54 (33)</td>
</tr>
<tr>
<td>RCA</td>
<td>147 (30)</td>
<td>60 (31)</td>
<td>40 (31)</td>
<td>47 (28)</td>
</tr>
<tr>
<td>Device (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>365 (88)</td>
<td>139 (89)</td>
<td>108 (90)</td>
<td>118 (86)</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>46 (11)</td>
<td>17 (11)</td>
<td>11 (9)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Laser</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arterial sheath (F)</td>
<td>8.1 ± 0.5</td>
<td>8.1 ± 0.5</td>
<td>8.1 ± 0.5</td>
<td>8.1 ± 0.5</td>
</tr>
</tbody>
</table>

LM = left main coronary artery; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; PTCA = percutaneous transluminal coronary artery; F = French. Group 1 = Continuous postprocedural heparin infusion; Group 2 = sheaths removed, reinstitution of postprocedural heparin; Group 3 = no heparin postprocedure.
receiving postprocedural heparin (Fig. 1). Minor bleeding was also evaluated by the measurement of baseline and nadir hemoglobin concentrations (Fig. 2): Although the preprocedure hemoglobin concentration was similar for all three groups, the nadir hemoglobin concentration was significantly lower in patients receiving postprocedure heparin infusion (p = 0.002). Factors associated with combined bleeding and vascular events were evaluated by univariate and multivariate analysis (Table 3). Although body weight <80 kg, body surface area <1.94 cm², age >62 years, creatinine >1.2 mg/dl, vascular sheath time >8 h and the use of heparin postprocedure were all associated with combined bleeding and vascular events by univariate analysis, only age >62 years and vascular sheath time >8 h were independent predictors by multivariate analysis. The size of the arterial sheath used was not associated with adverse bleeding events in the univariate or multivariate model.

Ischemic complications. The overall incidence of major ischemic complications was 2.2%, and there were no differences between groups. There were two patients in Group 1 who developed abrupt closure after the procedure; one was treated conservatively and developed a Q-wave myocardial infarction (MI), and the other developed non-Q-wave MI after emergency repeat PTCA. One patient in Group 1 died as a result of coronary perforation and cardiac tamponade, not responding to pericardiocentesis. Three patients in Group 2 had abrupt closure, including one who developed non-Q-wave MI. All three patients were treated with emergency percutaneous revascularization (PTCA alone in one, stent placement in two). One other patient in Group 2 developed asymptomatic non-Q-wave MI and was treated conservatively. Three patients in Group 3 developed ischemic complications: two patients developed MI and were treated conservatively (Q-wave in one, non-Q-wave in one), and one patient with multivessel disease underwent CABG during the same hospitalization because of recurrent angina.

Length of hospital stay and cost. The postprocedure length of hospital stay was significantly longer for patients who received prolonged heparin infusion (Groups 1 and 2) compared with Group 3 patients, who did not receive any heparin (p = 0.033). Patients with major bleeding and vascular events (6.2 days vs. 1.3 days; p ≤ 0.0001; 95% CI [confidence interval] 4.01, 5.69), minor bleeding and vascular events (1.7 days vs. 1.3 days; p = 0.003; 95% CI 0.15, 0.74), major ischemic complications (2.2 days vs. 1.3 days; p = ≤0.001; 95% CI 0.58, 1.29) and combined bleeding, vascular, and ischemic events (1.9 days vs. 1.2 days; p = 0.001; 95% CI 0.43, 0.95) had significantly longer hospital stay compared with patients without such complications (Fig. 3). The total adjusted Medicare cost was significantly higher in patients who received prolonged heparin infusion (Fig. 4, p = 0.0004; 95% CI 410.8, 1617.9). Because the adjusted pharmacy cost, catheterization laboratory cost and total cost per day were similar in all three groups, the incremental cost in the groups receiving additional heparin was largely attributed to the longer length of hospital stay.

Table 3. Bleeding and Vascular Events of Patients Undergoing Successful Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Event</th>
<th>p Value</th>
<th>95% Confidence Intervals (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight &lt;83 kg</td>
<td>0.009</td>
<td>0.253, 0.827</td>
</tr>
<tr>
<td>BSA &lt;1.94 cm²</td>
<td>0.02</td>
<td>0.289, 0.920</td>
</tr>
<tr>
<td>Age &gt;62 years</td>
<td>0.001</td>
<td>1.505, 4.860</td>
</tr>
<tr>
<td>Creatinine &gt;1.2 mg/dl</td>
<td>0.061</td>
<td>0.995, 12.394</td>
</tr>
<tr>
<td>Vascular sheath time &gt;8 h</td>
<td>0.001</td>
<td>1.712, 6.291</td>
</tr>
<tr>
<td>Postprocedural heparin use</td>
<td>0.012</td>
<td>0.210, 0.836</td>
</tr>
</tbody>
</table>

Multivariate Characteristics

<table>
<thead>
<tr>
<th>Event</th>
<th>p Value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;62 years</td>
<td>0.0002</td>
<td>2.605</td>
</tr>
<tr>
<td>Vascular sheath time &gt;8 h</td>
<td>0.0012</td>
<td>3.171</td>
</tr>
</tbody>
</table>

BSA = body surface area.
Follow-up. To evaluate the possibility that early hospital discharge might have precluded identification of ischemic and vascular complications, clinical follow-up was obtained in all patients at one-month following discharge. Delayed cardiac events occurred in 16 patients (4%), including death (n = 1, 0.2%), MI (n = 2, 0.5%), repeat intervention on the original lesion (n = 8, 1.9%), and CABG (n = 5, 1%). There were eight patients in Group 1, five patients in Group 2, and three patients in Group 3 who had late cardiac events (p = NS). Delayed major vascular events were identified in three patients (1%), including vascular repair in two and ultrasound compression of a pseudoaneurysm in one patient; there were no differences between groups (two patients in Group 2; one patient in Group 3).

DISCUSSION

Heparin during PTCA. Heparin is virtually always used during PTCA to reduce the risk of abrupt closure (6–8,13,14), but attempts to treat the patient, relieve coronary ischemia and prevent vessel thrombosis may complicate efforts to maintain hemostasis at the site of arterial access. Although the activated clotting time (ACT) is commonly used to monitor the “heparin-effect” (1,5) a standard therapeutic ACT level has not been firmly established (16,17). Although most interventional cardiologists utilize sufficient heparin to maintain the ACT >300 s during the procedure (1,9,15,18,19), the “average” heparin dose required to achieve an ACT >300 s is dependent on several factors, including the nature of the anginal syndrome (20), the influence of platelet IIb/IIIa receptor antagonists (21), arterial versus venous samples (19,22,23), body weight (24) and the type of ACT device (20,25). Although some studies suggest an inverse relationship between ACT levels and ischemic complication (17,26), higher ACT levels are also associated with more bleeding and vascular complications. No patients received platelet glycoprotein receptor antagonists.

Heparin after PTCA and ischemic complications. In contrast with the recognized value of intraprocedural heparin to prevent ischemic complications, the need for postprocedural heparin has not been confirmed in any subgroup of patients with either stable or unstable angina (27). Nevertheless, a recent national survey reported routine use of postprocedural heparin in 70% of procedures (9). Furthermore, because some studies suggest a relationship between dissection and acute abrupt closure (26), many interventionalists, fearing a subclinical dissection, are reluctant to discontinue heparin immediately after PTCA (1,28). However, postprocedural heparin does not reduce abrupt closure after successful PTCA (27), but does increase the incidence of bleeding and vascular complications (3,10,28–33). There are no data to suggest that routine postprocedural heparin decreases the risk of ischemic complications; several studies suggest the safety of omitting postprocedural heparin (10,27). The present study confirms and extends these findings to patients with a variety of unstable ischemic syndromes, including unstable angina and postinfarction angina, who were routinely excluded from earlier studies because of fear of ischemic complications.

Heparin and bleeding and vascular complications. In contrast with the lack of influence of postprocedural heparin on ischemic complications, this study and others (3,10,27–33) demonstrate a relationship between postprocedural heparin and bleeding and vascular complications. Use of postprocedural heparin (Groups 1 and 2) was associated with a significant drop in hemoglobin concentration in this study and others (34). There are a number of potential explanations for the association of prolonged heparin infusion with bleeding and vascular complications. First, prolonged heparinization exposes the patient to a sustained interval of anticoagulation. Although “therapeutic” anticoagulation may be well tolerated when mucosal and vascular integrity is maintained, breach of vascular integrity may increase the risk of iatrogenic bleeding and vascular complications. Second, prolonged heparinization may be associated with
delayed sheath removal (as in Group 1), which might inhibit normal elasticity of the arterial wall to aid in closing the entry site, leading to a “fixed opening.” Indeed, indwelling vascular sheath duration >8 h was a strong independent predictor of bleeding and vascular complications. Third, it is difficult for most patients to remain supine and immobile for prolonged periods, increasing the likelihood of excessive patient movement, back pain and general discomfort; these conditions can lead to tachycardia and hypertension, both of which can potentiate groin complications.

Finally, other technical, patient (29,30,32,35,36) and pharmacologic factors (36–38) may influence vascular complications. Although some studies (32,33,38) show a relationship between vascular sheath size and vascular events, others (29,30,39) (including the current study) did not.

Prevention of bleeding, vascular and ischemic complications. The most important way to reduce the risk of bleeding and vascular complications is to avoid the use of postprocedural heparin infusion after successful intervention, and to remove the vascular sheaths when the ACT is <150 s. When these principles are followed, the likelihood of such complications will be determined primarily by operator technique of vascular entry, groin compression and patient factors such as low body weight and advanced age. The role of vascular sealing devices is under investigation, and there is potential for further reduction in complications with these devices (40–42). In routine PTCA practice, the most important factors in preventing ischemic complications are the administration of aspirin and heparin before intervention. However, this study and others (10,27) indicate that after successful intervention, postprocedural heparin is not indicated to prevent ischemic complications, even in high-risk patients. Although postprocedural heparin infusions are often used after “suboptimal” PTCA, there are no data to indicate that any level of systemic heparinization is useful in preventing ischemic complications; further study is needed. The efficacy of other potent antithrombin agents, such as low molecular weight heparin, hirulog and hirudin (43–45), may be similar to heparin, but it is uncertain whether prolonged postprocedural use of these agents will enhance safety. Finally, the availability of potent platelet receptor antagonists has shown great promise in reducing ischemic, bleeding and vascular complications, particularly if postprocedural heparin is withheld (36,46–48).

Effects of postprocedural heparin on length of hospital stay and cost. Bleeding and vascular complications are important causes of patient morbidity after percutaneous interventions. In this study and others (10), bleeding and vascular complications were strongly associated with prolonged hospital stay and cost. If patients treated with prolonged heparinization incur an incremental cost of $1,000 per patient, it may be possible to have marked effect on cost by eliminating the routine use of postprocedural heparin: If 500,000 percutaneous interventions are performed in the U.S. each year (including 250,000 PTCAs), the incremental cost of postprocedural heparin is $250 million annually.

Study limitations. There are several potential study limitations. First, this study was powered to detect differences in bleeding and vascular complications, and was underpowered to detect differences in low-frequency outcomes such as death, myocardial infarction and CABG. It is possible that recruitment of more patients may have allowed a more powerful statement about ischemic complications. Second, this study evaluated the use of heparin after “optimal” intervention, and it was not designed to study another important clinical issue, namely the use of heparin after “suboptimal” intervention. Third, end points of this study were clinical, not angiographic, outcomes. It is possible that the patients enrolled represented a highly selected population with superior angiographic results, and not the usual “successful” PTCA. However, virtually all studies comparing stenosis severity using visual estimates or quantitative angiography suggest that postprocedural stenosis severity is always underestimated by visual techniques. Thus, it is likely that quantitative angiography would have revealed residual stenosis >35%. Fourth, clinical follow-up was conducted for one month after intervention to capture delayed complications. It is possible that later follow-up may have uncovered additional complications, but we attempted to avoid the dilemma of determining whether later ischemic complications were due to the index procedure or to restenosis.

Conclusions. In summary, IV heparin infusion after successful coronary interventions is associated with more minor bleeding and vascular injury, and with prolonged length of stay leading to increased hospital cost. Ischemic cardiac events rarely occur after successful intervention, irrespective of heparin use. Routine postprocedure heparin is not recommended, even in patients who present with unstable ischemic syndromes.

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