Randomized Prospective Evaluation of Prolonged Versus Abbreviated Intravenous Heparin Therapy After Coronary Angioplasty

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Objectives. This study was designed to prospectively evaluate the routine use of continuous heparin therapy after successful uncomplicated coronary angioplasty.

Background. The use of such therapy varies among institutions and may increase the incidence of complications. Evaluation of the risks and benefits of abbreviated heparin therapy combined with early sheath removal after coronary angioplasty is necessary to determine optimal postprocedure care.

Methods. We prospectively studied 284 patients who were scheduled for elective coronary angioplasty. Historical, clinical, physiologic and angiographic data were gathered. All patients received an initial bolus of heparin and then were randomized during the procedure to receive either no additional heparin therapy or an adjusted 24-h infusion. On the basis of specific criteria, additional heparin was not withheld if procedural results suggested an increased risk for complications.

Results. Two hundred thirty-eight patients completed the study; 46 others were excluded in the catheterization laboratory because of unfavorable procedural results. The patients with abbreviated (n = 118) and 24-h (n = 120) therapy did not differ with respect to demographic and angiographic findings. However, the former had fewer bleeding complications (0% vs. 7%, p < 0.001) and were discharged earlier (mean ± SD 23 ± 11 h vs. 42 ± 24 h, p < 0.001). One patient in this group had a major complication shortly after angioplasty. The mean savings in hospital charges in the abbreviated therapy group was $1,370 ($6,093 ± $1,772 vs. $7,463 ± $1,782, p < 0.001).

Conclusions. Omission of routine heparin therapy after successful coronary angioplasty reduces bleeding complications without increasing patient risk. Earlier discharge and significant cost savings are possible under proper conditions. (J Am Coll Cardiol 1994;24:1214–9)

Cardiac catheterization and percutaneous transluminal coronary angioplasty remain integral components in the management of patients with symptomatic coronary artery disease. Outpatient diagnostic cardiac catheterization is now an established technique and has been shown by many investigators (1–6) to be safe and cost-effective. Similarly, technical advances and greater operator experience have improved the safety and success of coronary angioplasty. A recent study at our institution (7) demonstrated that up to two thirds of selected patients undergoing elective angioplasty could be stratified by risk and safely discharged within 24 h of the procedure.

The duration of continuous heparin therapy significantly influenced the length of hospital stay by preventing early sheath removal. However, the prescribed duration and intensity of routine anticoagulant therapy to prevent acute vessel occlusion after uncomplicated coronary angioplasty varies widely among institutions and among angiographers (8–11), often as a matter of convenience. Prolonged continuous heparin infusion increases the incidence of bleeding, may not decrease the frequency of abrupt vessel reclosure and has no effect on the rate of late restenosis (12). For scientific and economic reasons, prospective evaluation of continuous prolonged heparin therapy versus abbreviated heparin therapy with early sheath removal after uncomplicated coronary angioplasty is necessary.

Methods

Patient selection and entry criteria. Between July 1989 and February 1991 all patients scheduled for elective coronary angioplasty were prospectively evaluated for study enrollment. All patients with documented stable angina pectoris were screened 2 days in advance of the procedure by a cardiologist and a nurse clinician, and informed consent was obtained according to Institutional Review Board guidelines. A complete blood count, electrocardiogram (ECG), biochemistry screen and coagulation profile were obtained at that time. All patients were routinely prescribed aspirin (325 mg daily) and a calcium channel antagonist to minimize vascular complications (13).

Enrollment was not restricted because of advanced age, presence of multivessel or multilesion coronary artery disease,

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previous coronary bypass surgery or previous coronary angioplasty. Patients were excluded if recent myocardial infarction, uncompensated left ventricular dysfunction, valvular heart disease, coagulopathy, significant renal dysfunction or unstable anginal symptoms were present. Patients scheduled for mechanical or laser atherectomy were also excluded as were patients with totally occluded target vessels or vessels associated with known thrombus, an ostial stenosis or excessive angulation (American College of Cardiology/American Heart Association [ACC/AHA] Type C lesions). Those who lived >1 h travel time from the hospital were also excluded.

Cardiac telemetry unit. All patients reported to a previously described 22-bed cardiac unit established for intermediate level postangioplasty nursing care (7). Patients were admitted 1 to 2 h before the procedure. The unit is equipped with hemodynamic and ECG telemetry monitoring. Preprinted order sheets were used to standardize patient care and minimize protocol deviations. The unit was administratively considered an outpatient facility but patients could be reassigned to inpatient status without need for bed transfers. Angioplasty procedures were performed only when a backup cardiovascular surgical team was available.

Procedural technique. Randomization was performed by means of sealed envelopes. Percutaneous 7F or 8F vascular sheaths were inserted by direct femoral artery approach. Alternatively, a direct arteriotomy was performed when brachial artery access was required. Every patient received an initial bolus of 10,000 to 15,000 U of intravenous heparin and 5,000 additional U every 60 min during the procedure. Intracoronary nitroglycerin (200 mcg) was administered before the lesion was crossed, and the dose was repeated when necessary. Percutaneous transluminal coronary angioplasty was performed by standard techniques (14,15). Transvenous pacing wires and nonionic contrast medium were not routinely used. Angiographic results were reviewed by digital or videotape replay, or both; cineangiograms were processed and available for detailed review by the operator whenever necessary before completion of the procedure.

Randomization. All patients with favorable angioplasty results were assigned to the abbreviated or the prolonged heparin infusion study arm (Fig. 1). Neither the patient nor the physician was aware of the randomized treatment assignment until coronary dilation was performed. Patients who developed significant intraprocedural complications or had recognized high risk angiographic abnormalities (complex or extensive arterial dissection or intracoronary thrombus formation) were excluded (7,16). These patients were directed to extended inpatient observation and management. Other contraindications to heparin randomization included abrupt vessel closure, need for emergency bypass surgery, use of thrombolytic therapy or severe intraprocedural hypotension or bleeding.

Postprocedural management. Patients were returned to the telemetry observation unit immediately after coronary angioplasty. Administration of aspirin, intravenous nitroglycerin and calcium channel antagonists was routinely continued. Patients in the abbreviated treatment arm had the vascular sheath removed within 3 to 4 h of the procedure unless the activated clotting time exceeded 150 s. Patients assigned to prolonged anticoagulation received a continuous heparin infusion (10 U/kg per h) for 24 h. The dose rate of heparin was titrated to maintain the activated clotting time level between 160 and 190 s according to a standard sliding scale employing serial activated clotting time measurements at 4- to 6-h intervals. All sheaths were removed manually by trained nonphysician personnel or by a cardiology fellow. In all cases, ambulation was encouraged after 6 h of strict bed rest and inguinal compression by a 10-lb (4.5 kg) sandbag. The inguinal area was inspected and the patient was given discharge instructions. Patients were contacted by a nurse clinician 1 to 2 days after discharge to assess for delayed vascular complications and symptom status. All participating physicians were required to report any related out-of-hospital complications.

Data collection. Historical details, clinical data and the results of coronary angioplasty were prospectively recorded. The length of hospital stay (total hours after coronary angioplasty) and reasons for transfer to an inpatient unit were recorded. If a complication or contraindication to heparin randomization was identified, the patient's location and the time in relation to coronary angioplasty were noted. Complications including death, acute myocardial infarction, need for emergency bypass surgery, acute coronary occlusion syndrome and unstable angina (with or without ECG changes) were considered major complications under all circumstances. Other clinical complications included arrhythmias, excessive local bleeding or hematoma formation, need for blood transfusion and need for subsequent reevaluation or readmission.

A computer-generated list of complete patient charges was obtained from the hospital financial services department. The total hospital charge for each patient was recorded.

Statistics. The chi-square and Fisher exact test were used to determine differences between treatment groups. Data are expressed as mean value ± SD. Sample size was modeled after previous studies of early hospital discharge after acute myocardial infarction (17) and elective cardiac catheterization (4). Sample size calculations based on end point analysis were not prospectively performed.
Table 1. Baseline Demographics

<table>
<thead>
<tr>
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<th>Abbreviated Heparin Therapy (n = 145)</th>
<th>24-h Heparin Therapy (n = 139)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>60 ± 10</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Angina class</td>
<td>2.4 ± 0.9</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Smoking</td>
<td>14%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or percent of patient group. No differences between groups were significant. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Results

Study patients. During the study period a total of 1,611 outpatients were evaluated as potential study candidates, and 400 patients (25%) consented to enrollment into the study. One hundred sixteen patients were excluded after enrollment either because they did not undergo anticipated concurrent angioplasty during diagnostic cardiac catheterization or because attempted balloon dilation could not be performed (Fig. 2).

Clinical characteristics. The baseline demographic characteristics of these patients are shown in Table 1. There were no statistically significant differences between the treatment groups. The prolonged and abbreviated heparin therapy groups were also similar with respect to preprocedure adverse prognostic risk factors. Of the 284 patients who underwent balloon dilation, 139 were randomized to receive 24 h of continuous heparin therapy and 145 to receive no additional heparin. A total of 368 stenoses were dilated (1.3/patient) with 210 patients undergoing single-vessel and 76 patients multivessel procedures.

Outcome. On the basis of angiographic findings assessed during the procedure, 46 patients were excluded after randomization in the catheterization laboratory and were triaged to inpatient management (Fig. 2). Excluded patients were evenly distributed between the two heparin therapy groups. All of the remaining 238 patients completed the study. Of the 46 excluded, 11 patients developed evidence for acute myocardial infarction, 2 received intraaortic balloon pump support and 2 required cardiopulmonary resuscitation. Two of these 46 patients required coronary bypass surgery and none of the 46 died. Additional reasons for angiographic exclusion are listed in Table 2.

Minor complications. Among the 118 patients randomized to abbreviated heparin therapy, 30 underwent additional observation because of physician preference related to minor postprocedure complications. Reasons included procedural complexity (n = 9), “hazy” or “irregular” results (n = 8), ventricular arrhythmias (n = 2), atypical chest pain (n = 2), gastric bleeding (n = 1), dye allergy (n = 1) and guide catheter-induced dissection (n = 1). The remaining six patients were observed solely because of patient or physician request. Twenty-seven of these patients received additional intravenous heparin for a median period of 13 h. Ingual hematoma formation and episodes of local bleeding were significantly more common in the group receiving 24-h anticoagulation. Data reflecting treatment received are shown in Table 3.

Major complications. One major event occurred 2 h after angioplasty in the abbreviated heparin therapy group. The patient developed acute vessel occlusion syndrome and despite successful catheter-directed thrombolysis, a non-Q wave myocardial infarction developed (Table 3). There were no other major cardiac complications in either group. No delayed complications were reported by the participating physicians.

Hospital utilization. The average length of hospital stay for all patients randomized to the abbreviated heparin therapy group was 23 ± 11 h in contrast to the significantly longer stay (42 ± 24 h, p < 0.001) in the prolonged heparin infusion group. Eighty-five patients (72%) in the abbreviated therapy group were discharged within 24 h and 22% were discharged within 14 h of the procedure (Fig. 3). The mean hospital charge was $6,093 ± $1,772 for those receiving abbreviated heparin therapy versus $7,463 ± $1,782 for those receiving 24-h heparin infusion (p < 0.001).

Table 2. Angiographic Exclusions

<table>
<thead>
<tr>
<th>Dissection</th>
<th>17</th>
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<tr>
<td>Thrombolytic therapy</td>
<td>11</td>
</tr>
<tr>
<td>Abrupt vessel closure</td>
<td>10</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>3</td>
</tr>
<tr>
<td>Intracoronary thrombus</td>
<td>2</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>1</td>
</tr>
<tr>
<td>Left main coronary artery spasm</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
</tr>
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</table>

CABG = coronary artery bypass graft surgery.
equipment design and procedural techniques, less scientific attention has been applied to improving or streamlining management strategies after the procedure (7.X,11). Outpatient diagnostic cardiac catheterization has already become widely accepted at most institutions. The incidence of observed complications in outpatients is equal to or less than that for procedures previously performed on an inpatient basis (1-5).

Similarly, outpatient peripheral angioplasty has gained favor and has been shown to be safe (18,19). On the basis of data from our pilot study (7), we expected that a similar approach with carefully selected patients after an uncomplicated coronary angioplasty procedure could be safe, clinically practical and less expensive.

**Patient safety and risk stratification.** The baseline clinical characteristics in our study group are similar to those of the National Heart, Lung, and Blood Institute Registry Cohort, Emory University, Cleveland Clinic and other larger study populations (9,10,20,21). Nevertheless, we emphasize that patient selection and triage algorithms developed for the current study were deliberately conservative and always favored in-hospital management when clinical uncertainties arose. Only patients with a low risk profile and uncomplicated coronary anatomy were considered, and only patients with stable angiographic appearance after coronary angioplasty were studied. Patients presenting with the specific adverse prognostic risk factors identified in the Methods section were excluded from the study and preferentially directed to inpatient management because of their higher rate of acute procedural failure (15,22,23). Conversely, scheduled catheterization with possible concurrent angioplasty was not specifically excluded by our protocol because others (24) have shown combined procedures to be safe and effective.

Catheterization laboratory triage criteria focused primarily on immediate procedural results. For this reason predilation angiographic morphology as such was not used to evaluate eligibility for study. Important predictors of delayed complications are provided by postprocedure angiographic and clinical findings (22,25). Moreover, it has been shown (15,17) that a significant residual stenosis or a complex intimal dissection increases the risk of abrupt closure. The presence of an intraluminal thrombus has also been associated with a marked increase in acute complications (23,26). We believe that the present study is the first to attempt to use these data in a prospective fashion to stratify patients by risk after coronary angioplasty. The benign course for the 284 patients enrolled in either treatment arm suggests that clinically low risk cases can be prospectively defined.

**Complications.** Despite the excellent immediate angiographic results of coronary angioplasty, 2% to 4% of patients experience sudden vessel occlusion unexpectedly. Up to 80% of acute coronary complications occur before the patient leaves the catheterization laboratory and 90% of complications occur within 6 h after the procedure (9,10,20,22,25). Moreover, nearly two thirds of these patients with initially “uncomplicated” results will demonstrate hypotension, persistent ECG...

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**Table 3. Clinical Outcome**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Heparin Therapy</th>
<th>24-h Heparin Therapy</th>
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</thead>
<tbody>
<tr>
<td>Entered/Enrolled</td>
<td>118/145</td>
<td>120/139</td>
</tr>
<tr>
<td>Delayed closure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemothroma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Length of stay (h)</td>
<td>23.2 ± 11</td>
<td>43.3 ± 24</td>
</tr>
<tr>
<td>Charge ($)</td>
<td>6,093 ± 1,772</td>
<td>7,463 ± 1,782*</td>
</tr>
</tbody>
</table>

*p < 0.001. Data presented are mean value ± SD or number of patients in group. Abbreviations as in Table 1.

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**Discussion**

Percutaneous transluminal coronary angioplasty is now an established and relatively safe alternative to coronary bypass surgery for the management of coronary artery disease. Despite the remarkable emphasis on improving imaging quality, equipment design and procedural techniques, less scientific attention has been applied to improving or streamlining management strategies after the procedure (7,8,11). Outpatient diagnostic cardiac catheterization has already become widely accepted at most institutions. The incidence of observed complications in outpatients is equal to or less than that for procedures previously performed on an inpatient basis (1-5).

**Figure 3. Duration of hospital stay for 284 patients randomized before angioplasty to receive either an adjusted 24-h heparin infusion (solid bars) or saline solution (open bars) after a successful procedure.**
changes or prolonged chest pain during the balloon procedure. The rare instance of delayed acute occlusion after a totally uncomplicated procedure most often occurs shortly after discontinuation of heparin therapy (27). As a matter of practice, a patient with such delayed occlusion would necessarily have developed complications before hospital discharge in the current study, because ambulation occurs at least 8 to 10 h after normalization of blood coagulation. Whether continuous prolonged intravenous heparin administration reduces the incidence of subacute coronary complications cannot be answered by this study; however, Ellis et al. (12) have shown that a similar strategy—prolonged heparin infusion after early sheath removal—does not decrease the frequency of abrupt vessel closure.

Our study design also prevents meaningful assessment of any adverse events that developed 3 to 7 days after the procedure, although none were reported. Experience suggests that the risk of unforeseen abrupt vessel closure occurring ≥3 days after an uncomplicated angioplasty procedure is extremely low (7). In addition, recent ACC/AHA Task Force guidelines (23) indicate that patients can be safely discharged within 24 to 48 h after an uncomplicated angioplasty procedure.

Bleeding complications related to vascular access were significantly more frequent in the group with prolonged heparin infusion. Despite strict guidelines, heparin was prematurely discontinued because of bleeding in 10% of patients. Similarly, Ellis et al. (12) have shown that an 18- to 24-h heparin infusion, despite early removal of the vascular sheaths after angioplasty, doubles the incidence of significant bleeding to ≥8%. The two major factors that have been shown to affect local hemostasis are vascular sheath size and the duration of anticoagulation (28-30). Our data are consistent with the latter observation. Potential late vascular sequelae such as pseudoaneurysm and arteriovenous fistula formation may not have been identified in the current study because of the brief follow-up period. The incidence of such complications ranges between 0.5% to 1.0% and the diagnosis is usually delayed for several days to weeks (29).

Cost savings. As a result of early sheath removal and ambulation, patients who did not receive a prolonged heparin infusion were often ready for discharge within 12 h of the angioplasty procedure. Some patients were observed for a slightly longer period, usually to avoid late night or predawn discharge. Nonetheless, early ambulation and discharge were significantly more economic. By reducing hospital utilization, total charges were reduced by nearly $1,400/patient in the abbreviated heparin therapy group. This finding parallels outpatient diagnostic cardiac catheterization charge savings that have been reported to range from $580 to $933 (4.31). On the basis of our study enrollment rate, 25% (400 of 1,611) of the patients undergoing the estimated 300,000 coronary angioplasty procedures performed annually in the United States would be eligible for consideration and three fourths of these patients could be successfully treated. The health care cost savings yielded by this strategy could approach $100 million/year.

Study limitations. It must be emphasized that a stable, low risk group of patients with acceptable angiographic results after coronary angioplasty were randomized. These findings cannot be extrapolated to patients with an acute ischemic syndrome or unstable angiographic results. Because of the need for informed consent, patients were enrolled before the catheterization procedure. Forty-six patients were subsequently excluded and operator bias may have influenced this decision. Finally, the small sample study precludes definitive proof of safety. During this study cumulative major cardiac events (death, myocardial infarction or emergency bypass surgery) occurred in 6.7% of patients in our institution. To have sufficient power to detect a 50% increase in cardiac events would have required a study of 800 patients. The rate of major adverse events (1 of 238, 0.4%) was in fact so low that thousands of patients would have been required to adequately power this end point.

Conclusions. Our study suggests that early discontinuation of intravenous administration of heparin and vascular sheath removal after uncomplicated coronary angioplasty is convenient and reduces bleeding complications without increasing patient risk. Early discharge and significant cost savings are possible if prudent patient selection and conservative triage criteria are observed. As experience increases, expanding the protocol to include patients with reduced left ventricular function or concurrent medical illnesses may be feasible.

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References


