Randomized Trial Comparing Intravenous Nitroglycerin and Heparin for Treatment of Unstable Angina Secondary to Restenosis After Coronary Artery Angioplasty

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Background—The treatment of unstable angina targets the specific pathophysiological thrombotic process at the site of the active culprit lesion. In unstable angina due to a restenotic lesion, smooth muscle cell proliferation and increased vasoreactivity may play a more important role than thrombus formation. Therefore, the relative benefits of nitroglycerin and heparin might differ in unstable angina associated with restenosis compared with classic unstable angina.

Methods and Results—We randomized 200 patients hospitalized for unstable angina within 6 months after angioplasty (excluding those with intracoronary stents) to double-blind administration of intravenous nitroglycerin, heparin, their combination, or placebo for 63±30 hours. Recurrent angina occurred in 75% of patients in the placebo and heparin-alone groups, compared with 42.6% of patients in the nitroglycerin-alone group and 41.7% of patients in the nitroglycerin-plus-heparin group (P<0.003). Refractory angina requiring angiography occurred in 22.9%, 29.2%, 4.3%, and 4.2% of patients, respectively (P<0.002). The odds ratios for being event free were 0.24 (95% CI, −0.13 to 0.45, P=0.001) for nitroglycerin versus no nitroglycerin and 0.98 (95% CI, −0.55 to 1.73, P=NS) for heparin versus no heparin. No patient died or suffered myocardial infarction.

Conclusions—Intravenous nitroglycerin is highly effective in preventing adverse ischemic events (recurrent or refractory angina) in patients with unstable angina secondary to restenosis, whereas heparin has no effect. (Circulation. 2000;101:955-961.)

Key Words: angina □ restenosis □ nitroglycerin □ heparin □ ischemia

The central role of an active atheromatous plaque in the pathophysiological substrate of unstable angina is well recognized. Flow reductions causing acute ischemia are mainly due to platelet aggregation and thrombus formation on ulcerated plaques and active vasoconstriction, mediated by such substances as serotonin, thromboxane A₂, thrombin, and endothelin. Unstable angina may also involve a systemic procoagulant state with increased proaggregant platelet activity and decreased fibrinolytic activity. Accordingly, anticoagulant therapy with heparin and antiplatelet therapy with aspirin or glycoprotein IIb/IIIa receptor antagonists are effective to prevent complications in unstable angina.

Restenosis after PTCA remains a major limitation, occurring in 25% to 45% of dilated lesions. Symptomatic restenosis usually presents within 3 months of the procedure. The presenting symptom in most cases is exertional angina, but unstable angina occurs in up to 41% of patients and in 68% of patients whose PTCA was initially performed for rest angina.

Neointima formation caused by smooth muscle cell proliferation and extracellular matrix production is a prominent feature in restenotic lesions. Angioscopy in patients with restenosis commonly reveals white, unpigmented, smooth, and fibrotic lesions, in contrast to the yellow or brown pigmentation observed in primary nonrestenotic lesions. One report of angioscopic findings in 4 patients with unstable angina after PTCA described white, unpigmented lesions with intracoronary mural thrombi firmly attached to the wall of the artery, contrasting with the lining, or protruding white thrombus and unstable plaques, often ulcerated, in nonrestenotic unstable angina. Various authors have shown an association between coronary vasoconstriction and restenosis, and unpublished data from our laboratory indicate increased vasoreactivity to acetylcholine at PTCA sites in the 6 months after the procedure. These findings, along with the favorable prognosis of unstable angina associated with restenosis, suggest different pathophysiological mechanisms compared with classic unstable angina. The differences are also

Received July 23, 1999; revision received September 14, 1999; accepted September 29, 1999.
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reflected in a different clinical course of unsuccessfully treated unstable angina associated with restenosis versus the classic form: in the latter, death and myocardial infarction are the main complications, whereas in post-PTCA cases, refractory angina is the major problem.

On the basis of the importance of smooth muscle cell proliferation and increased vasoreactivity in unstable angina secondary to restenosis, we speculated that intravenous nitroglycerin might be particularly effective in preventing recurrent ischemia and that heparin might be less useful, considering the rarity of more severe thrombotic complications (myocardial infarction and death) in this setting. This study was therefore designed as a 2×2 factorial double-blind, placebo-controlled, randomized trial comparing intravenous nitroglycerin, heparin, a combination of the 2, or neither in the treatment of unstable angina secondary to restenosis.

Methods

Patient Population

All patients admitted to the Montreal Heart Institute with a diagnosis of unstable angina within 2 weeks to 6 months after coronary angioplasty were considered for the study. The 2-week asymptomatic period was necessary to exclude patients with poor initial angioplasty results and the 6-month upper limit to exclude patients more likely to show progression in native coronary disease than restenosis.\(^{24,25}\) Unstable angina was defined as recurrent or increased frequency of chest pain lasting >5 minutes at rest or with minimal exertion within 24 hours before randomization. In the absence of ischemic ECG changes (>1 mm ST-segment depression or new T-wave abnormalities), inclusion required independent confirmation of the diagnosis of unstable angina by 2 cardiologists.

Exclusion criteria included vein or internal mammary artery bypass graft as the target lesion, ST-segment elevation lasting ≥30 minutes, indication for thrombolytic treatment, new Q wave on the postangioplasty ECG, stent implantation or atherectomy during the last procedure, contraindication to heparin or nitroglycerin, bypass surgery within the previous 6 months, previous participation in the trial, or medical contraindication to repeated angiography and/or angioplasty. The protocol was approved by the Institutional Review Board, and all patients signed an informed consent form. Recruitment began November 25, 1993, and ended on July 20, 1996.

Study Medication and Protocol

The trial medications were prepared and coded for each patient by the hospital pharmacist. The 4 treatment groups were (1) intravenous nitroglycerin infusion plus placebo heparin, (2) intravenous heparin 5000 U bolus followed by infusion at 1000 U/h (1200 U/h for patients weighing ≥80 kg) plus placebo nitroglycerin, (3) intravenous nitroglycerin plus intravenous heparin, and (4) placebo nitroglycerin plus placebo heparin.

Intravenous nitroglycerin/placebo was diluted in 5% dextrose in water and infused at an initial rate of 30 μg/min. If well tolerated, the infusion rate was increased by 25 μg/min every 12 hours to overcome nitrate tolerance. When headache occurred, acetaminophen (325 to 650 mg every 6 hours) was given, and the nitroglycerin/placebo infusion was decreased by 10 μg/min. The heparin infusion rate was lowered by 10 μg/min for systolic pressure <100 mm Hg and was temporarily interrupted for pressure <80 mm Hg. The heparin infusion rate was adjusted according to the activated partial thromboplastin time (aPTT). aPTT results were known only to the pharmacist, who modified the infusion rate according to a predefined algorithm to maintain the aPTT at 1.5 to 2 times control values. Infusion rates of placebo solutions were also modified to maintain blinding. Recurrent chest pain was treated with sublingual nitroglycerin (0.4 to 0.8 mg) followed by an increase of the nitroglycerin/placebo infusion by 25 μg/min. An acceleration of symptoms despite treatment was an indication for urgent catheterization or administration of open-label heparin and nitroglycerin, without unblinding.

Aspirin (325 mg/d) was given to all patients. β-Blockers or calcium antagonists were allowed, but the use of open-label nitroglycerin and any nitrate preparation was prohibited (except for patients with accelerated symptoms, as described in the preceding paragraph). Only 2 patients were receiving long-acting nitrates at the time of randomization. ECGs were obtained before randomization, daily thereafter, and whenever chest pain occurred. Creatine kinase and MB fraction were measured before randomization, every 6 hours for 24 hours, and daily until coronary angiography. A coronary angiogram was performed 48 to 96 hours after randomization or earlier if clinically required. Study medications were stopped just before angiography, marking the end of the trial and the time for collection of end-point data. After administration of 2000 U heparin and of intracoronary nitroglycerin (0.3 mg), multiple orthogonal views of the previously dilated coronary segment were obtained. Quantitative angiographic measurements in the single projection showing the most severe stenosis were made by experienced cardiovascular radiologists blinded to treatment assignment.

End Points

Recurrence of angina was the primary end point of the trial, because unstable angina associated with restenosis rarely results in myocardial infarction or death but has a high rate of recurrent symptoms.\(^{16,24}\) Angina was classified as class 1 in the absence of ECG changes, class 2 when accompanied by transient ST-T changes, class 3 when lasting ≥20 minutes with ST-T changes, and class 4 when refractory to medical management and requiring administration of open-label nitroglycerin and heparin or urgent angiography.

Statistical Analysis

On the basis of an expected 50% rate of recurrent angina, 200 patients were necessary to detect a 40% risk reduction at a power of 80% with a 2-tailed α-value of 0.05. All events were classified before unblinding. Baseline characteristics were compared by t-test and χ² statistics. Event rates were compared by 2-tailed χ² statistics, odds ratios, and 95% confidence limits. Logistic regression analysis was used to test potential interactions between treatments. Results were analyzed by the intention-to-treat principle.

Results

The study population included 11% (200 of 1810) of all patients who had angiography at the Montreal Heart Institute because of recurrent chest pain after angioplasty during the recruitment period. Of the 1810 patients, 1176, or 65%, had exertional angina and were excluded. Of the 634 remaining patients with unstable angina, 434 had exclusion criteria or were initially admitted to another institution, precluding their participation in the trial. Selected baseline characteristics of the study groups are shown in Tables 1 and 2. No significant differences were observed. Protocol deviations were noted in 9 patients. The study medication was started >24 hours after the most recent episode of chest pain in 2 patients. Repeat angiography was not performed in 2 patients (1 patient referred to surgery and the other treated medically). One patient had had a stent implanted at the previous angioplasty, and the target lesion was a vein graft in one. The study drug was discontinued prematurely in 2 patients who refused continued participation in the trial, and 1 patient was included in the trial twice during different hospitalizations. Of the patients with protocol violations, 3 were in the nitroglycerin-alone group, 2 in the heparin group, 2 in the combination group, and 2 in the placebo group. The results were unchanged by inclusion or exclusion of these patients.
Of the 191 remaining patients, 157 (83%) had angiographic restenosis (≥50% by quantitative angiography). Of the 34 patients without restenosis, 11 (5.6%) had a new stenosis ≥50% in a coronary artery segment different from the one that had been dilated. The patients without restenosis were equally distributed among the 4 study groups. Use of concomitant oral medication was comparable among treatment groups.

**End Points**

Recurrence of angina was observed in 112 patients (58.6%): class 1, 29.8%; class 2, 7.3%; class 3, 6.3%; and class 4 (refractory angina), 15.2%. The distribution of different angina classes for each treatment group is provided in Table 3.

Recurrent angina occurred in 42.6% of patients treated with nitroglycerin alone, 41.7% of patients treated with nitroglycerin + heparin, 40.8% of patients treated with heparin, and 41.7% of patients treated with placebo. The distribution of different angina classes for each treatment group is provided in Table 3.
nitroglycerin plus heparin, 75% of patients treated with heparin alone, and 75% of patients receiving placebo ($P<0.003$ for nitroglycerin alone and for nitroglycerin plus heparin versus placebo, Figure 1A). Refractory angina (class 4) occurred in 2 of 47 patients (4.3%) for nitroglycerin, 2 of 48 patients (4.2%) for combined treatment, 14 of 48 patients (29.2%) for heparin, and 11 of 48 patients (22.9%) for placebo ($P<0.002$ for nitroglycerin and nitroglycerin plus heparin versus placebo, Figure 1B). No interaction was detected between nitroglycerin and heparin effects by logistic regression ($P=0.954$ for recurrent angina and $P=0.757$ for class 4 refractory angina). In the absence of interaction, the factorial design permits analysis of all patients receiving nitroglycerin versus those treated with nitroglycerin placebo. The combined analysis, shown in Figure 2, indicates a highly significant difference in outcome by presence or absence of nitroglycerin therapy but no difference for heparin. The odds of recurrent angina for nitroglycerin versus no nitroglycerin was 0.24 (95% CI, 0.13 to 0.45, $P=0.0001$) and for heparin versus no heparin, 0.98 (95% CI, 0.55 to 1.73, $P=NS$). The results were unchanged by multivariate analyses controlling for all variables included in Tables 1 and 2. There were no deaths or myocardial infarctions in the study. Complications and side effects were relatively infrequent (Table 4).

Of the patients with protocol violations, 2 of the 5 receiving nitroglycerin and 3 of the 4 without nitroglycerin had recurrent angina. Inclusion of these patients did not change the results, with recurrent angina in 40% of patients with nitroglycerin alone, 44% with combined nitroglycerin and heparin treatment, 76% with heparin alone, and 74% with placebo ($P<0.0001$). Results were also analyzed by severity of restenosis, with severe stenosis defined as ≥70%. The recurrent angina rate with nitroglycerin therapy was 32% in the 53 patients with restenotic lesions <70% and 56% in 34 patients with restenotic lesions ≥70%. In the group that did not receive nitroglycerin, 74% of the 57 patients with no severe restenosis and 71% of 28 patients with severe restenosis had recurrent angina. In a multivariate logistic regression including the severity of the restenosis, nitroglycerin use remained highly predictive of absence of angina ($P=0.0003$), with odds of 0.17 (95% CI, −0.07 to 0.38) for recurrent angina in patients with severe restenosis and of 0.51 (95% CI, −0.18 to 1.47) for patients whose restenosis was not severe ($P=0.11$ for <70% versus ≥70%).

**Discussion**

In the present study, the administration of intravenous nitroglycerin markedly reduced the occurrence of angina and the

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**TABLE 3. Recurrence of Angina (Class 1 to 4) for Each Treatment Group**

<table>
<thead>
<tr>
<th>Complication, %</th>
<th>Nitroglycerin (n=47)</th>
<th>Heparin (n=48)</th>
<th>Nitroglycerin+Heparin (n=48)</th>
<th>Placebo (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>32</td>
<td>33</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Class 2</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Class 3</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Class 4</td>
<td>4</td>
<td>29</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

Class 1 indicates no ECG changes; class 2, transient ST-T changes; class 3, pain lasting ≥20 minutes with ST-T changes; and class 4, angina refractory to medical management and requiring administration of open-label nitroglycerin and heparin and/or urgent angiography.

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**Figure 1.** Rates of recurrent angina for the 4 study groups. A, Classes 1 to 4. B, Class 4 only, refractory angina.

**Figure 2.** Rates of recurrent angina for (A) nitroglycerin-treated patients versus no-nitroglycerin–treated patients (heparin alone or placebo) and for (B) heparin-treated patients versus no-heparin–treated patients (nitroglycerin alone or placebo).
The diagnosis of unstable angina is partly subjective and the end point of recurrent pain relatively soft. Transient diagnostic ST-T changes were not required for enrollment, because many patients presenting with unstable angina due to restenosis fail to show ECG changes. Nitroglycerin was more effective in preventing episodes of chest pain associated with severity of recurrent angina among patients hospitalized for unstable angina within 6 months of coronary angioplasty. Heparin alone showed no such benefit, and the addition of heparin to nitroglycerin did not improve treatment efficacy.

**Comparison With Previous Findings in the Literature**

The accepted standard therapy for unstable angina has been aspirin and heparin. The pathophysiological mechanism of ischemia in unstable angina unrelated to PTCA is a primary reduction in myocardial oxygen supply by thrombosis and ischemia in unstable angina unrelated to PTCA. Common clinical practice is to apply the same medical therapy as for other patients with this diagnosis, specifically heparin and aspirin, and to perform coronary angiography and angioplasty to relieve the recurrent obstruction.

No comparative studies exist on the efficacy of medical therapy in patients with unstable angina within 6 months of PTCA. Common clinical practice is to apply the same medical therapy as for other patients with this diagnosis, specifically heparin and aspirin, and to perform coronary angiography and angioplasty to relieve the recurrent obstruction.

The present study showed that nitroglycerin was very effective in preventing symptoms due to recurrent ischemia in such patients, whereas heparin was not.

**Potential Implications**

The clinical pattern and the timing of presentation are important predictors of restenosis when a patient returns with chest pain after PTCA. Patients presenting with unstable angina after angioplasty are at very high risk of having angiographic restenosis, consistent with our angiographic findings. The rate of recurrent angina was high in our patients and was strongly reduced by intravenous nitrates (from 75% in the placebo/heparin groups to 42% in the nitrate/combined groups). The effect on refractory angina was even more striking, reaching an 85% reduction with nitroglycerin (decreasing from 26% in the no-nitroglycerin groups to 4% in the nitroglycerin groups). These findings suggest that intravenous nitroglycerin may have a particularly useful role to play in the treatment of patients with unstable angina within 6 months of PTCA. Conversely, the lack of efficacy of heparin in these patients and the low rate of serious complications suggest that routine heparin therapy is not indicated and, indeed, that hospitalization in a coronary care unit environment may not be necessary.

Our observations have potential pathophysiological implications. The superior efficacy of nitroglycerin compared with heparin therapy in preventing recurrent ischemic events points to a primary role of abnormalities in coronary vasoreactivity, rather than thrombosis, in patients with unstable angina due to restenosis after PTCA, consistent with previous observations in the literature. In view of the apparently important role of coronary vasoreactivity, some patients with borderline lesions may be managed with nitrates (assuming that this vasospastic phase is only transient); repeat angioplasty may occasionally not be necessary. Another potential approach could be the systematic use of nitrate therapy after coronary angioplasty. Given the fact that spontaneous regression of mild restenotic lesions over time has been observed, nitrates or other coronary vasodilators could help to overcome the period of exaggerated and abnormal vasoreactivity and allow stabilization and better healing of the restenotic plaque in the first 6 months after angioplasty. This strategy might avoid unnecessary invasive procedures, prevent a “restenosis cycle,” and result in significant cost savings. Because restenosis remains a major drawback of coronary angioplasty, even with the widespread use of stents, new avenues to lower the need for reintervention are desirable, and further study of this approach is warranted.

**Study Limitations**

The diagnosis of unstable angina is partly subjective and the end point of recurrent pain relatively soft. Transient diagnostic ST-T changes were not required for enrollment, because many patients presenting with unstable angina due to restenosis fail to show ECG changes. Nitroglycerin was more effective in preventing episodes of chest pain associated with...
ischemic ST segment changes and more severe ischemic episodes requiring urgent intervention. The lesser efficacy of nitroglycerin among patients without ECG abnormalities may have been due to dilution by patients with nonischemic chest pain.

We found that nitroglycerin was associated with greater efficacy in patients with less severe angiographic restenosis (stenoses <70%). It is tempting to speculate that these patients had a more important vasoconstrictive component to their symptoms, accounting for the greater efficacy of nitroglycerin. However, before we conclude that nitroglycerin has more benefit for patients with less severe restenotic lesions because symptoms due to such lesions involve a larger element of vasospasm, it should be remembered that all angiograms were obtained after intracoronary nitroglycerin administration. Thus, these lesions may have appeared less severe at angiography because they were more responsive to nitroglycerin, explaining the greater benefit.

It is uncertain whether our results can be extrapolated to patients with in-stent restenosis causing unstable angina. Recent studies, particularly serial intravascular ultrasound observations, have demonstrated that the mechanism of restenosis after angioplasty without a stent involves not only neointimal hyperplasia but also chronic geometric remodeling of the treatment site. Conversely, restenosis after stent implantation seems to be caused purely by stent-related increases in cellular proliferation. If increased vasoreactivity and smooth muscle cell proliferation explain the efficacy of intravenous nitroglycerin in unstable angina after angioplasty, in-stent restenosis should also be responsive to nitroglycerin. An appropriately designed clinical trial including patients with in-stent restenosis is needed to resolve this important issue. For the moment, it should be kept in mind that unstable angina early after stent implantation may be due to stent thrombosis, for which intravenous heparin may constitute an important part of the therapy. This complication usually occurs in the first 2 weeks after angioplasty.

Another point to remember is that unstable angina after PTCA is not a monolithic entity. Although most cases are related to restenosis, some may occur in association with new severe coronary artery lesions and might therefore display a pathophysiology more similar to classic unstable angina. Such patients may benefit from heparin therapy. Prolonged rest pain and presentation >3 months after angioplasty might help identify such individuals. In our trial, only 11 patients (5.7% of the study population) had a new stenosis of ≥50% in another coronary segment.

It can be concluded from our study that intravenous nitroglycerin is highly effective to prevent recurrent angina and refractory angina requiring urgent intervention in patients with unstable angina in the 6 months after PTCA, whereas heparin has no benefit. This patient population constitutes a low-risk subgroup in which the antithrombotic therapy used for classic unstable angina is not usually needed. These observations have significant practical implications for the management of patients presenting with unstable angina after coronary artery angioplasty.

References


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_Circulation_. 2000;101:955-961
doi: 10.1161/01.CIR.101.9.955
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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