Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial

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ABSTRACT The value of the addition of β-blockers to coronary vasodilator therapy in the treatment of patients with unstable angina at rest is controversial. We conducted a double-blind, randomized, placebo-controlled 4 week trial of propranolol in 81 patients with unstable angina, 39 of whom were assigned to placebo and 42 of whom received propranolol in a dose of at least 160 mg daily. All patients were also treated with coronary vasodilators, including 80 mg nifedipine daily and long-acting nitrates. The incidences of cardiac death, myocardial infarction, and requirement for bypass surgery or coronary angioplasty did not differ between the two groups (propranolol = 16; placebo = 18). The propranolol group had a lower cumulative probability of experiencing recurrent resting angina than the placebo group (p = .013), and over the first 4 days of the trial the mean number of clinical episodes of angina (propranolol 0.9 ± 0.2, placebo 1.8 ± 0.3, p = .036), duration of angina (propranolol 15.1 ± 4.3 min, placebo 38.1 ± 8.4, p = .014), and nitroglycerin requirement (propranolol 1.1 ± 0.3 tablets, placebo 3.5 ± 0.8, p = .003) were also fewer. Continuous electrocardiographic recording for ischemic ST segment changes revealed fewer daily ischemic episodes in the propranolol group (2.0 ± 0.5) than in the placebo group (3.8 ± 0.7, p = .03), and a shorter duration of ischemia (propranolol 43 ± 10 min, placebo 104 ± 28 min, p = .039). Thus propranolol, in patients with unstable angina, in the presence of nitrates and nifedipine is not detrimental and reduces the frequency and duration of symptomatic and silent ischemic episodes.


THE EFFICACY of β-blockers in the treatment of patients with stable, demand-related angina has been demonstrated.1–3 Their use is controversial, however, in patients with resting angina. Although the negative inotropic and chronotropic properties of β-blockers are theoretically advantageous in the treatment of myocardial ischemia, the primary pathophysiologic event in these patients is often a reduction in coronary flow caused by coronary vasoconstriction and/or platelet aggregation.4,5 Vasoconstriction is known to occur in atherosclerotic portions of coronary arteries,6–8 and to be potentiated by β-blockade.6,9–11 Coronary vasodilator therapy, consisting of nitrates and often nifedipine, is generally used in the therapy of resting angina12–15 and these drugs may prevent the potential undesirable effects of β-blockade. Conversely, treatment with vasodilators alone may in some instances produce a significant reflex sympathetic tachycardia that may increase myocardial oxygen demand and therefore be detrimental in patients with high-grade coronary artery stenoses.16 Thus, patients with fixed atherosclerotic coronary disease and resting angina in whom coronary spasm may be superimposed on obstructive lesions may benefit from the anti-ischemic effects of
β-blockers when they are added to routine coronary vasodilator therapy.

To address this question we conducted a double-blind, randomized, placebo-controlled trial to examine whether propranolol, when administered to patients with unstable resting angina concomitantly with nitrates and nifedipine, influences (1) the incidence of myocardial infarction, death, and need for revascularization for persistent ischemia, and (2) symptoms and electrocardiographic evidence of myocardial ischemia detected by continuous electrocardiographic monitoring.

Patients and methods

Patient selection. The study population consisted of hospitalized patients with unstable angina characterized by chest pain at rest of at least 10 min duration with associated electrocardiographic changes consisting of transient ST segment depression (n = 35) or ST elevation (n = 26) of at least 1 mm 0.08 sec after the J point, or transient T wave inversion or pseudonormalization (n = 20). Informed written consent was obtained on a form that had been approved by the hospitals’ Joint Committee on Clinical Investigation. Patients were excluded if the episode of chest pain was due to or occurred within 30 days of a myocardial infarction, as evidenced by elevation of creatine kinase to twice the normal level, or if the systolic blood pressure was less than 90 mm Hg, the resting heart rate lower than 50 beats/min, or if the PR interval was 0.24 sec or more or higher degree atrioventricular block was present without a pacemaker. Patients with bronchospastic pulmonary disease, congestive heart failure, prior coronary bypass surgery, significant valvular or congenital cardiac abnormalities, or symptomatic cerebrovascular disease were also excluded.

Study design and rationale. The population studied, hospitalized patients with resting angina and accompanying electrocardiographic changes, have a relatively high incidence of early myocardial infarction, malignant ventricular arrhythmias, and continued chest pain. Aggressive medical treatment is begun, usually in the coronary care unit setting, as soon as the diagnosis is made. Long-acting nitrates and calcium antagonists are considered an integral part of this initial therapy, but the use of β-blockers, the question addressed by this study, is controversial because of the vasoconstrictor pathophysiology in these patients. For these reasons, all patients were treated immediately after randomization and without a placebo run-in period with concomitant long-acting nitroglycerin, the study drug consisting of propranolol or placebo, and a calcium antagonist. Nifedipine was chosen because of its demonstrated benefit in these patients and because there would be less likelihood of myocardial depression and conduction abnormalities in the setting of β-blockade with this drug than with other currently available calcium antagonists.

Over 90% of the patients enrolled in the study were randomly assigned to a treatment group within 24 hr of the diagnosis of unstable angina. All patients were treated with intravenous or long-acting oral or topical nitrates and nifedipine, 20 mg every 6 hr, concomitantly with the study drug—either 40 mg propranolol every 6 hr or an identical placebo tablet. The use of aspirin was not dictated by protocol because data demonstrating its beneficial effect were not available at the time of the study.

Patients who experienced recurrent episodes of resting angina associated with electrocardiographic changes on this regimen were managed according to the following protocol: The study drug dose was doubled, in a blinded fashion, to two placebo tablets or 80 mg of propranolol every 6 hr, and the nifedipine dose was increased to 30 mg every 6 hr. If patients experienced two or more episodes of pain at rest with documented electrocardiographic changes while they were on this high-dose regimen, coronary angioplasty or coronary artery bypass surgery was recommended. All patients were treated with this standard approach to the management of unstable angina, with the exception of six patients with significant left main disease and three patients with high-grade proximal single-vessel disease who were treated with coronary bypass surgery and angioplasty, respectively, on the basis of coronary anatomy alone.

Patients underwent continuous two-channel electrocardiographic monitoring during the first 2 study days. The leads used were those that had shown the most pronounced changes on the initial 12-lead electrocardiogram obtained during chest pain. The recordings were analyzed blindly and the number and total duration of ischemic episodes, defined by either ST segment depression or elevation of 1 mm or more and lasting longer than 1 min were noted. The number and duration of recurrent symptomatic episodes of chest pain and angina and the requirement for sublingual nitroglycerin tablets during hospitalization were also recorded.

Outcome variables. The primary outcome variables include the combined incidences of coronary bypass surgery or angioplasty for recurrent symptoms, myocardial infarction (prolonged chest pain associated with persistent electrocardiographic changes and elevation of creatine kinase levels to greater than twice normal with positive MB isoenzymes), and cardiac death (death occurring suddenly or after myocardial infarction). Secondary outcome variables include the number and duration of recurrent symptomatic episodes of angina, nitroglycerin consumption, and the frequency and duration of ischemic episodes on continuous electrocardiographic recordings.

Data analysis. Noncontinuous data were examined by contingency-table analysis with the chi-square test. The proportion of patients in each study arm who experienced clinical outcome events and the time dependence of these outcomes were analyzed by Kaplan-Meier actuarial curves, which were compared by a log-rank test with a two-tailed significance level. Continuous variables were analyzed by nonpaired t tests of significance. The long-term electrocardiographic data were randomized and blindly reviewed by two independent observers, an experienced technician and a physician investigator. Data are presented as mean ± SEM. The analyses include all patients originally assigned to each treatment according to the intention-to-treat principle.

Results

Patient population. Clinical characteristics of the study population are presented in table 1. Eighty-one patients were randomized; 42 were assigned to propranolol and 39 to placebo. The patients were 37 to 82 years of age and 49% were men. The majority of the patients (70%) were hospitalized in the coronary care unit at the time of randomization. There was no significant difference between the randomized groups with regard to demographic characteristics, other medications, including intravenous nitroglycerin, antiplatelet or heparin therapy, left ventricular function, or other risk factors for poor cardiovascular outcomes. Forty-nine patients underwent cardiac catheterization during
TABLE 1
Comparison of baseline characteristics of patients in the propranolol and placebo study groups.\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Propranolol (n = 42)</th>
<th>Placebo (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62 ± 11</td>
<td>61 ± 11</td>
</tr>
<tr>
<td>Nifedipine dose on entry (mg/day)</td>
<td>80 ± 19</td>
<td>76 ± 15</td>
</tr>
<tr>
<td>Topical nitrates on entry (cm²/day)</td>
<td>19 ± 9</td>
<td>21 ± 12</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>60 ± 14</td>
<td>63 ± 18</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Aspirin on entry (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dipyridamole on entry (n)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Heparin on entry (n)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Intravenous nitroglycerin on entry (n)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Prior myocardial infarction (n)</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Current cigarette use (n)</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>ST segment elevation (n)</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>&gt;70% obstruction (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Single vessel</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Double vessel</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Triple vessel</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Left main</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^a^\)Plus or minus values are mean ± SD.
\(^b^\)There is no significant difference between the two groups for any characteristic listed.

The study period and the extent of fixed obstructive disease was similar in the two groups, with 78% of the patients having double or triple vessel coronary artery disease (table 1). The mean arterial blood pressures before administration of the study drug were 94 ± 13 mm Hg in the propranolol and 91 ± 12 mm Hg in the placebo group (NS). After 2 days of therapy, the mean arterial pressures were similarly reduced in both groups and averaged 89 ± 11 mm Hg in the propranolol and 86 ± 11 mm Hg in the placebo group, respectively.

**Clinical outcomes.** Four patients (two on propranolol, two on placebo) were withdrawn from the study due to side effects. The side effects of propranolol were excessive bradycardia in one patient and hypotension and dizziness in the other. The analyses include data from all patients assigned to each treatment. The proportions of patients who experienced cardiac death, infarction, and persistent ischemia requiring angioplasty or bypass surgery are presented in table 2. There was no significant difference between the groups with regard to the incidence or the cumulative probability of experiencing any of these outcomes. Although the cumulative probabilities of these outcomes at 4 weeks were 31% and 38% in the propranolol and placebo groups, respectively (NS), almost 90% of these were surgery or angioplasty end points for persistent symptoms. There were nine myocardial infarctions, six in the propranolol group (one of which was fatal), and three in the placebo group (NS). One of the patients in the propranolol group suffered a myocardial infarction before receiving the first dose of study drug and data from this patient are included in the analysis.

Fifteen patients in the propranolol group and 19 in the placebo group required an increase in the dose of study medications due to recurrent angina (NS). The number of symptomatic episodes of resting angina, the duration of the episodes, and nitroglycerin consumption were recorded prospectively for each patient and are presented in figure 1. The mean number of total episodes of resting angina during the first 2 days of the study was significantly lower in the propranolol (0.43 ± 0.16) than in the placebo group (1.2 ± 0.27, \(p = .012\)). The total duration of angina was also shorter (propranolol 7.6 ± 2.8 min, placebo 24.3 ± 6.3 min, \(p = .016\)) and the patients assigned to propranolol required fewer sublingual nitroglycerin tablets (0.7 ± 0.3) than those assigned to placebo (2.3 ± 0.6, \(p = .012\)). Similar differences are present over the first 4 days: the propranolol group experienced significantly fewer symptomatic episodes (0.9 ± 0.2, vs 1.8 ± 0.3 in the placebo group, \(p = .036\)), a shorter duration of angina (15.1 ± 4.3 min vs 38.1 ± 8.4 in the placebo group, \(p = .014\)), and required fewer nitroglycerin tablets (1.1 ± 0.3 vs 3.5 ± 0.8 in the placebo group, \(p = .003\)). In addition, the propranolol group demonstrated a lower cumulative probability of experiencing recurrent resting angina over the 4 week study period (\(p = .013\), figure 2).

**Continuous electrocardiographic (ECG) monitoring.**
The results of continuous electrocardiographic monitoring for ischemia are presented in figure 3. The mean number of ischemic episodes per day over the first 2 days, defined as ST segment elevation or depression of 1 mm or more and at least 1 min in duration, was significantly lower in the propranolol (2.0 ± 0.5) than in the placebo group (3.8 ± 0.7, p = .03). The mean duration of ischemic episodes in minutes per day was also shorter in the propranolol (43 ± 10 min) than in the placebo group (104 ± 28 min, p = .039). Patients with T wave changes only on the initial electrocardiogram obtained during chest pain were included in the anticipation that continuous electrocardiographic monitoring would demonstrate ischemic ST segment changes as well. This in fact was found in 65% of the patients with initial T wave changes compared with 69% of those in the group with ST segment changes on the initial qualifying 12-lead electrocardiogram. When the group of patients with ST segment changes on the initial electrocardiogram was examined separately, a similar reduction in ischemic episodes was noted in the propranolol group (1.5 ± 0.5 episodes/day) compared with the placebo group (4.0 ± 0.7, p = .005).

The average heart rate during continuous electrocardiographic monitoring was lower in the propranolol (66 ± 1.5 beats/min) than in the placebo group (81 ± 2 beats/min, p < .001; table 3). The average heart rate at the onset of ischemic episodes as detected by continuous ECG recording was 70 ± 2.5 beats/min in the propranolol group and 81 ± 3.5 beats/min in the placebo group (p = .018). During the first 10 min of ischemia, the propranolol group experienced an insignifi-
TABLE 3
Heart rates (beats/min) by continuous electrocardiographic monitoring at rest and during ischemic episodes in the propranolol and placebo study groups

<table>
<thead>
<tr>
<th></th>
<th>Propranolol (n = 42)</th>
<th>Placebo (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average heart rate during first 2 days</td>
<td>66 ± 1.5</td>
<td>81 ± 2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Average heart rate prior to ischemic episodes</td>
<td>70 ± 2.5</td>
<td>81 ± 3.5</td>
<td>.018</td>
</tr>
<tr>
<td>Average heart rate during ischemic episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 min</td>
<td>73 ± 2.7</td>
<td>84 ± 3.5</td>
<td>.011</td>
</tr>
<tr>
<td>4 min</td>
<td>73 ± 2.7</td>
<td>88 ± 3.9</td>
<td>.003</td>
</tr>
<tr>
<td>6 min</td>
<td>73 ± 2.4</td>
<td>91 ± 4.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8 min</td>
<td>72 ± 2.1</td>
<td>92 ± 4.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10 min</td>
<td>72 ± 2.1</td>
<td>92 ± 4.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

FIGURE 3. The number and duration of ischemic episodes per 24 hr as detected by continuous two-channel electrocardiographic monitoring during the first 2 study days. There were significantly fewer ischemic episodes (p = .03) and a shorter duration of ischemia (p = .039) in the propranolol group.

cant change in heart rate, from 70 ± 2.5 to 72 ± 2.1 beats/min, while the patients in the placebo group had a marked increase, from 81 ± 3.5 to 92 ± 4.2 beats/min, during the same time period (p < .001). These findings indicate that adequate β-blockade was achieved in the propranolol group.

Discussion

The pathophysiology of unstable resting angina is complex, but it is currently believed to involve an interaction between fixed atherosclerotic coronary artery disease and dynamic coronary obstruction resulting from transient coronary vasoconstriction and/or thrombotic occlusion. Although propranolol is a proven therapeutic agent for stable, exertion-related angina,1–3 its benefit in patients with unstable angina when used in combination with long-acting nitrates and calcium antagonist therapy has not been thoroughly evaluated. Prior uncontrolled studies have suggested a benefit of β-blockade when used alone in this patient group,20,21 and randomized trials have reported no difference between propranolol and nitrates compared with nifedipine22 or diltiazem23 as initial therapy for unstable angina. Other studies, however, have suggested that β-blocker therapy may have no benefit, or may even provoke or exacerbate coronary vasoconstriction and anginal symptoms in some patients with resting angina.6,9–11,24,25 Concomitant vasodilator treatment may protect against any potentiation of coronary vasoconstriction by β-blockers, thereby allowing the beneficial negative inotropic and chronotropic effects to predominate.

This double-blind, randomized, placebo-controlled study examined the usefulness of propranolol, in combination with nitrates and nifedipine, in patients with angina at rest. No significant difference was noted between the propranolol and placebo groups with respect to the early incidences of cardiac death or myocardial infarction. The overall occurrence of these outcomes (11%) is consistent with that in prior studies demonstrating a 10% to 15% incidence of progression to infarction in patients with unstable angina25,26 and suggests that the short-term occurrence of infarction in patients with unstable angina is not significantly altered by β-blocker therapy. There was also no statistically significant difference between the two groups with respect to the number of patients who required early bypass surgery or angioplasty for persistent symptomatic angina (10 in propranolol group; 15 in placebo group). Thus, there are no adverse effects in terms of major clinical outcomes of the addition of propranolol to vasodilator therapy for unstable angina. In fact, the addition of propranolol to nifedipine and
nitrates is beneficial because it significantly reduces the number and duration of symptomatic episodes of ischemia as well as the total number and duration of both symptomatic and silent episodes detected by continuous electrocardiographic monitoring.

The anti-ischemic effect of propranolol is probably related to several factors. Theoretical advantages of β-blockers include the negative inotropic and chronotropic properties that decrease myocardial oxygen demand and that probably increase coronary flow as well by increasing the diastolic period. Studies in animals have demonstrated that propranolol results in a favorable redistribution of myocardial blood flow toward the subendocardium. In addition, propranolol treatment has been associated with a rightward shift of the oxyhemoglobin dissociation curve in patients with ischemic heart disease and should thus facilitate oxygen delivery to marginally perfused myocardium. There is also evidence that β-blockade decreases catecholamine-induced platelet aggregation. The propranolol group had a significantly lower heart rate at rest as well as at the onset of and during the ischemic episodes. The observation that heart rates in the placebo group increased after the onset of electrocardiographic evidence of ischemia is consistent with the finding of Maseri and his colleagues that the central event in resting angina is a primary reduction of coronary flow without a preceding increase in myocardial oxygen demand. The higher heart rate in the placebo group during ischemia, however, is detrimental in the setting of fixed atherosclerotic disease and the patients in the propranolol group undoubtedly benefited from the negative inotropic and chronotropic properties of the drug. β-Blocker therapy would also inhibit the reflex, sympathetically induced tachycardia that has been reported to occur in some patients who are treated with vasodilator therapy alone.

There are some limitations of this study. First, these results apply only to patients with resting angina who are concomitantly treated with nitrates and nifedipine. Whether propranolol would demonstrate a similar anti-ischemic effect when given alone in this group of patients is not known. If propranolol alone significantly exaggerates coronary vasospasm in some patients with resting angina, our findings suggest that concomitant vasodilator therapy may reduce or eliminate this potential risk. We can only apply these findings to the specific combination of propranolol and nifedipine that was studied. Second, the length of the study, 4 weeks, was relatively short and this may have limited the ability to detect a statistically significant difference in major clinical outcomes. Although the number of patients experiencing cardiac death or myocardial infarction was small and the possibility of a beta error cannot be entirely excluded, the 14% incidence in the propranolol group is virtually identical to the findings of several other trials with and without β-blocker therapy. In order for a difference between 7% and 14% to reach significance with a beta error of 20%, approximately 10 times as many patients as were included in this study would be required.

We limited our study to 4 weeks because most unfavorable outcomes in patients with unstable angina occur early and a large proportion of the patients who stabilized on medical therapy and no longer experienced pain at rest had subsequent demand-related ischemia for which β-blocker therapy was indicated. Third, the double-blind placebo-controlled study design permitted only a limited degree of dose titration and it is possible that further individualization of the propranolol dose may have provided additional benefit for some patients. The propranolol dose range of 160 to 320 mg daily used in this study did appear, however, to achieve effective β-blockade, as evidenced by the lack of a significant increase in heart rate during ischemic episodes in the propranolol-treated group.

In summary, this study demonstrates that the addition of propranolol to nitrates and nifedipine is not detrimental with regard to the early occurrence of cardiac death, myocardial infarction, or the requirement for revascularization for persistent symptoms. The continuous electrocardiographic data and symptomatic episodes of angina indicate a beneficial effect of propranolol in reducing both the number and duration of episodes of both symptomatic and silent myocardial ischemia in patients with angina at rest. These findings suggest that patients with resting angina and significant atherosclerotic disease have an important component of both dynamic and fixed obstruction and that, although the addition of propranolol to nitrates and nifedipine does not modify the percentage of patients who progress to myocardial infarction, it does reduce the frequency and duration of symptomatic and silent ischemic episodes. Although nitrates and nifedipine can be effective therapy when used alone in the treatment of unstable angina, there is a potential risk for an increase in heart rate that can be detrimental. The addition of propranolol to nitrates and nifedipine to produce β-blockade and lower myocardial oxygen demand provides an effective triple combination for the treatment of unstable angina.

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