The Effect of Timolol vs Placebo on Angina Pectoris

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SUMMARY The effect of timolol vs placebo on the frequency of anginal episodes, nitroglycerin consumption and exercise performance was investigated in a double-blind, randomized, crossover study in 23 patients with angina pectoris. The optimal dose of timolol (10-30 mg twice daily) for each patient was titrated by exercise studies. Compared with placebo, timolol decreased the weekly number of anginal attacks and the weekly number of nitroglycerin tablets consumed, reduced the resting heart rate, systolic and diastolic blood pressure, and product of systolic blood pressure times heart rate, decreased the heart rate, systolic and diastolic blood pressure, and product of systolic blood pressure times heart rate at the onset of angina pectoris or marked fatigue, prolonged exercise duration, and diminished electrocardiographic evidence of myocardial ischemia. Timolol is an excellent antianginal agent when prescribed twice daily, with the optimal dose titrated by exercise studies.

TIMOLOL, (-) 1-tert-butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-2-propranol hydrogen maleate, a β-adrenergic blocking drug approximately eight times more potent than propranolol, has been found to be effective in the treatment of hypertension. In a double-blind, randomized, multicenter study Brailovsky showed that timolol 15-45 mg daily was more effective than placebo in reducing the frequency of anginal attacks (p < 0.01) and the number of nitroglycerin tablets consumed (p < 0.01). In a double-blind, randomized, crossover study performed on two consecutive days in 16 patients with angina pectoris, Villa and associates showed that, compared with placebo, timolol (10 mg) increased treadmill exercise duration from 355 to 395 seconds (p < 0.01), decreased resting heart rate times systolic blood pressure (p < 0.01), decreased heart rate times systolic blood pressure at maximal exercise (p < 0.01), and delayed the onset of ischemic ST-segment depression (p < 0.01).

We performed a double-blind, randomized, crossover study in 23 patients with angina pectoris comparing the efficacy of timolol 20-60 mg/day, the optimal dose titrated for each patient by exercise studies, vs placebo on the number of anginal episodes, the number of nitroglycerin tablets consumed, exercise performance until angina pectoris or marked fatigue, and the exercise ECG. This paper reports the results from this investigation.

Materials and Methods

The subjects included 24 patients, 23 men and one woman, mean age 56 ± 8 years, with six to 14 weekly episodes of angina pectoris, at least 1.0 mm of ischemic ST-segment depression after exercise-induced angina, and coronary angiographic evidence of more than 70% luminal narrowing of at least one major coronary vessel. Fifteen of the 24 patients (63%) had a documented healed myocardial infarction. Two of the 24 patients (8%) had previous coronary artery bypass graft surgery. Written informed consent was obtained from all 24 patients with angina pectoris who participated in this study.

The subjects practiced exercising upright on a constant-load bicycle ergometer (Warren E. Collins, Inc., Braintree, Massachusetts) before the study. The subjects did not take any medication except sublingual nitroglycerin for anginal attacks and the study drugs during the 16-week study. Table 1 shows the study design.

The subjects exercised upright in the fasting state on the bicycle ergometer with a progressive work load at the end of week 2 on single-blind placebo, weeks 3, 4 and 5 on timolol, week 6 on no medication, week 10 on double-blind, randomized timolol or placebo, week 11 on no medication, and week 15 on crossover medication. The exercise test at the end of week 6 was considered to be the control period for the exercise test performed at the end of week 10 on double-blind medication. The exercise test at the end of week 11 was considered to be the control period for the exercise test performed at the end of week 15 on double-blind crossover medication. No subject smoked for at least 12 hours before the exercise tests.

The subjects performed the exercise tests 2 hours after their morning dose of medication. The subjects exercised until the onset of angina pectoris or marked fatigue, and the duration of exercise was measured with a stopwatch. The patients were monitored by telemetry with leads II and V5 throughout exercise. An ECG with simultaneous leads II and V5 was recorded with the patient sitting on the bicycle ergometer immediately before exercise and at the onset of angina pectoris or marked fatigue. The heart rates at rest and at the onset of angina or marked fatigue were obtained from these ECGs. The blood
pressure was measured with a mercury sphygmomanometer with the patient sitting on the bicycle ergometer immediately before exercise and at the onset of angina pectoris or marked fatigue, with the patient continuing to exercise until the blood pressure was obtained.

Simultaneous leads II and V₅ were recorded with the patient in the supine position and in the upright position immediately before exercise, in the upright position at the onset of angina pectoris or marked fatigue, and in the supine position immediately after exercise and at 1-minute intervals after exercise for at least 6 minutes. The maximal amount of exercise-induced ST-segment depression below the resting level was determined for each exercise test.

The data were statistically analyzed using Grizzle’s parametric analysis and Koch’s nonparametric analysis appropriate for a two-period crossover design.¹³,¹⁴

**Results**

Pill counts showed that the patients took their medications during the 16-week study. Of the 24 patients, 24 completed the titration period and 23 entered and completed the double-blind study. The optimal dose of timolol used was 10 mg twice daily for 11 patients, 20 mg twice daily for eight patients, and 30 mg twice daily for four patients.

During the titration period, five of 24 patients (21%) developed fatigue on timolol, and one of 24 patients (4%) developed dizziness on timolol. During the double-blind study, none of 23 patients developed adverse symptoms from placebo, and one of 23 patients (4%) developed fatigue from the dose of timolol used. During the double-blind study, 23 of 23 patients (100%) exercised until angina pectoris on placebo, 18 of 23 patients (78%) exercised until angina pectoris on timolol, and five of 23 patients (22%) exercised until marked fatigue on timolol.

Table 2 shows the weekly number of anginal attacks and the weekly number of nitroglycerin tablets consumed on timolol and on double-blind placebo for the double-blind portion of the study (weeks 7–10 and 12–15). Significantly fewer anginal episodes occurred and significantly fewer nitroglycerin tablets were consumed while the patients were on timolol than when they were on placebo (both \( p < 0.001 \)).

Table 3 shows the mean exercise duration and the mean maximal amount of exercise-induced, ischemic ST-segment depression for the patients during the timolol and placebo control periods, on double-blind timolol, and on double-blind placebo. The mean exercise duration on timolol minus its control was increased 51% more than the mean exercise duration on double-blind placebo minus its control (\( p < 0.001 \)). The mean maximal amount of exercise-induced, ischemic ST-segment depression was decreased on timolol minus its control compared with double-blind placebo minus its control (\( p < 0.01 \)).

Figure 1 shows the net percentage change in exercise for each patient on timolol minus placebo (14–126% improvement). The net percentage change in exercise was determined using the following formula: (timolol exercise time minus timolol control exercise time)/(timolol control exercise time) \( \times 100 \) minus (placebo exercise time minus placebo control exercise time)/(placebo control exercise time) \( \times 100 \).

Table 4 shows the percentage of patients who had at least 50% reduction in anginal attacks and nitroglycerin consumption on timolol compared with

**Table 3. Exercise Duration and Maximal Amount of Exercise-induced ST-segment Depression During Control Periods, on Timolol, and on Double-blind Placebo**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Timolol control</th>
<th>Timolol</th>
<th>Placebo control</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exercise duration (sec)</td>
<td>285.6</td>
<td>467.7*</td>
<td>286.4</td>
<td>322.6</td>
</tr>
<tr>
<td>±51.8</td>
<td>±111.2</td>
<td>53.8</td>
<td>±60.9</td>
<td></td>
</tr>
<tr>
<td>Mean maximal amount of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise-induced ST-segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>depression (mm)</td>
<td>1.48</td>
<td>0.93†</td>
<td>1.56</td>
<td>1.57</td>
</tr>
<tr>
<td>±0.63</td>
<td>±0.57</td>
<td>±0.69</td>
<td>±0.71</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*\( p < 0.001 \).

†\( p < 0.01 \).
double-blind placebo. None of the patients had more anginal attacks or consumed more nitroglycerin tablets on timolol than on placebo. Eighteen of 23 patients (78%) had at least a 25% increase in exercise duration on timolol minus its control minus placebo minus its control. None of the patients had a better exercise duration on placebo than on timolol. Five of 23 patients (22%) had no angina after exercise while receiving double-blind timolol, and six of 23 patients (26%) had at least 1.0 mm less ischemic ST-segment depression after exercise on double-blind timolol.

Table 5 shows the mean resting heart rate, systolic and diastolic blood pressure, and product of systolic blood pressure times heart rate at the end of exercise during the timolol and placebo control periods, on double-blind timolol, and on double-blind placebo.

**Discussion**

Angina pectoris occurs when the myocardial oxygen demand exceeds the myocardial oxygen supply. By decreasing the heart rate, blood pressure, and the strength of contraction during exercise, timolol reduces the myocardial demand.

It is important to titrate the optimal dose of antianginal medication for each patient. During the titration period in this study, optimal improvement in exercise duration occurred in 11 of 23 patients (48%) on timolol 10 mg twice daily, in eight of 23 patients (35%) on timolol 20 mg twice daily, and in four of 23 patients (18%) on placebo.

**Table 4. Incidence of Improvement in Anginal Frequency, Consumption of Nitroglycerin Tablets, and Exercise Performance on Timolol Compared with Double-blind Placebo**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% reduction in anginal attacks on timolol compared with placebo</td>
<td>18/23</td>
<td>78</td>
</tr>
<tr>
<td>≥ 50% reduction in nitroglycerin consumption on timolol compared with placebo</td>
<td>18/23</td>
<td>78</td>
</tr>
<tr>
<td>≥ 25% increase in exercise duration on timolol minus its control minus placebo minus its control</td>
<td>18/23</td>
<td>78</td>
</tr>
<tr>
<td>No angina after exercise on timolol</td>
<td>5/23</td>
<td>22</td>
</tr>
<tr>
<td>≥ 1.0 mm less ischemic ST-segment depression after exercise on timolol</td>
<td>6/23</td>
<td>26</td>
</tr>
</tbody>
</table>

**Table 5. Resting Heart Rate, Systolic and Diastolic Blood Pressure, and Product of Systolic Blood Pressure × Heart Rate/100 in the Control Periods, on Timolol, and on Placebo**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Timolol control</th>
<th>Timolol</th>
<th>Placebo control</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.1 ± 6.6</td>
<td>52.2* ± 3.3</td>
<td>76.1 ± 8.7</td>
<td>77.5 ± 6.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134.7 ± 7.6</td>
<td>117.7* ± 7.3</td>
<td>134.0 ± 8.2</td>
<td>134.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85.9 ± 5.3</td>
<td>75.7* ± 5.0</td>
<td>85.7 ± 5.8</td>
<td>86.0</td>
</tr>
<tr>
<td>Heart rate × systolic blood pressure /100</td>
<td>101.4 ± 5.3</td>
<td>61.6* ± 5.4</td>
<td>102.3 ± 15.3</td>
<td>104.6 ± 11.8</td>
</tr>
</tbody>
</table>

Values are mean ± sd. *p < 0.001.

**Table 6. Heart Rate, Systolic and Diastolic Blood Pressure, and Product of Systolic Blood Pressure × Heart Rate/100 at Onset of Angina or Marked Fatigue in the Control Periods, on Timolol, and on Placebo**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Timolol control</th>
<th>Timolol</th>
<th>Placebo control</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>132.7 ± 12.8</td>
<td>95.0* ± 9.1</td>
<td>135.5 ± 16.1</td>
<td>136.1 ± 15.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>154.3 ± 15.1</td>
<td>158.5* ± 12.4</td>
<td>185.6 ± 15.7</td>
<td>186.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>93.9 ± 6.6</td>
<td>85.0* ± 5.8</td>
<td>94.3 ± 6.8</td>
<td>94.2</td>
</tr>
<tr>
<td>Heart rate × systolic blood pressure /100</td>
<td>244.8 ± 33.7</td>
<td>150.5* ± 18.8</td>
<td>252.1 ± 40.9</td>
<td>254.2 ± 40.1</td>
</tr>
</tbody>
</table>

Values are mean ± sd. *p < 0.001.
patients (17%) on timolol 30 mg twice daily. Using the optimal dose of timolol titrated by exercise tests for each patient, we showed that timolol was superior to double-blind placebo in reducing the resting heart rate, systolic and diastolic blood pressure and the product of systolic blood pressure times heart rate, in decreasing the heart rate, systolic and diastolic blood pressure and the product of systolic blood pressure times heart rate at the onset of angina pectoris or marked fatigue, in reducing the frequency of anginal attacks and the number of nitroglycerin tablets consumed, in prolonging exercise duration and in diminishing electrocardiographic evidence of myocardial ischemia.

In conclusion, timolol is a \( \beta \)-adrenergic blocking agent that is an excellent antianginal agent when prescribed twice daily. The optimal dose of timolol titrated by exercise tests for each patient effectively reduced the frequency of anginal attacks and nitroglycerin consumption, improved exercise duration and diminished electrocardiographic evidence of myocardial ischemia in the majority of patients and did not cause severe adverse effects in any of the patients in this study.

Acknowledgment

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