Effects of Methylprednisolone on the Ischemic Damage in Patients with Acute Myocardial Infarction

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SUMMARY In this double-blind randomized study, 19 patients with acute transmural myocardial infarction were treated with methylprednisolone administered 4.4 ± 0.7 hours (± SEM) after the onset of chest pain, and were compared with 21 patients who received placebo 4.5 ± 0.4 hours after the start of clinical symptoms. The two groups were comparable in reference to sex, prevalence of risk factors, clinical status on admission, location of myocardial infarction and magnitude of ischemic injury as assessed by standard ECGs and precordial ST-segment and QRS maps. The treated patients, however, were older than the patients who received placebo. Methylprednisolone in an i.v. dose of 2.0 g was administered on admission and a similar dose was infused 3 hours later. Placebo administration followed an identical schedule.

Mortality, cardiac rupture, incidence of ventricular arrhythmias, blocks, extension of myocardial infarction, pericarditis, postinfarction chest pain, persistent ST-segment elevation at discharge, and change in Killip class during hospitalization were the same in both groups. Peak enzyme values, and changes in ECG variables pertaining to resolution of ST-segment elevation or development of QRS evolutionary alterations were similar in both groups. Follow-up for 6 months did not reveal any differences in the clinical course of the two groups.

Methylprednisolone infused in a total dose of 4.0 g within 12 hours after the onset of chest pain in patients with acute transmural myocardial infarction does not result in any demonstrable beneficial or harmful effects.

MORTALITY in patients with acute myocardial infarction as a result of lethal ventricular arrhythmias has been curbed with the application of therapy currently in use in the CCU. \(^1\) Death in patients who have suffered a myocardial infarction is primarily the result of an increased magnitude of the ischemic damage. \(^2\)

Various therapeutic protocols have been tried in an effort to limit the infarct size. Steroids and other pharmacologic agents have been used in the early course of infarction. Barzilai et al. \(^3\) reported the efficacy of hydrocortisone in reducing mortality in patients with acute myocardial infarction. Controversy has arisen from the clinical studies that followed. \(^4\) The effect of steroids in reducing the ischemic injury in various animal models is also controversial. \(^7\)-\(^12\)

In the present study, we evaluated the effect of high doses of i.v. methylprednisolone administered early in the course of acute myocardial infarction. The extent of ischemic injury and necrosis in these patients was monitored using data from precordial maps and standard ECGs. In-hospital clinical course and morbidity and mortality during 6 months of follow-up were compared in a treatment and a placebo group.

Materials and Methods

Patients

We studied 40 patients admitted to the coronary care unit at Boston City Hospital with acute transmural myocardial infarction between January 1976 and October 1979. The diagnosis of acute myocardial infarction was based on the classic clinical presentation of persistent chest pain on admission and stable ST-segment elevation on the ECG. This preliminary diagnosis was subsequently confirmed by ECG evolutionary changes and increases in creatine kinase (CK), glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH). With one exception, only patients in whom the study drug was administered within 10 hours after the onset of chest pain were entered in the protocol. Patients with evidence of infection, gastrointestinal, genitourinary tract or other bleeding or who were in pulmonary edema or cardiogenic shock (Killip classes III and IV) were excluded from the study. All patients gave informed consent.

There were 31 males, and nine females, mean age 55.1 ± 2.2 years (± SEM) (range 31–97 years). Twenty patients had ECG changes in anterior and 20 in inferior ECG leads. Each of these two groups included treated patients who received methylprednisolone and control patients who received placebo.

Protocol

A randomized double-blind design was used in this study, and the drug was "forced in sixes": After six patients had been enrolled in sequence into the study, an equal number of subjects had received methylprednisolone and placebo. When reconstituted with 16.0 ml of the accompanying diluent, each 16.0 ml of the placebo formulation contained 1012.5 mg of lactose, plus the buffers and preservatives, which were in the same concentrations as in the methylprednisolone formulation.

Patients with anterior myocardial infarction had a precordial ECG map recorded just before administration of the study drug. Details of the technique have been published. \(^13\)-\(^18\) Briefly, ECG mapping consisted of recording unipolar precordial ECGs from 49 locations on the anterior thorax, arranged in seven transverse rows, each including seven recording sites. The area of the chest thus covered extended from the second intercostal space to 6–8 cm below the xiphoid process and from the right parasternal line to the left posterior axillary line. A skin marker was used to
assure comparability of serial ECG maps and standard ECGs. Patients with inferior myocardial infarction had a standard 12-lead ECG recorded just before the drug administration. All ECGs were recorded with the patient supine. Standardization was 1.0 mV = 1.0 cm, and the paper speed was 25 mm/sec. The response curve of the electrocardiograph was found to have a roll off at 45 Hz equal to 3 Db, and it was flat down to 0.2 Hz.

After the ECGs were recorded, the first dose of 2.0 g of methylprednisolone or the placebo solution was infused intravenously over 20 minutes. Three hours after the first infusion, a second 2.0-g dose of the same solution (methylprednisolone or placebo) was again administered over 20 minutes.

Precordial 49-lead ECG maps for the patients with anterior myocardial infarction and standard 12-lead ECGs for the patients with inferior myocardial infarction were repeated 24 hours and 7 days after entry into the study.

Routine management of these patients included enzyme measurements for CK, SGOT and LDH three times in the first 24 hours and once daily until values returned to baseline. More enzyme measurements were done if chest pain recurred. Upper normal values were 75 IU/l for CK, 20 IU/l for SGOT and 110 IU/l for LDH. Oxygen, 3.0 l/min, was administered by nasal prongs to all patients for 3 days and thereafter as clinically warranted. Morphine sulfate was given for chest pain, and antiarrhythmic drugs, diuretics, digitalis, sedatives and hypnotics were administered as clinically indicated.

The prevalence of previous myocardial infarction, angina, hypertension, family history of myocardial infarction, lipid abnormalities, and smoking was noted in all patients on admission. Patients were also classified on admission as Killip class I or II. The interval between beginning of treatment and onset of chest pain in each patient was noted.

Peak CK, SGOT and LDH were recorded and taken as rough biochemical indexes of ischemic damage, along with the ECG indicators. Clinical classification at discharge or death, change in clinical classification, and occurrence of ventricular fibrillation, ventricular tachycardia, ventricular ectopy, intraventricular conduction delay or block, atrioventricular blocks, pericarditis and recurrence of chest pain were recorded. Extension of myocardial infarction was diagnosed if recurrence of chest pain was followed by reelevation of enzymes after their initial rise and fall. Persistent ST-segment elevation at discharge, in-hospital mortality, mortality due to cardiac rupture and the results of autopsy were noted.

All the patients who were discharged were followed for 6 months at the Cardiac Clinic of Boston City Hospital.

Analysis of Data

Results of the study were analyzed in two ways. First, the prevalence of the various risk factors, the morbidity and mortality, and the clinical and laboratory data after admission were examined in the treatment and control groups, regardless of the infarct location. The second analysis took into consideration the location of the infarction and was used in the statistical treatment of the ECG data. Thus, for patients who had an anterior transmural myocardial infarction, treated patients were compared with patients who received placebo. Likewise, for patients who suffered an acute inferior myocardial infarction the treated patients were compared with the placebo patients. This variation in the analysis of data was necessitated by the different ECG methods used in the patients with anterior and inferior myocardial infarctions.

Each of the 49 precordial ECG leads for patients with anterior myocardial infarction and standard leads 2, 3 and aVF for patients with inferior myocardial infarction were analyzed for the following ECG characteristics: presence and amplitude of Q-waves, height of R-waves and presence and amplitude of ST-segment elevation (figs. 1 and 2). These variables were measured to the nearest 0.5 mm using the TP segment as the isoelectric line. ST-segment elevations were measured 60 msec after the nadir of S-wave or, in its absence, from the peak of R-wave. None of these patients showed differences exceeding 0.02 second in the duration of QRS complex among the three ECGs used in the analysis. QRS prolongation has been shown to influence the magnitude of ST-segment elevation.

In addition, each of the 49 ECG leads of the maps and the three standard inferior leads was scored using a previously described scoring system. Briefly, this scoring system of the QRS complexes was applied as follows: 0 = normal QRS appearance with q waves < 2 mm and < 40 msec in duration; 1 = QRS com-

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ST-segment Elevation (mm)</strong></td>
<td>5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>R-wave (mm)</strong></td>
<td>17</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Q-wave (mm)</strong></td>
<td>1.5</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td><strong>QRS Score</strong></td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Figure 1.** Evolution of ECG variables from a 63-year-old man with anterior myocardial infarction who received methylprednisolone. D, refers to an ECG lead from the precordial map positioned at the fourth intercostal space and midclavicular line. Administration of the drug did not prevent development of Q waves.
Day | 1 | 2 | 7
---|---|---|---
Lead aVF | | |
ST-Segment Elevation (mm) | 2 | 0.5 | 1
R-Wave (mm) | 8 | 3 | 1.5
Q-Wave (mm) | 1 | 5 | 5
QRS Score | 0 | 3 | 3

**Figure 2.** Evolution of ECG variables from a 36-year-old man with an inferior myocardial infarction who received placebo. ST-segment elevation was followed by development of Q waves and progressive reduction of the amplitude of R waves.

complexes that showed a drop of R-wave amplitude ≥ 2 mm and ≥ 50% of the R-wave height recorded on the ECG before treatment; 2 = development of Q waves with amplitude ≥ 2 mm and ≥ 40 msec in duration with a Q/R ratio ≤ 1.0; 3 = complexes similar to the ones with score 2, but with a Q/R ratio > 1.0; 4 = complexes with a QS pattern. ECG leads with ST-segment elevation and QRS scores of 0, 2 and 3 were considered to indicate vulnerable, injured myocardium and were followed serially for development of higher QRS scores (figs. 1 and 2). Increases in QRS scores were thought to denote progression of ischemic injury (ST-segment elevation) to myocardial necrosis (loss of R-waves and development of Q-waves).

The following variables were calculated from ECG measurements:

The sum of ST-segment elevation (in mm) from all precordial ECG leads for patients with anterior myocardial infarction and leads 2, 3, and aVF for patients with inferior myocardial infarction, on admission (day 1), day 2 and day 7, as well as percent decreases of these sums between admission and day 2 and admission and day 7.

The number of leads showing ST-segment elevation on admission, and percent decreases of these sums. Measurements and comparisons as above.

The sum of R-wave amplitudes (in mm) of all ECG complexes showing ST-segment elevation on admission, and percent decreases of these sums. Measurements and comparisons as above.

The number of complexes with QRS scores of 0–4 on admission, day 2 and day 7, and percent change ≥ 1 or ≥ 2 points in the scoring system between above time intervals.

The ST-segment elevation, R-wave amplitude, QRS score of the lead aVF, and percent change in ST-segment elevation, R-wave amplitude and number of points in the QRS score between the above time intervals.

Chi-square and unpaired *t* tests were used in the statistical analysis of the data.

**Results**

**Clinical Characteristics of Patients on Admission**

**Anterior Myocardial Infarction**

Nineteen patients were treated with methylprednisolone and 21 with placebo. Ten patients in the first group had anterior and nine had inferior myocardial infarction. In the placebo group, 10 patients had anterior and 11 inferior myocardial infarction. The treated and placebo groups were not statistically different with respect to sex, occurrence of anterior vs inferior myocardial infarction, history of angina pectoris, previous myocardial infarction, hypertension, cigarette smoking, lipid abnormalities, family history of myocardial infarction, Killip classification, or interval between onset of chest pain and treatment. For the 18 of 19 patients who received methylprednisolone, this interval was 1.5–8.0 hours. One patient received the drug 16.5 hours after onset of chest pain. The control group received the placebo 1.5–9.0 hours after the onset of symptoms. The patients who received therapy with methylprednisolone were older than those in the placebo group (*p* < 0.02) (table 1).

**ECG Characteristics of Patients on Admission**

**Anterior Myocardial Infarction**

The methylprednisolone and placebo patients with anterior myocardial infarction did not differ with respect to sum of ST-segment elevation, number of leads showing ST-segment elevation, sum of R waves of leads with ST-segment elevation, or number of leads with QRS scores of 0, 2 and 3 (table 2).

**Inferior Myocardial Infarction**

The sum of ST-segment elevation from leads 2, 3 and aVF was higher in the placebo than the treatment

<table>
<thead>
<tr>
<th>Data</th>
<th>Methylprednisolone (n = 19)</th>
<th>Placebo (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.7 ± 3.3</td>
<td>50.0 ± 2.5</td>
</tr>
<tr>
<td>Male/ female</td>
<td>15/4</td>
<td>16/5</td>
</tr>
<tr>
<td>Hx of angina</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Hx of MI</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hx of hypertension</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Hx of smoking</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Hx of lipid abnormalities</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Family Hx of MI</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Interval from onset of chest pain to start of treatment (hours)</td>
<td>4.4 ± 0.7</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>Killip class I/II ratio on admission</td>
<td>11/8</td>
<td>16/5</td>
</tr>
<tr>
<td>Anterior/inferior MI ratio</td>
<td>10/9</td>
<td>10/11</td>
</tr>
</tbody>
</table>

Abbreviations: Hx = history; MI = myocardial infarction.
group. All inferior leads showed ST-segment elevation in both groups on admission. The sum of R waves from inferior leads and the number of leads with QRS score of 0, 2 and 3 were not different in the two groups of patients. The amplitude of ST-segment elevation and the height of the R wave in lead aVF were not different in the treated and placebo groups on admission (table 2).

**Effects of Methylprednisolone on Heart Rate, Blood Pressure, ECG, and Symptoms**

Neither infusion of methylprednisolone produced changes in the heart rate (78.5 ± 1.8 vs 78.6 ± 1.8 beats/min), systolic pressure (138.4 ± 3.5 vs 137.7 ± 3.4 mm Hg) or diastolic pressure (89.6 ± 2.0 vs 89.6 ± 1.8 mm Hg). No changes in the 12-lead ECG were noted immediately after the infusion. In one patient, ventricular ectopy was intensified during one infusion period but was easily controlled by increasing the rate of lidocaine administration. Four patients had intensification of their chest pain during one infusion period and required additional morphine sulfate for relief. Three patients had nausea during one of the infusion periods, but were receiving morphine sulfate, concomitantly with methylprednisolone, for relief of chest pain. In one of these patients, slowing of the rate of the methylprednisolone infusion, which had inadvertently increased, abolished nausea. Except in this last case, it was not clear whether these symptoms were definitely related to the administration of methylprednisolone. Such complications commonly accompany acute myocardial infarction, and probably were not due to the infusion of the drug. In addition, the occurrence of complications during one of the two infusion periods makes it unlikely that they were caused by the drug.

**Clinical and Laboratory Characteristics of Patients After Therapy**

There was no demonstrable difference in peak CK, SGOT and LDH between the treated and the placebo patients. All 40 patients had premature ventricular complexes. Also, the prevalence of ventricular fibrillation, ventricular tachycardia, extension of myocardial infarction, postinfarction chest pain, pericarditis, persistent ST-segment elevation at discharge, atrioventricular block and intraventricular conduction delay or block was not different in the two groups. Worsening in Killip classification was not different in the two cohorts of patients (table 3).

**Changes in ECG Variables Between Admission and Days 2 and 7 of Hospitalization**

**Anterior Myocardial Infarction**

There was no demonstrable difference between treated and placebo patients in percent decrease of sums of ST-segment elevation, sums of R-wave amplitude, number of areas showing ST-segment elevation, and change in QRS score by at least 1 or 2 points, as assessed by comparing ECG data from admission and days 2 and 7 of hospitalization (table 4).

**Inferior Myocardial Infarction**

There was no discernible difference in percent decrease in sums of ST-segment elevation, number of ECG leads showing ST-segment elevation, and change in QRS score by at least 1 or 2 points between treated and control patients. Changes were evaluated by comparing between admission and day 2 and admission and day 7 data from the three standard inferior ECG leads. Also, the percent decrease in ST-segment elevation, R-wave amplitude, and point change of the QRS score of lead aV_{F} were not different in the treated and control patients between admission and days 2 and 7 of hospitalization. There was a statistically significant attenuation only of the percent reduction in the R-wave amplitude in treated patients compared with controls with inferior myocardial infarction during the first 24 hours of hospitalization (table 4).

**Mortality and Autopsy Data**

In-hospital mortality and death from cardiac rupture were not different in the treated and control groups (table 3). Four patients died in the treated group. Three had an anterior myocardial infarction. In this latter group, one patient died in cardiogenic shock on the twelfth day of hospitalization. The other two patients died from cardiac rupture, one on day 5 and the other less than 3 hours after the first dose of methylprednisolone. The latter patient was the only one who received a single dose of this drug. The fourth patient in the treated group had recurrent chest pain, cardiac arrest and electromechanical dissociation, and probably died of massive ischemia. She had initially

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**TABLE 2. Electrocardiographic Characteristics of Patients at Admission**

<table>
<thead>
<tr>
<th>ECG variable</th>
<th>Methylprednisolone</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΣST (mm)</td>
<td>70.8 ± 16.7</td>
<td>69.5 ± 27.9</td>
<td>NS</td>
</tr>
<tr>
<td>NST</td>
<td>28.5 ± 2.2</td>
<td>26.9 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>ΣR (mm)</td>
<td>130.6 ± 27.7</td>
<td>87.7 ± 23.3</td>
<td>NS</td>
</tr>
<tr>
<td>SC-0</td>
<td>19.8 ± 2.6</td>
<td>19.7 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>SC-2</td>
<td>3.8 ± 1.9</td>
<td>0.5 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>SC-3</td>
<td>0.2 ± 0.2</td>
<td>1.1 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΣST (mm)</td>
<td>5.1 ± 0.4</td>
<td>9.4 ± 1.6</td>
<td>0.02 &lt; p &lt; 0.05</td>
</tr>
<tr>
<td>NST</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>ΣR (mm)</td>
<td>17.2 ± 3.0</td>
<td>22.1 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>SC-0</td>
<td>2.4 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>SC-2</td>
<td>0.1 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>SC-3</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>ST-F (mm)</td>
<td>1.6 ± 0.1</td>
<td>2.9 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>R-F (mm)</td>
<td>5.1 ± 1.0</td>
<td>7.0 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: ΣST = the sum of all ST-segment elevations in precordial or standard inferior ECG leads; ST-F = the ST-segment amplitude in lead aV_{F}; NST = the number of leads displaying ST-segment elevation; ΣR = the sum of R waves of all ECG complexes showing ST-segment elevation; R-F = the R-wave height in lead aV_{F}; SC-0, SC-2, SC-3 = the number of leads with scores 0, 2 and 3, respectively.
suffered an inferior myocardial infarction. Two patients from the placebo group died on days 3 and 12, both of cardiac rupture. One had an anterior and the other an inferior myocardial infarction.

Autopsy was performed on four of the six patients who died. All had extensive anterior myocardial infarction. Three were in the treated and one in the placebo group. Diagnosis of rupture was confirmed by autopsy in three patients, two of whom had received methylprednisolone and the other placebo. The fourth patient who died of cardiac rupture was in the control group, and the cause of death was diagnosed by pericardiocentesis.

**Six-month Follow-up**

None of the 34 patients who were discharged died within the 6 months after the hospitalization for acute myocardial infarction. No patient suffered a recurrence of acute myocardial infarction. Eight patients in the treated group and seven in the placebo group were admitted for recurrence of chest pain, arrhythmias or shortness of breath. The rates of readmission were not different in the two groups (table 3).

**Discussion**

Therapeutic techniques for protecting the ischemic myocardium are based on the assumption that myocardial infarction is a dynamic process characterized by varying gradual transformation of the ischemic tissue to necrotic regions. Since a fraction of this tissue is reversibly damaged, the potential of beneficial intervention exists in the few hours after the onset of infarction. Along with mortality and common clinical indicators of morbidity, serial sampling of CK⁎⁎, 10 and ECG mapping⁎, 18, 17, 21 have been used to evaluate techniques for protecting ischemic myocardium.

We used ECG methods to monitor ischemic injury in our patients because changes in the ST-segment are early indicators of ischemia, and application of steroid therapy can start immediately after admission to the hospital.
hospital. Enzymatic techniques require serial serum CK values to calculate predicted infarct size before initiation of therapeutic intervention. ECG methods have been found to be effective in monitoring ischemic injury, and constitute clinical extension of intensive animal experimentation. Since there are no data correlating ECG changes with quantitative measurements of the extent of infarction in man, ECG techniques should be considered directional, semiquantitative indexes of ischemia, which should be always complemented by traditional markers of morbidity in the evaluation of therapeutic interventions.

Animal studies designed to assess the effects of steroids in the acute myocardial infarction have rendered conflicting results. In some, mortality, infarct size, preload and afterload were decreased and coronary circulation was augmented with the drug. Beneficial effects were maintained even when steroids were administered as long as 6 hours after coronary ligation. However, other studies showed no reduction in infarct size or beneficial alterations in hemodynamics with the drug.

Barzilai et al. concluded that treatment with hydrocortisone decreased mortality in patients with myocardial infarction, but subsequent clinical studies led to controversy about the effects of steroids (table 5). Morrison et al. noted a reduction in infarct size by enzymatic techniques, and their data tend to support the conclusions of Barzilai et al. Using multiple doses of methylprednisolone, detected augmentation in infarct size measured enzymatically and accentuation of malignant arrhythmias. Peters et al. did not find a difference in the completed infarct measured enzymatically, mortality, malignant arrhythmias, extension of infarction or congestive heart failure between the treated and placebo groups. Heikkila and Nieminen found no improvement in the mechanical function of the heart assessed by echocardiography, ST-segment elevation, hemodynamic derangement, and chest pain with the drug. Bush et al. did not find beneficial effects on infarct size, ventricular function, or complications in their patients who received steroids. Left ventricular function was studied by echocardiography and systolic time intervals. A slight increase of malignant ventricular arrhythmias, of borderline statistical significance, was noted with the use of the drug.

We found no beneficial or harmful effects of steroids in our patients. It could be argued that the beneficial effect of methylprednisolone was blunted by the older age of the treated group in comparison with the placebo cohort. However, monitoring of several variables showed no difference between young and old patients in the treated group. Also, one might suggest that steroids do not have any harmful effect because the drug did not result in increased morbidity and mortality in patients older than those who received placebo. Beneficial or detrimental effect might have been established if a much larger number of patients had been studied. However, it is unlikely that mortality will be found to be lower or higher in a large series, as morbidity variables in several studies did not suggest any beneficial or harmful effects of steroids.

Comparison of our study with previous investigations (table 5) reveals several differences in the drug schedules, total amount of drug administered, duration of treatment and assessment periods and study objectives. Only the present study was designed as a

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**Table 5. Comparison of Clinical Studies of Steroids Administered to Patients with Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Onset of therapy*</th>
<th>Mode of therapy</th>
<th>Assessment period</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barzilai et al.</td>
<td>446</td>
<td>Within 48 hours of onset of pain</td>
<td>500-mg i.v. bolus; then 500 mg every 8–10 hours for 3 days</td>
<td>21 days</td>
<td>Reduction in mortality</td>
</tr>
<tr>
<td>Morrison et al.</td>
<td>20</td>
<td>Average 8.9 (7–25) hours from initial rise of CK†</td>
<td>Single 2.0-g dose</td>
<td>11 months</td>
<td>Reduction of infarct size and mortality</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td></td>
<td>Two 2.0-g doses 3, 6, or 12 hours apart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts et al.</td>
<td>10</td>
<td>7 hours after initial rise of CK</td>
<td>Single 30-mg/kg dose</td>
<td>3 days</td>
<td>Increase of infarct size and ventricular arrhythmias with multiple doses</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>Eight 30-mg/kg doses; every 6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peters et al.</td>
<td>9</td>
<td>Average 7 hours from onset of pain</td>
<td>Two 15-mg/kg doses 10 hours apart</td>
<td>Duration of hospitalization</td>
<td>No benefits or adverse effects</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td>Two 30-mg/kg doses 3 hours apart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heikkila et al.</td>
<td>10</td>
<td>Average 13 (within 24) hours from onset of pain</td>
<td>Single 2.0-g dose</td>
<td>1 hour</td>
<td>No benefits or adverse effects</td>
</tr>
<tr>
<td>Bush et al.</td>
<td>15</td>
<td>Average 9.6 (within 24) hours from onset of pain</td>
<td>Four 30-mg/kg doses; every 6 hours</td>
<td>2 weeks</td>
<td>No benefits; slight increase in ventricular arrhythmias</td>
</tr>
<tr>
<td>Present study</td>
<td>19</td>
<td>Average 4.4 (1.5–16.5) hours from onset of pain</td>
<td>Two 2.0-g doses 3 hours apart</td>
<td>6 months</td>
<td>No benefits or adverse effects</td>
</tr>
</tbody>
</table>

*Methylprednisolone was used in all studies except that of Barzilai, in which hydrocortisone was used.
†Initial rise of CK follows by several hours the onset of chest pain.
randomized, double-blind clinical trial with a single drug schedule. Although decreased mortality and limitation of infarct size have been noted in two studies, such beneficial effects have not been demonstrated in a double-blind, randomized clinical trial. The timing of administration of steroids in relation to onset of clinical syndrome varies widely. Thus, the interval between the onset of symptoms and drug administration has been as much as 48 hours, compared with an average of 4.4 hours in our study. All of our patients except one received the drug infusion within 8 hours after the onset of chest pain. In fact, 17 of 19 patients received steroids within 5½ hours of the onset of chest pain. Animal studies have suggested that the earlier a drug is administered after coronary ligation, the more beneficial it is found to be. Thus, infarct size in dogs was reduced only when hyaluronidase was administered within 6 hours, and propranolol was of benefit at 3 but not at 6 hours after coronary occlusion. The beneficial effects of hyaluronidase were also noted in a clinical study in which the drug was administered within 8 hours after the onset of symptoms. Amelioration of ST-segment elevation and QRS alterations indicative of infarction reported previously were not detected in our study. That steroids did not retard the development of QRS changes indicative of necrosis should be interpreted as evidence of ineffectiveness of the drug to protect the ischemic myocardium. Beneficial effects of steroids have been attributed to stabilization of cellular and lysosomal membranes, or to improved hemodynamics. However, in our experience and that of Roberts et al., no effect on hemodynamics was noted with single or multiple doses of the drug.

Harmful effects of treatment with steroids, particularly development of ventricular aneurysm, have been always of great concern to the clinician. However, ST-segment elevation at discharge, thought to be an insensitive but specific indicator of ventricular aneurysm, was equally prevalent in both groups of our patients. Animal studies suggest that prolonged administration of large doses of steroids results in retardation of healing of infarction or mummification of necrotic region. Despite rare clinical indications, there is no evidence that steroids, even in high doses, administered within the first few hours after onset of chest pain in patients with acute myocardial infarction delay healing of necrosis or predispose to cardiac rupture. Multiple large doses of the drug may be harmful by inducing increases in infarct size, which could predispose to cardiac rupture. However, a large infarct is not a prerequisite to cardiac rupture. One could speculate that infarct expansion induced by multiple doses of steroids rather than increase in infarct size could lead to cardiac rupture. This hypothesis has not been explored. Finally, in the only two studies that suggested a harmful effect of steroids in patients with acute myocardial infarction, multiple doses of the drug were used.

In conclusion, infusion of methylprednisolone in two large doses within a few hours of onset of chest pain in patients with acute myocardial infarction does not have a demonstrable beneficial effect. Although we detected no harmful effect, the possibility of adverse incidents with methylprednisolone cannot be totally excluded, especially when administration of the drug is prolonged.

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