Meta-Analysis of Corticosteroid Treatment in Acute Myocardial Infarction

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Acute and chronic inflammation play a central role in the pathophysiology of atherosclerosis. Corticosteroids are the gold standard anti-inflammatory agent and may have a role in treating acute myocardial infarction. However, concern exists regarding the potential for impaired wound healing and wall thinning. The MEDLINE and PreMEDLINE databases were searched for articles from 1966 through May 2002. A total of 186 articles and 16 English-language publications were identified. A meta-analysis of mortality in controlled trials was performed. Sensitivity analyses and 2 tests for publication bias were used to test the robustness of the results. Sixteen studies involving 3,793 patients were reviewed. Most studies were small (<100 patients) and revealed conflicting efficacy using surrogate outcome measures, such as infarct size. No clear association with myocardial rupture was observed. Meta-analysis of 11 controlled trials (2,646 patients) revealed a 26% decrease in mortality with corticosteroids (odds ratio 0.74, 95% confidence interval [CI] 0.59 to 0.94; p = 0.015). Sensitivity analyses limited to large studies and randomized controlled trials revealed odds ratios of 0.76 (95% CI 0.53 to 1.09) and 0.95 (95% CI 0.72 to 1.26), respectively. Two tests revealed no evidence for publication bias. Thus, the review of available clinical studies demonstrated no harm and a possible mortality benefit of corticosteroids in acute myocardial infarction. ©2003 by Excerpta Medica, Inc.

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Despite the role of corticosteroids in attenuating the inflammatory response and potential therapy in the acute myocardial infarction (AMI) setting, their use has not been accepted into standard clinical practice due to concerns that the risk–benefit ratio is too great. We hypothesized that corticosteroid therapy would be associated with decreased inflammatory damage but would impair wound healing and increase cardiac rupture, resulting in a null effect on mortality.

METHODS

Literature search: The MEDLINE and PreMEDLINE databases were searched for articles containing the Medical Subject Heading index terms steroids, MI, heart rupture, heart aneurysm, and methylprednisolone from 1966 through May 2002. Medical Subject Heading terms were combined using simple Boolean connectors. Two reviewers extracted additional data sources from the bibliographies of articles that were identified. Studies were then chosen if they were performed in humans, written in English and had both treatment (corticosteroid) and control groups. Studies1–11 with available mortality data were used for the meta-analyses.

Statistical analyses: The odds ratio (OR) and 95% exact confidence interval (CI) for death was calculated for each study. A half-integer correction was used if there were no deaths in 1 arm of a study. The DerSimonian-Laird meta-analytic approach12 was then used to calculate a summary OR. Inverse-variance weighting was applied to calculate random-effects summary estimates to account for inter-trial and intra-trial variability. The Mantel-Haenszel test for heterogeneity was performed and intra-study variance (tau-squared) was calculated. Non-zero values of tau-squared were used to identify between study heterogeneity. Statistical significance was considered at p <0.05. We performed 2 sensitivity analyses to address trial heterogeneity by limiting the meta-analysis to only randomized controlled trials and to studies with >100 subjects. An influence analysis13 was performed in which the summary OR was computed omitting 1 study at a time to assess for any 1 study’s dominance. The Begg and Mazumdar14 adjusted rank correlation test and the Egger et al15 regression asymmetry test were used to evaluate publication bias. Analyses were performed using STATA (version 7.0; STATA Corporation, College Station, Texas).

RESULTS

Of 186 articles identified, 16 English-language studies (3,793 patients) met our inclusion criteria, including 1 case-series, 2 retrospective case-control, and 13 prospective studies, of which 8 were randomized (Table 1). Five studies1–4,6 did not provide mortality data and were excluded from the meta-analysis. Retrospective case-control studies: Dellborg et al16 reported on a consecutive series of 1,746 patients admitted within 48 hours of AMI onset. Fifty-six patients (3.2%) with rupture were identified as cases...
and 2 control groups were matched for age and gender. Control group A (nonrupture cardiac death) and control group B (AMI survivors) each contained 56 patients. There was a nonsignificant trend toward more rupture in patients treated with prednisolone compared with controls (OR 2.5, 95% CI 0.93 to 6.76; p = 0.07). Women with sustained chest pain and those with first infarcts were more likely to develop rupture.

A substudy of the Multicenter Investigation of the Limitation of Infarct Size (MILIS) prospective, randomized trial (n = 849) evaluating the effect of hyaluronidase versus propranolol on infarct size analyzed predictors of cardiac rupture. Overall, 26 patients (3.1%) received corticosteroids, but none of the 14 (1.6%) myocardial rupture cases had received corticosteroids. Therefore, the investigators concluded that the use of corticosteroids was not strongly associated with cardiac rupture.

Prospective, nonrandomized clinical trials: Barzilai et al11 studied 446 patients with AMI who were administered 500 mg of intravenous hydrocortisone every 8 to 10 hours for 3 days, with the initial dose given within the first 48 hours of chest pain onset. The control group (n = 491) was given “usual care” by a separate group of physicians on a different ward. A significant decrease in mortality was observed with hydrocortisone at 3 weeks (14.5% vs 23.2%, relative risk reduction 37%, 95% CI 17% to 52%; p = 0.0009).

Morrison et al7 studied 101 patients with AMI in a nonrandomized, unblinded trial. Two grams of intravenous methylprednisolone were administered to 66 patients at a mean of 8.9 hours from the initial increase in creatine kinase. Forty-six patients received a similar second dose 3, 6, or 12 hours later. Three of 66 patients (4.5%) in the treatment group and 6 of 35 patients (17.1%) in the control group died (p = 0.09 using Fisher’s exact test). A significant difference in

TABLE 1 Comparison of Clinical Studies That Used Corticosteroids in Patients With Acute Myocardial Infarction (AMI)

<table>
<thead>
<tr>
<th>First Author, yr</th>
<th>n</th>
<th>Time of Treatment</th>
<th>Agent Administered</th>
<th>Treatment Duration</th>
<th>Follow-up</th>
<th>Outcome Measure</th>
<th>Steroid Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silverman, 1987</td>
<td>68</td>
<td>NA</td>
<td>D, P, MP, NSAID</td>
<td>NA</td>
<td>NA</td>
<td>Rupture</td>
<td>—</td>
</tr>
<tr>
<td>Retrospective case-control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dellborg, 1985</td>
<td>168</td>
<td>NA</td>
<td>PP</td>
<td>NA</td>
<td>17.5 d</td>
<td>Rupture</td>
<td>—</td>
</tr>
<tr>
<td>Pohjola-Sintonen, 1989</td>
<td>849</td>
<td>NA</td>
<td>MP</td>
<td>NA</td>
<td>2 yrs</td>
<td>Rupture</td>
<td>0</td>
</tr>
<tr>
<td>Prospective, nonrandomized, unblinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baroody, 1965</td>
<td>72</td>
<td>&lt;48 h</td>
<td>ACTH</td>
<td>48 h</td>
<td>NA</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Barzilai, 1972</td>
<td>937</td>
<td>&lt;48 h</td>
<td>HC</td>
<td>72 h</td>
<td>3 wk</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Morrison, 1976</td>
<td>101</td>
<td>Mean 8.9 h</td>
<td>MP</td>
<td>12 h</td>
<td>11 mo</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Roberts, 1976</td>
<td>44</td>
<td>Mean 7 h</td>
<td>MP</td>
<td>48 h</td>
<td>3 d</td>
<td>Infarct size</td>
<td>—</td>
</tr>
<tr>
<td>Welman, 1979</td>
<td>45</td>
<td>&lt;4 h</td>
<td>MP</td>
<td>1 h</td>
<td>3 d</td>
<td>Infarct size</td>
<td>+</td>
</tr>
<tr>
<td>Prospective and randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sievers, 1964</td>
<td>132</td>
<td>&lt;24 h</td>
<td>PP</td>
<td>12 d</td>
<td>12 d</td>
<td>Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Semple, 1964</td>
<td>87</td>
<td>&lt;48 h</td>
<td>HC</td>
<td>12 d</td>
<td>28 d</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Gilboa, 1977</td>
<td>342</td>
<td>&lt;24 h</td>
<td>HC</td>
<td>72 h</td>
<td>11–21 d</td>
<td>Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Peters, 1978</td>
<td>29</td>
<td>Mean 7 h</td>
<td>MP</td>
<td>20 h</td>
<td>NA</td>
<td>Mortality</td>
<td>—</td>
</tr>
<tr>
<td>Bush, 1980</td>
<td>30</td>
<td>Mean 9.6 h</td>
<td>MP</td>
<td>24 h</td>
<td>2 wk</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Henning, 1981</td>
<td>28</td>
<td>&lt;12 h</td>
<td>MP</td>
<td>5 h</td>
<td>NA</td>
<td>Mortality</td>
<td>+</td>
</tr>
<tr>
<td>Madias, 1982</td>
<td>40</td>
<td>Mean 4.4 h</td>
<td>MP</td>
<td>6 h</td>
<td>6 mo</td>
<td>Mortality</td>
<td>—</td>
</tr>
<tr>
<td>Solumedrol Studies Group, 1986</td>
<td>847</td>
<td>&lt;12 h</td>
<td>MP</td>
<td>6 h</td>
<td>1 and 6 mo</td>
<td>Mortality</td>
<td>—</td>
</tr>
</tbody>
</table>
| ACTH = adrenocorticotropic hormone; D = dexamethasone; HC = hydrocortisone; MP = methylprednisolone; NSAID = nonsteroidal anti-inflammatory drug; P = prednisolone; PP = prednisone; NA = not available; 0 = null effect; + = beneficial; — = adverse.

FIGURE 1. Mortality rates, ORs, and 95% exact CIs for trials of corticosteroids in AMI. Random effects model meta-analytic ORs were determined using the DerSimonian-Laird method. The area of the square representing the point estimate is proportional to the number of patients in the study.
the simple linear regression models of predicted versus completed infarct size \( p < 0.001 \) using analysis of covariance) suggested that corticosteroid therapy led to smaller completed infarct size.

Three additional small trials studied early corticosteroid use after AMI.\(^5,18,19\) Corticosteroids were associated with smaller infarct size,\(^18\) fewer ventricular arrhythmias,\(^18\) and improved lysosomal membrane stabilization,\(^19\) but there was no mortality difference.\(^5\)

**Randomized controlled trials:** Sievers et al.\(^8\) studied 132 hemodynamically stable patients with suspected AMI. Patients \( n = 64 \) received prednisone (30 mg daily for 3 days and tapered over the following 9 days) or placebo \( n = 68 \) in a randomized, double-blinded trial initiated within 24 hours of the onset of clinical symptoms. There were no significant differences in rhythm/conduction disturbances \( 4 \text{ vs } 3 \text{ events, treatment vs control, } p = 0.71 \), myocardial rupture \( 2 \text{ vs } 2, \text{ treatment vs control, } p > 0.99 \), or mortality \( 20.3\% \text{ vs } 16.2\%, \text{ treatment vs control, } p = 0.65 \) through 12 days.

Gilboa and Brauman\(^9\) randomly assigned patients with electrocardiographic and enzymatic evidence of AMI within 24 hours of symptom onset to receive either standard care \( n = 172 \) or the addition of hydrocortisone to standard care \( n = 170 \) in an unblinded, open-label fashion. Hydrocortisone was administered as a 500-mg intravenous infusion plus a 100-mg intramuscular injection every 8 hours for 3 days. The primary end point was in-hospital mortality, which was not statistically different between the groups \( 22.3\% \text{ vs } 22.7\%, \text{ treatment vs control, } p > 0.99 \).

The Solu-Medrol Sterile Powder AMI Studies Group evaluated the effect of high-dose Solu-Medrol (Upjohn Company, Kalamazoo, Michigan) versus placebo in 849 patients with complicated AMI in a randomized, double-blinded trial.\(^10\) Patients were assigned to group 1 \( n = 387 \) or group 2 \( n = 462 \) if they received the study medication \( 6 \text{ hours or between } 6 \text{ and } 12 \text{ hours of the onset of chest pain, respectively. Two doses of } 30 \text{ mg/kg intravenous Solu-Medrol or matched placebo were given } 3 \text{ hours apart. There were no differences in mortality between steroid treatment and placebo in either group at } 28 \text{ days } (11.7\% \text{ vs } 9.9\%, p = 0.63 \text{ in group } 1; 10.4\% \text{ vs } 14.7\%, p = 0.21 \text{ in group } 2). \text{ Similarly, there remained no significant differences in mortality at } 6 \text{ months } (15.8\% \text{ vs } 14.8\%, p = 0.89 \text{ in group } 1; 13.7\% \text{ vs } 20.3\%, p = 0.08 \text{ in group } 2). \text{ In a Cox regression model adjusted for survival time, mortality was similar for Solu-Medrol treatment and placebo in group } 1. \text{ In group } 2 \text{ there was a significantly increased risk of death for placebo-treated patients compared with patients treated with Solu-Medrol (relative risk } 1.87, p < 0.01). \text{ The number of cardiac aneurysms } (1.2\% \text{ vs } 0.5\%, p = 0.45), \text{ cardiac ruptures } (1.7\% \text{ vs } 2.5\%, p = 0.001).
0.47), and arrhythmias (8.1% vs 5.4%, \( p = 0.17 \)) through 6 months were similar.

Five additional small randomized controlled trials compared either methylprednisolone\(^1\)–\(^4\) or hydrocortisone\(^6\) to placebo. No significant differences were observed in mortality,\(^1\)–\(^4\) infarct size,\(^1\)–\(^4\) rupture,\(^2\)–\(^4\) dysrythmias,\(^2\)–\(^4\) or congestive heart failure.\(^2\)–\(^3\) One study demonstrated improved hemodynamics after hydrocortisone treatment but also an unfavorable increase in blood lactate levels.\(^1\)

**Mortality data:** Eleven studies reported mortality data\(^1\)–\(^11\) in 2,646 patients. Eight studies suggested a benefit with corticosteroid therapy,\(^1\)–\(^3\),\(^5\)–\(^7\),\(^9\)–\(^11\) although only 1 of these\(^11\) reached statistical significance. The remaining 3 studies\(^2\),\(^4\),\(^8\) favored placebo, but none were statistically significant. The meta-analytic OR for mortality was 0.74 (95% CI 0.59 to 0.94, \( p = 0.015 \), tau-squared = 0.048) consistent with a 26% decrease in the odds of mortality for patients treated with corticosteroids (Figure 1).

Secondary analyses limited to randomized controlled trials\(^1\)–\(^4\),\(^6\)–\(^10\) and to studies with >100 patients\(^7\)–\(^11\) revealed ORs of 0.95 (95% CI 0.71 to 1.29, \( p = 0.75 \), tau-squared = 0) and 0.76 (95% CI 0.54 to 1.08, \( p = 0.12 \), tau-squared = 0.08), respectively (Figure 2). Influence analysis demonstrated that no single study in the 11-study meta-analysis significantly altered the summary OR (Figure 3). Begg’s test (\( p = 0.6 \)) and Egger’s test (\( p = 0.8 \)) for publication bias were both nonsignificant (Figures 4 and 5).

**DISCUSSION**

Methods to minimize damage in AMI have evolved from simply improving the supply–demand oxygen ratio\(^20\) in the infarcting myocardium (using supplemental oxygen and \( \beta \) blockers) to optimizing epicardial and microvascular reperfusion using pharmacologic and/or mechanical reperfusion strategies.\(^21\) Currently, there are investigations using experimental combinations of interventional and pharmacologic therapies that include total body cooling, therapies to limit reperfusion injury, aggressive antiplatelet and/or antithrombotic regimens, thrombus removal, and distal protection devices. Corticosteroid therapy may be a potential addition to the above “cocktail therapy” approach and may serve to decrease infarct size by delaying the destructive inflammatory response. The anti-inflammatory properties of corticosteroids are modulated through a complex mechanism of action on the microvasculature, cell membranes, and intracellular messengers, including the stabilization of lysosomal membranes, inhibition of phospholipase A2, and their inhibitory activity against macrophages that may minimize the damage caused by ischemia–reperfusion injury.\(^22\) Corticosteroids impair cell-mediated immunity by depleting the circulating T-cells, inhibiting T-cell growth factor, and antagonizing the action of migration-inhibiting factor. A combination of these mechanisms has also been cited as the cause of delayed wound healing and subsequent risks of myocardial rupture.\(^18\)–\(^22\),\(^24\) These complex mechanisms of action are likely time-dependent, dose-dependent, and may additionally depend on interactions with other drug therapies commonly used in the setting of acute coronary syndromes.

Animal infarct models in dogs, rats, and rabbits have been used to study the effects of corticosteroid therapy on experimentally induced coronary ischemia. Intravenous methylprednisolone administered to dogs preserved systolic cardiac function early after ischemic injury.\(^25\) However, dose-dependent and time-dependent ventricular wall thinning and decreased cardiac function were identified after intravenous methylprednisolone in both rat\(^26\) and dog\(^27\) models. Intravenous hydrocortisone administered to ischemic dogs reduced myocyte necrosis.\(^28\) Prednisolone in a rabbit ischemia model showed a dose-dependent delay in infarct healing.\(^29\) These heterogeneous results in animals were subsequently followed by human trials.

A recent review in animals and humans\(^30\) identified dysrhythmia and ventricular rupture as the more serious potential adverse cardiovascular effects of corticosteroids. These hazards must be carefully considered when evaluating the potential benefits of limiting the acute inflammatory response of AMI using corticosteroids. Available human data regarding the use of steroids in AMI are limited to small and moderate sized heterogenous studies (varying trial designs, treatments administered, timing, and types of end points). No large, adequately powered, randomized controlled trials with corticosteroids in AMI have...
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been performed to assess clinical end points. Nonetheless, our meta-analysis of 11 trials (2,646 patients) suggests a possible mortality decrease with corticosteroids. Although the benefit seen in the overall meta-analysis was no longer statistically significant when we limited the analysis to either larger studies or randomized controlled trials only, we did not find conclusive evidence of a detrimental effect of corticosteroids in any analysis.