Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven

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Summary

Background: There is controversy regarding the effectiveness of corticosteroids in tuberculous pericarditis, particularly in patients who are immunocompromised by HIV.

Aim: To determine the effectiveness of adjuvant corticosteroids in tuberculous pericarditis.

Design: Systematic review of randomized controlled trials.

Methods: We searched the Cochrane Infectious Diseases Group trials register (June 2002), the Cochrane Controlled Trials Register (Issue 2, 2002), MEDLINE (January 1966 to March 2003), EMBASE (1980 to May 2002), and the reference lists of existing reviews, for randomized and quasi-randomized controlled trials of adjuvant corticosteroids in the treatment of suspected tuberculous pericarditis. We also contacted organizations and individuals working in the field. Two reviewers independently assessed trial quality and extracted data. We used meta-analysis with a fixed effects model to calculate the summary statistics, provided there was no statistically significant heterogeneity, and expressed results as relative risk.

Results: Four trials with a total of 469 participants met our criteria. Three (total n = 411) tested adjuvant steroids in participants with suspected tuberculous pericarditis in the pre-HIV era. Fewer participants died in the intervention group, but the potentially large reduction in mortality was not statistically significant (relative risk RR 0.65, 95%CI 0.36–1.16, n = 350; p = 0.14). One trial with 58 patients that enrolled HIV-positive individuals also showed a promising but non-significant trend on mortality (RR 0.50, 95%CI 0.19–1.28; p = 0.15). There was no significant beneficial effect of steroids on re-accumulation of pericardial effusion or progression to constrictive pericarditis. Patients with pericardial effusion were significantly more likely to be alive with no functional impairment at 2 years following treatment. However, the effect was not sustained in a sensitivity analysis that included patients who were lost to follow-up.

Discussion: Steroids could have large beneficial effects on mortality and morbidity in tuberculous pericarditis, but published trials are too small to be conclusive. Large placebo-controlled trials are required, and should include sufficient numbers of HIV-positive and HIV-negative participants, and an adequate adjuvant steroid dose.

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Introduction

Pericardial disease is a potentially curable cause of heart disease that accounts for about 10% of all patients hospitalized for cardiac failure in sub-Saharan Africa. The main cause of pericardial disease in poor countries is tuberculosis. Recently, a rise in the incidence of tuberculous pericarditis in hospitalized patients has been noted, and attributed to the HIV/AIDS epidemic. Before anti-tuberculous drugs were discovered, tuberculosis of the pericardium was fatal in almost all cases, either in the acute stages owing to cardiac tamponade or later as a result of constriction. The advent of effective anti-tuberculous chemotherapy in the 1940s resulted in a decrease in case fatality rate to about 35% by 1970. Even with the anti-tuberculous drug regimens that contain rifampicin and isoniazid (INH) that have been used over the past 30 years, the fatality rate remains high, with case fatality estimates ranging from 8–18%.

It has been suggested that the addition of corticosteroids to anti-tuberculous chemotherapy may result in further reduction in mortality and morbidity in patients with tuberculous pericarditis. Steroids are anti-inflammatory drugs that may be expected to reduce the accumulation of pericardial fluid or prevent the development of adhesions in the pericardium that are induced by the tuberculous infection. However, there are no uniform recommendations regarding the use of steroids in patients with tuberculous pericarditis. Some authorities recommend routine use of these agents in all patients, while others advise the use of steroids only in critically ill patients with recurrent large effusions who do not respond to anti-tuberculous drugs and drainage. Furthermore, there is concern that the use of immunosuppressive agents such as steroids in patients who are immunocompromised by HIV infection may be associated with adverse effects.

We conducted this systematic review to assess the impact of steroids on death, serious disability and need for pericardiocentesis and pericardiectomy in patients with tuberculous pericarditis. We also explored whether the effects of steroids depend on the type of disease (effusive or constrictive) and HIV status.

The role of steroids in patients with HIV disease deserves specific mention. There are potentially harmful side effects that may occur in people who are already immunocompromised. Observational studies have, for instance, demonstrated that steroid use may lead to an increased incidence of bacterial infections, herpes zoster and Kaposi sarcoma in HIV-infected patients.

Methods

Criteria for considering studies for this review

We considered randomized and quasi-randomized placebo controlled trials comparing the use of corticosteroids with placebo in patients of all ages with a diagnosis of tuberculous pericarditis. We included the following outcome measures: (1) death due to all causes; (2) death attributed to pericarditis; (3) death or disability at 1–2 years follow-up (disability was defined as restricted physical activity, combined with signs of cardiac compromise, i.e. clinical, radiographic, echocardiographic, and electrocardiographic evidence of persisting pericardial disease); (4) occurrence of tamponade requiring pericardiocentesis; (5) need for pericardiectomy; and (6) corticosteroid-related adverse effects.

We identified studies from the following sources: (1) the Cochrane Infectious Diseases Group specialized trials register for relevant trials (June 2002) using the search terms 'pericarditis' and 'tuberculosis' (the methods used are published in The Cochrane Library in the section on Collaborative Review Groups); (2) electronic databases, including MEDLINE (January 1966 to June 2002) and EMBASE (January 1980 to May 2002), using the topic search terms in combination with the search strategy developed by the Cochrane Collaboration and detailed in the Cochrane Reviewers’ Handbook; and (3) organizations and individuals in the field of trials, tuberculosis and heart disease. External referees were asked to check the completeness of the search strategy, and to identify any additional unpublished, ongoing, and planned trials.

Data analysis

Two reviewers independently applied the inclusion criteria to all identified trials. We analysed the data using Review Manager (RevMan version 4.1) statistical software. We assessed the methodological quality of each included trial for their adequacy of concealment of allocation, generation of allocation sequence, blinding, and follow-up of participants, using the standard methods of the Cochrane Infectious Diseases Group. Using data from published articles and unpublished information supplied by the trialists, we performed an analysis of all participants as they were randomized. We excluded only those who were lost to follow-up and in whom it had not been possible to determine the relevant outcomes.

We used meta-analysis with a fixed effects model to calculate the summary statistics, provided there
was no statistically significant heterogeneity ($p > 0.1$), and expressed results as relative risks (RR) with associated 95% CIs. We combined trials that included non-HIV tested participants with the different clinical syndromes of tuberculous pericarditis (pericardial effusion and constrictive pericarditis) to estimate the magnitude of the effect of adjuvant corticosteroids on each of the outcomes. HIV-positive patients were analysed separately.

**Results**

**Description of studies**

Four trials with a sample size varying from 28 to 240 and a total of 469 participants met the inclusion criteria.\textsuperscript{10–13} Details of these studies are provided in Table 1. The three South African trials were conducted in the period before the onset of human immunodeficiency virus (HIV) epidemic.\textsuperscript{10–12} The fourth trial was conducted in Zimbabwe in HIV-positive patients.\textsuperscript{13} Participants either had suspected tuberculous pericardial effusion\textsuperscript{10,12,13} or constrictive pericarditis.\textsuperscript{11}

In the studies conducted in the pre-HIV era, the diagnosis of pericarditis was made on clinical grounds with objective echocardiographic confirmation available for a small minority of the patients;\textsuperscript{10–12} one trial did not report how the diagnosis was made.\textsuperscript{10} By contrast, all participants in the trial involving patients with HIV had echocardiographic confirmation of pericardial effusion.\textsuperscript{13} The aetiology of the pericarditis was established using a compatible history plus \textit{Mycobacterium tuberculosis} cultured from pericardial fluid or by exclusion of other causes where cultures were negative.

The proportion of patients in whom a definitive diagnosis of tuberculosis was made varied across the studies. In the trial of adjuvant steroids in suspected tuberculous constrictive pericarditis, a definite diagnosis of tuberculosis was made in only 10% (14/143) of the participants.\textsuperscript{11} This figure compares with 144/240 (60%) of participants with evidence confirming or supporting a diagnosis of active tuberculosis in the trial of adjuvant steroids in suspected tuberculous pericardial effusion.\textsuperscript{12} The diagnosis of tuberculosis was confirmed in 22/58 (38%) participants in the trial of adjuvant steroids in HIV-positive patients with suspected tuberculous pericardial effusion (12 [41%] and 10 [35%] in the treatment and control groups, respectively).\textsuperscript{13} The length of follow-up was unspecified in Schrire’s study,\textsuperscript{10} 18 months in Hakim’s trial,\textsuperscript{13} and 2 years in the Strang studies.\textsuperscript{11,12}

The outcomes measured in the trials are listed in Table 1. All-cause mortality was not given in the published reports in either of the Strang studies;\textsuperscript{11,12} information about the outcome of all patients enrolled in these trials was obtained directly from the authors to allow for determination of all-cause mortality. In these two studies, ‘favourable clinical status at 24 months’ was present if the following criteria were fulfilled or if only one was still abnormal: unrestricted physical activity; pulse rate < 100 bpm; jugular venous pulse < 5 cm; arterial pulsus paradoxus < 10 mmHg; absence of ascites or oedema; cardiothoracic ratio < 55%; electrocardiogram voltage > 6 mm in V6 or > 4 mm along the frontal axis. Hakim \textit{et al.}\textsuperscript{13} did not report deaths from pericarditis, need for repeat pericardiocentesis or need for pericardiectomy.

**Methodological quality of studies**

Overall, the trials were of good quality. The sequence of allocation of patients was adequately concealed in three trials,\textsuperscript{11–13} but in the remaining study allocation was alternate and was therefore not concealed.\textsuperscript{10} Randomization in the Strang studies was conducted using a register drawn up centrally in the UK.\textsuperscript{11,12} The investigators in South Africa entered participants into the trials consecutively according to the register, without prior knowledge of who was receiving active or placebo treatment. In the Zimbabwean study, randomization was achieved using a computer-generated randomization list with an equal number assigned to receive prednisolone and placebo.\textsuperscript{13} These three trials were double blind.\textsuperscript{11–13}

The Strang trials did not use an intention-to-treat analysis, resulting in the exclusion of participants from analysis because of failure to comply with the study protocol. In the published data, 29/143 participants (20%) were excluded from analysis in the pericardial constriction study\textsuperscript{11} and 42/240 participants (17.5%) in the pericardial effusion trial.\textsuperscript{12} Additional unpublished data obtained from the authors regarding the participants who were not included in the analyses indicated that < 10% of participants were lost to follow-up. This review represents a re-analysis of these trials that includes all patients in the groups to which they were randomized.

**Main findings**

**Trials of adjuvant steroids in the pre-HIV era**

Figure 1 shows a combined analysis of participants with effusive and constrictive pericarditis, which suggests that steroids may be associated with
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
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<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Schrire 1959 (Cape Town, South Africa)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Patients with suspected tuberculous pericarditis.</td>
<td>28</td>
<td>Intervention: adjuvant cortisone, 300 mg loading dose, 100 mg/day maintenance dose for several weeks in 14 participants. At a later date, prednisolone 60 mg/day with a maintenance dose of 30 mg/day was substituted. Control: placebo.</td>
<td>Constriction requiring pericardiectomy.</td>
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<td>Strang 1987 (Umtata, South Africa)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Patients with suspected tuberculous constrictive pericarditis aged 5 years or older.</td>
<td>143</td>
<td>Intervention: adjuvant prednisolone for the first 11 weeks of antituberculous chemotherapy. Adult dose: 60 mg/day for first 4 weeks, 30 mg/day for weeks 5–8, 15 mg/day for weeks 9–10, 5 mg/day for week 11. Control: placebo.</td>
<td>Death from pericarditis; favourable clinical status at 24 months; pericardiectomy for constriction.</td>
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<tr>
<td>Strang 1988 (Umtata, South Africa)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Patients aged 5 years or older with suspected tuberculous pericardial effusion.</td>
<td>240</td>
<td>Intervention 1: adjuvant prednisolone for the first 11 weeks of antituberculous chemotherapy. Adult dose: 60 mg/day for first 4 weeks, 30 mg/day for weeks 5–8, 15 mg/day for weeks 9–10, 5 mg/day for week 11. Control: placebo. Intervention 2: complete open surgical drainage compared to no open drainage (122/240 participants consented to this comparison).</td>
<td>Death from pericarditis; pericardiocentesis for pericardial tamponade; favourable clinical status at 24 months; pericardiectomy for constriction.</td>
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<tr>
<td>Hakim 2000 (Harare, Zimbabwe)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>HIV-positive patients with suspected tuberculous pericardial effusion.</td>
<td>58</td>
<td>Intervention: adjuvant prednisolone for the first 6 weeks of antituberculous chemotherapy at a dose of 60 mg/day for the first week, and tapering by 10 mg/day every week. Control: placebo.</td>
<td>Death from all causes; resolution of pericardial effusion, pre-treatment signs and symptoms, and ECG changes; corticosteroid-related side-effects.</td>
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fewer deaths. However this finding is not statistically significant (RR 0.65, 95%CI 0.36–1.16, \( p = 0.14 \)).\(^{11,12}\) A similar trend was found for other measured outcomes (need for repeat pericardiocentesis RR 0.45, 95%CI 0.20–1.05, \( p = 0.07 \); need for pericardiectomy RR 0.85, 95%CI 0.51–1.42, \( p = 0.5 \)). In the Schrire trial of 28 participants, all four participants who required pericardiectomy were in the treatment group (RR 9.00, 95%CI 0.53–152.93, \( p = 0.5 \)) (Figure 2).

A combined end-point of death or persisting pericardial disease at 2 years follow up was also assessed. There was significant statistical heterogeneity between the trial of participants with effusion and the trial of participants with constriction with regard to this outcome (\( \chi^2 = 4.88, \text{df} = 1, p < 0.05 \)), so results were considered separately. Participants on steroids for pericardial effusion were more likely to be cured at 24 months (alive and symptom-free) than participants on placebo (RR 0.48, 95%CI 0.29–0.80, \( p = 0.04 \)). No difference was demonstrated in status at 24 months in the trial of participants with suspected constrictive pericarditis (RR 1.08, 95%CI 0.65–1.81, \( p = 0.1 \)).

We conducted a sensitivity analysis to explore potential effects of patient loss to follow-up on this outcome. In the ‘worst case scenario’, assuming all participants lost to follow-up died, statistical significance was lost (12 lost in treatment group, seven in placebo group; sensitivity analysis assuming all died: RR 0.78, 95%CI 0.52–1.18, \( p = 0.1 \)).

Adjuvant steroids in HIV-positive participants

Steroids were associated with fewer deaths in HIV-positive participants, but this was not statistically significant (RR 0.50, 95%CI 0.19–1.28, \( p = 0.15 \)). No difference in the risk of constrictive pericarditis (RR 1.00, 95%CI 0.15–6.63, \( p = 1 \)) or in the frequency of steroid-related complications was demonstrated.

Discussion

We have conducted a systematic review of randomized controlled trials to evaluate the effectiveness of adjuvant steroids in patients with suspected tuberculous pericarditis. Our comprehensive
search for studies confirmed the paucity of rigorous evidence on this topic. We identified only four small trials with a total of 469 patients, and only one of these included patients known to be HIV-positive.\textsuperscript{10–13} Our findings indicate that the use of steroids in addition to anti-tuberculous drugs may reduce case-fatality rate and the likelihood of re-accumulation of pericardial effusion, and confer a favourable clinical status after 18–24 months of follow-up. While the point estimates suggest potentially large beneficial effects in terms of morbidity and mortality (e.g. about 50% reduction in case fatality rate), these findings are statistically inconclusive because of the small number of patients included in these studies. Thus the effectiveness of adjuvant corticosteroids in suspected tuberculous pericarditis remains unproven.

The limitations of currently available evidence should be recognized. Firstly, the existing trials are small, and the results therefore susceptible to the play of chance. Furthermore, none of the studies was adequately powered to assess the effect of steroids on mortality. Secondly, loss to follow-up was as high as 20% in some of the earlier studies, and the results therefore susceptible to bias.\textsuperscript{11,12} Thirdly, the clinical and bacteriological characterization of patients was limited, as 30–60% of cases in these trials lacked a bacteriological diagnosis of tuberculosis.\textsuperscript{11,12} Some of the studies were commenced before echocardiography became widely available,\textsuperscript{10,11} leading to inadequate separation of patients into the different categories of tuberculous pericarditis (effusive, effusive-constrictive, and constrictive pericarditis). It is possible that steroids may be more effective in the earlier stages of the disease (effusive and effusive-constrictive) with limited effects in the later stages of constriction when fibrosis is established. Finally, rifampicin induces the hepatic metabolism of steroids, so it is possible that the steroid dose used in the trials to date is too low, and that 120 mg of prednisolone rather than 60 mg may be more appropriate.\textsuperscript{14,15}

**Implications for practice**

On the basis of the currently available data, adjuvant prednisolone cannot be recommended for routine use in all patients with tuberculous pericarditis. However, it may be reasonable to reserve corticosteroids for critically ill patients with recurrent large effusions who do not respond to pericardial drainage and antituberculous drugs alone, as has been recommended by others.\textsuperscript{6}

**Implications for research**

There is a need for large, multi-centre prospective randomized controlled trials assessing the effectiveness of adjuvant steroids in tuberculous pericarditis, with careful attention to echocardiographic and bacteriological characterization of participants. Such trials should include sufficient numbers of HIV-positive and HIV-negative participants, and use an adequate adjuvant steroid dose.

**Acknowledgements**

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