Meta-Analysis of Randomized Trials Focusing on Prevention of the Postpericardiotomy Syndrome

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The natural history of postpericardiotomy syndrome (PPS), a relatively common complication of cardiac surgery, varies from mild self-limited episodes to cases with protracted courses, recurrences, and readmissions. Preventive strategies may be valuable to decrease morbidity and management costs. We thus aimed to conduct a comprehensive systematic review on available data for pharmacologic primary prevention of PPS. Controlled clinical studies were searched in several databases and were included provided they focused on pharmacologic primary prevention of PPS. Random-effect odds ratios (ORs) were computed for occurrence of PPS. From the initial sample of 343 citations, 4 controlled clinical trials for primary prevention of PPS were finally included (894 patients); 3 studies were double-blind randomized controlled trials (RCTs). Treatment comparisons were colchicine versus placebo (2 RCTs enrolling 471 patients), methylprednisolone versus placebo (1 RCT on 246 pediatric patients), and aspirin versus historical controls (1 nonrandomized study on 177 pediatric patients). Meta-analytic pooling showed that colchicine was associated with decreased risk of PPS (OR 0.38, 0.22 to 0.65). Data on methylprednisolone (OR 1.13, 0.57 to 2.25) or aspirin (OR 1.00, 0.16 to 6.11) were negative but inconclusive because these were based on 1 study and/or a nonrandomized design. In conclusion, clinical evidence for primary prevention of PPS is still limited to few studies of variable quality. Nevertheless, available data suggest a beneficial profile for colchicine and open a new therapeutic strategy for prevention of PPS. **(Am J Cardiol 2011;108:575–579)**

Postpericardiotomy syndrome (PPS) is a troublesome complication affecting 10% to 40% of patients after cardiac surgery.[1–4] PPS may prolong hospital stay and lead to severe and life-threatening complications such as cardiac tamponade. Anti-inflammatory therapy is empiric and interventions (pericardiocentesis and thoracentesis) may be necessary. Additional complications include recurrences and readmissions. On this basis, prevention of PPS may improve quality of life and morbidity and decrease management costs. In recent decades several drugs usually adopted for PPS treatment have been also proposed for its prevention. Such treatments include aspirin, corticosteroids, and colchicine. Despite the possible clinical importance of primary prevention of PPS, systematic reviews and meta-analyses are lacking on this topic. We thus aimed to conduct a systematic review of controlled clinical trials on pharmacologic prevention of PPS.

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Methods

No individual beyond the listed authors and no other organization contributed in any substantive way to the analysis and writing of the article. The authors are solely responsible for the design and conduct of the study; analysis, drafting, and editing of the article; and its final contents.

Potentially relevant studies published up to January 2011 were searched in BioMedCentral, the Cochrane Collaboration Database of Randomised Trials (CENTRAL), *http://ClinicalTrials.gov*, EMBASE, Google Scholar, MEDLINE/PubMed, and Scopus. The PubMed search was performed with the term "post-pericardiotomy syndrome." Recent (2005 or later) conference proceedings from the American College of Cardiology, American Heart Association, and European Society of Cardiology were electronically or manually searched. All searches were conducted independently by 2 separate reviewers. No language restriction was enforced. In addition, references of retrieved studies were scanned for additional unpublished studies.

Initially retrieved references were checked at the title/abstract level for pertinence. Potentially pertinent studies were retrieved as full reports for further appraisal according to the following selection criteria. Inclusion criteria to be fulfilled for data extraction were (1) controlled clinical trial, (2) head-to head comparisons of treatments or versus placebo, and (3) primary prevention of PPS. Exclusion criteria were (1) duplicate publication and (2) lack of comparative data.

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Table 1
Mean features of included studies

Study	Location/Publication Year	Design	Setting	Therapeutic Class	Patient Number*	Follow-Up (months)
Mott et al[7]	United States/2001	double-blind RCT	single center	steroid	246	1
Finkelstein et al[4]	Israel/2002	double-blind RCT	multicenter	colchicine	111	3
Gill et al[8]	Canada/2009	retrospective	single center	aspirin	177	NA
Imazio et al[9] (COPPS)	Italy/2010	double-blind RCT	multicenter	colchicine	360	12

* Real study population included for results analysis in the original study.
NA = not available.

Table 2
Baseline features of patients in included studies

Study	Mean Age (years)	Men (%)	Intervention
Mott et al[7]	3.1 vs 3.7*	137/246 (55.7%)	intravenous methylprednisolone 1 mg/kg preoperatively + 4 additional doses over 24 hours after congenital heart disease surgery
Finkelstein et al[4]	64	81/111 (73.0%)	oral colchicine 1.5 mg/day (divided in 3 doses) starting third postoperative day for 1 month after cardiac surgery
Gill et al[8]	4.8 vs 4.7*	61/177 (34.5%)	oral aspirin 20–50 mg/kg/day for 1–6 weeks after surgical closure of atrial septal defects
Imazio et al[9] (COPPS)	66	239/360 (66.4%)	oral colchicine 1.0 mg 2 times/day for first day followed by maintenance dose 0.5 mg 2 times/day for 1 month in patients ≥70 kg and 1/2 doses for patients <70 kg or intolerant to highest dose

* Mean age of treatment versus control group.

Final study selection for inclusion in the review was performed by 2 independent reviewers with divergences resolved by consensus.

Baseline, procedural, and outcome data were retrieved from included studies, focusing on pharmacologic treatment (dose, timing, and duration of administration) and primary and secondary clinical end points. The primary end point of the present study was rate of PPS. A separate analysis was conducted on adverse drug effects leading to index drug discontinuation. Data abstraction and validity/risk of bias appraisal were performed on prespecified electronic forms by 2 independent reviewers with divergences resolved by consensus.

Continuous variables are reported as mean ± SD. Categorical variables are reported as percentage. Statistical homogeneity and consistency were checked by chi-square test and I^2. I^2 is computed as $100\% \times (Q - df)/Q$, where Q is Cochran heterogeneity statistic and df is degrees of freedom. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.[5] Dichotomous variables were pooled as odd ratios (ORs) according fixed- and random-effects methods (with 95% confidence intervals). The Egger regression test was adopted for detection of publication bias.[6] Agreement between reviewers was appraised with Cohen kappa. Statistical significance was set at the 2-tailed 0.05 level. Computations were carried out with RevMan 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark) and SPSS 13.0 (SPSS, Inc., Chicago, Illinois).

Results

From the initial sample of 343 citations, 13 citations were appraised in complete form because these concerned clinical trials, leading to a final inclusion of 4 controlled clinical trials for primary prevention of PPS (Table 1).[4,7–9] Agreement for study selection before consensus appeared satisfactory (Cohen kappa 0.86, 0.76 to 0.94). Included studies enrolled 894 patients. Specifically 3 were double-blind randomized controlled trials[4,7,9] and 1 nonrandomized study.[8] Baseline features of selected studies are presented in Table 2. Two studies involved a pediatric population after cardiac surgery for congenital heart diseases and the other 2 an adult population after cardiac surgery for coronary artery bypass grafting, valve diseases, and aortic diseases. Treatment comparisons were colchicine versus placebo (2 studies enrolling 471 patients),[4,9] methylprednisolone versus placebo (1 randomized controlled trial [RCT] on 246 pediatric patients),[7] and aspirin versus historical controls (1 nonrandomized study on 177 pediatric patients).[8] Adopted diagnostic criteria for PPS were different in the 2 studies with pediatric patients. In a study by Mott et al[7] "noncomplicated PPS" was defined as a temperature >100.5°F, patient irritability, pericardial friction rub, and small pericardial effusion with or without pleural effusion. "Complicated PPS" was defined as PPS with an additional need for hospital readmission with or without the need for pericardiocentesis with or without thoracentesis. In a study by Gill et al[8] diagnostic criteria for PPS included ≥2 of the following symptoms/signs occurring ≥72 hours postoperatively: fever >38°C, pericardial or pleural rub, and worsening or recurring anterior pleuritic chest pain. Almost identical diagnostic criteria were adopted in the 2 RCTs comparing colchicine to placebo in adult patients.[4,9] A diagnosis of PPS was made from ≥2 of the following criteria: fever lasting beyond the first postoperative week without evidence of systemic or focal infection, pleuritic chest pain, friction rub, evidence of pleural effusion, and evidence of new or worsening pericardial effusion.