The Role of Colchicine in Pericarditis – A Systematic Review and Meta-analysis of Randomised Trials

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Introduction	Colchicine has been used in diverse clinical settings. Primary idiopathic pericarditis is complicated by recurrence in 15 to 30% of cases. Aspirin, non-steroidal anti-inflammatory drugs, colchicine and steroids are the commonly prescribed medications. We synthesised the available evidence from the randomised trials to assess the efficacy and safety of colchicine in primary and recurrent pericarditis.
Methods	A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data was abstracted from each study and used to calculate an odds ratio (OR) and 95% confidence interval (95% CI).
Results	Seven randomised trials comprising 1275 patients met full criteria for analysis. Two open label randomised controlled trials and five double-blind randomised controlled trials were included. Colchicine was useful in reducing the incidence of primary pericarditis (OR: 0.38, 95% CI: 0.22- 0.65) as well as recurrent pericarditis (OR: 0.31, 95% CI: 0.22-0.44). The most common side-effects were related to the gastrointestinal system and no severe adverse events were observed. Colchicine cessation either by patient or physician was similar in both groups (OR: 1.53, 95% CI: 0.86-2.71).
Conclusion	Colchicine is effective in preventing both primary and recurrent episodes of pericarditis. The number needed to treat for preventing recurrent pericarditis was five. Gastrointestinal side-effects were the most common adverse events.
Keywords	Colchicine • Primary pericarditis • Recurrent pericarditis • Randomised controlled trials • Systematic reviews • Meta-analysis

Introduction

Colchicine has been used in diverse clinical settings such as gout, familial Mediterranean fever, liver cirrhosis, Behcet's disease and pericarditis [1]. Colchicine was introduced in 1987 for the treatment of recurrent pericarditis [2].

Postpericardiotomy syndrome (PPS) is a troublesome complication of cardiac surgery, occurring in 10-45% of cases [3]. Primary idiopathic pericarditis is complicated by recurrence in 15 to 30% of cases. Aspirin, non-steroidal anti-inflammatory drugs and corticoids are the commonest prescribed medications [4,5]. However, only colchicine has been proven

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to be useful in both primary and secondary prevention of the pericarditis.

The precise pathophysiology of recurrent pericarditis is unclear, and both innate and acquired immunity seem to be involved. Despite extensive investigations, up to 80% of recurrent pericarditis remains idiopathic. Colchicine along with non-steroidal anti-inflammatory drugs is the first line treatment whereas immunosuppressive drugs are exceptionally required [6].

Colchicine has been well studied in the last few years with the help of multiple meta-analyses [7–10] which have reviewed its benefits in primary prevention and prevention of recurrent pericarditis. However, recently, trials regarding first episode (ICAP trial) [11] and multiple recurrences (CORP 2) [12] of pericarditis have been published in leading journals. In these scenarios the role of colchicine is unclear.

We synthesised the available evidence from the randomised trials to assess the efficacy and safety of colchicine in primary and recurrent pericarditis. We have doubled the number of subjects which will strengthen the evidence further.

Methods

Study Protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses PRISMA guidelines where possible in performing our systematic review [13]. We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to April 2014. The search terms included ''pericarditis,'' ''Colchicine,'' ''recurrent pericarditis,'' and ''primary prevention of pericarditis''. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study Selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with pericarditis.
- Randomised controlled trials comparing efficacy of colchicine for primary and recurrent pericarditis with placebo.

Data Extraction

We performed the data extraction using a standardised data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals were calculated.

Statistical Analysis

Pooled odds ratio, event rate and 95% confidence intervals used a random effects model [14]. We tested heterogeneity with Cochran's Q statistic, with $P<0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity respectively [15]. The quantified publication bias used the Egger's regression model [16] with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical nonsignificance at the $p<0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, with n being the number of studies included in the meta-analysis [17]. All analyses were performed with Comprehensive Meta-analysis (version 2.0).

Results

The original search strategy retrieved 130 citations (Fig. 1). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only seven studies (1275 patients) met full criteria for analysis and are summarised in Table 1. Four meta-analyses [7–10] were excluded from the analysis which have demonstrated the efficacy of colchicine in different settings. However, recently a few large trials [11,12] have been published and we have doubled the number of subjects which will strengthen the evidence further. The years of publication ranged from 2002 to 2014.

Odds Ratios

Colchicine was useful in reducing the incidence of overall prevention (OR: 0.33, 95% CI: 0.25-0.44) primary pericarditis (OR: 0.38, 95% CI: 0.22- 0.65) and recurrent pericarditis (OR: 0.31, 95% CI: 0.22-0.44) (Figs. 2 and 3). The number needed to treat for preventing recurrent pericarditis was five. The most common side-effects were related to the gastrointestinal system and no severe adverse events were observed. Colchicine cessation either by patient or physician was similar in both groups (OR: 1.53, 95% CI: 0.86-2.71). The incidence of adverse events was similar in both cohorts (OR: 1.13, 95% CI 0.70-1.83). Gastrointestinal side-effects were similar in the both cohorts (OR: 1.23, 95% CI: 0.79-1.92). All results have been tabulated in Table 2.

Heterogeneity and Publication Bias

The heterogeneity of outcomes has been summarised in Table 2. There was no heterogeneity among the studies. No publication bias was detected using the Egger's regression model.

Discussion

Pathophysiology of Recurrent Pericarditis

Recurrent pericarditis is the most troublesome complication of primary pericarditis and occurs in 15% to 32% of cases [18].