Impact of Colchicine on pericardial inflammatory syndromes — An analysis of randomized clinical trials☆,☆☆

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Recurrent pericarditis (RP) complicates up to 50% of the cases of acute pericarditis and is believed to be an autoimmune process [1–5]. Colchicine has proven to be an effective agent for secondary prevention of recurrent pericarditis [6–9]. Colchicine has also been used in prevention of post-pericardiotomy syndrome (PPS) that complicates post-operative recovery in 10–45% of the patients undergoing cardiac surgery [10–12].

Existing literature evaluating the role of Colchicine in the prevention of RP and PPS is limited. The European Society of Cardiology (ESC) practice guidelines (2004) for treatment of pericarditis provided Class I recommendation for Colchicine use in the prevention of pericarditis based largely on observational studies [13]. Results of several RCTs have become available since then. However, these trials are limited by a small size and lack of power to evaluate the safety of Colchicine in pericardial inflammatory syndromes given a low incidence of side effects. In order to obtain stronger effect size, we conducted a meta-analysis of all existing RCTs evaluating the efficacy and safety of Colchicine for the prevention of RP and PPS by pooling available data.

A comprehensive and time limited (01/01/2000 to 06/30/2011) literature search using PubMed and Clinicaltrials.gov for RCTs evaluating Colchicine in the setting of acute or recurrent pericarditis and PPS using keywords "Pericarditis OR Post-pericardiotomy syndrome" was performed. Only randomized clinical trials evaluating the efficacy and safety of Colchicine compared to placebo or active control in prevention of recurrent pericarditis or primary prevention of PPS were included. Each of the included studies was thoroughly reviewed and baseline and outcome data were extracted independently by two reviewers (M.A. and S.J.B). Disputes among extractors were resolved by consensus among the group.

Percentages and means ± standard deviation (SD) were calculated to describe the distributions of categorical and continuous variables, respectively. Continuous variables were compared using the two-tailed independent samples Student's *t* test. Categorical variables were compared using Chi-square with Yates' correction when applicable. Measures of heterogeneity, including Cochran's Q-statistic, I^2 index and the tau-squared tests were computed. Publication bias was assessed using Funnel Plot (not shown). Odds Ratios (OR) and their 95% Confidence Intervals (CI) were utilized to summarize the effect size for primary endpoint using random-effects model. A p value ≤ 0.05 was considered statistically significant. The baseline data were analyzed using the Statistical Package for Social Sciences (SPSS; IBM Inc., version 19.0). The meta-analyses were performed using Review Manager (version 5.0, Cochrane Collaboration). Two additional sub-analyses were performed to evaluate the impact of Colchicine on RP and PPS. The author(s) of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [14].

A total of 5 RCTs met the inclusion criteria [12,15–18]. Two of the included RCTs evaluated the primary prevention of PPS [12,15] and 3 RCTs studied RP with Colchicine use [16–18]. All enrolled studies were high quality with 4 being multi-center and 3 being double blind. Intention to treat analysis was performed in all but one study. Characteristics of the included RCTs and doses of Colchicine used are presented in Table 1.

A total of 795 patients with 389 in Colchicine group and 406 in control group were included in the final analysis. Patients in the Colchicine and conventional therapy (control) groups had comparable mean ages (59.8 vs. 60.7 years, respectively, p = 0.99) and majority of the patients were male (61.2% vs. 56.2%, p = 0.13 respectively). Average follow-up of 18.8 ± 8.4 months and 17.9 ± 8.7 months was reported in the Colchicine and control groups respectively (p = 0.12). Patients enrolled in Colchicine and control arms had similar clinical presentation [chest pain (49.4% vs. 54.1%; p = 0.61), pericardial friction rub (15.5% vs. 17.1%; p = 0.61) and ST-segment changes on ECG (81.4% vs. 80.4%; p = 0.66)], respectively. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) (97.5% vs. 96.9%, p = 0.56) and corticosteroids (16.7% vs. 19.1%, p = 0.78) was reported in the Colchicine and control groups respectively.

Results of the meta-analysis using random effects model are shown in Table 2. Colchicine significantly reduced the rates of PPS and RP in the pooled analysis (Odds Ratio [OR] 0.25, 95% Confidence Interval [CI] 0.13–0.47), Fig. 1(A). This translated in 20.3% absolute risk reduction (ARR) in the Colchicine group (15.68% vs. 35.96%, number needed to treat [NNT] = 4.9), Fig. 2. On a sub-group analysis of 471 patients undergoing cardiac surgery, Colchicine was associated with significant reduction in the incidence of PPS (OR 0.38, 95% CI 0.22–0.65) and an ARR of 12.1% (NNT = 8.3) compared to conventional therapy (Figs. 1(B), 2). The overall benefit was much greater in the prevention of RP (OR 0.18, 95% CI 0.06–0.49) and an ARR of 33.3% (NNT = 3.0), Figs. 1(C), 2.

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Table 1
Summary of randomized clinical trials included in the meta-analysis.

Authors	Year	Study design	Colchicine (n)	Control (n)	Primary end point	Colchicine dose	Follow-up (months)
Finkelstein et al. [12]	2002	Double blind, placebo controlled, multicenter	47	64	Incidence of PPS	1.5 mg/d starting on day 3 after surgery for 1 month	3
Imazio et al. (COPPS) [15]	2010	Double blind, placebo controlled, multicenter	180	180	Incidence of PPS at 12 months	1.0–2.0 mg for 1 day followed by 0.5–1.0 mg/d for 3 months	12
Imazio et al. (CORE) [16]	2005	Open label, active control, single center	42	42	Recurrence rate of pericarditis after first recurrence	1.0–2.0 mg for 1 day followed by 0.5–1.0 mg/d for 6 months	18
Imazio et al. (COPE) [17]	2005	Open label, active control, multicenter	60	60	Rate of recurrence of pericarditis after index episode	1.0–2.0 mg for 1 day followed by 0.5–1.0 mg/d for 3 months	24
Imazio et al. (CORP) [18]	2011	Double blind, placebo controlled, multicenter	60	60	Recurrence rate of pericarditis after first recurrence	1.0–2.0 mg for 1 day followed by 0.5–1.0 mg/d for 6 months	24
Total			389	406			

PPS = post-pericardiotomy syndrome, RP = recurrent pericarditis, AP = acute pericarditis.

Table 2
Meta-analysis outcomes.

Outcome	Follow-up (average)	n[a]	N[b]	Event rate Colchicine		Event rate control		Odds Ratio (random)	Q[c]	f	I^{2d}	τ^{2e}
				N/total	%	N/total	%					
Recurrent pericarditis or PPS	18 months	5	795	61/389	15.7	146/406	36.0	0.25 (0.13–0.47)	9.5	0.05	58.0	0.3
PPS	16 months	2	471	21/227	9.2	52/244	21.3	0.38 (0.22–0.65)	0.1	0.81	00.0	0.0
Recurrent pericarditis	24 months	3	324	40/162	24.7	94/162	58.0	0.18 (0.06–0.49)	6.3	0.04	68.0	0.5
Drug discontinuation	18 months	4	684	28/342	8.2	13/342	3.8	1.96 (0.92–4.18)	3.2	0.36	7.0	0.1
Gastrointestinal adverse effects	18 months	4	684	28/342	8.2	21/342	6.1	1.36 (0.74–2.52)	3.1	0.38	2.0	0.0

[a] Number of studies reporting the outcome.
[b] Number of patients included in the analysis.
[c] Cochran's Q-score for heterogeneity.
[d] I^2 index for degree of heterogeneity.
[e] Tau-squared measure of heterogeneity.
[f] P- value for Cochran's Q-score.

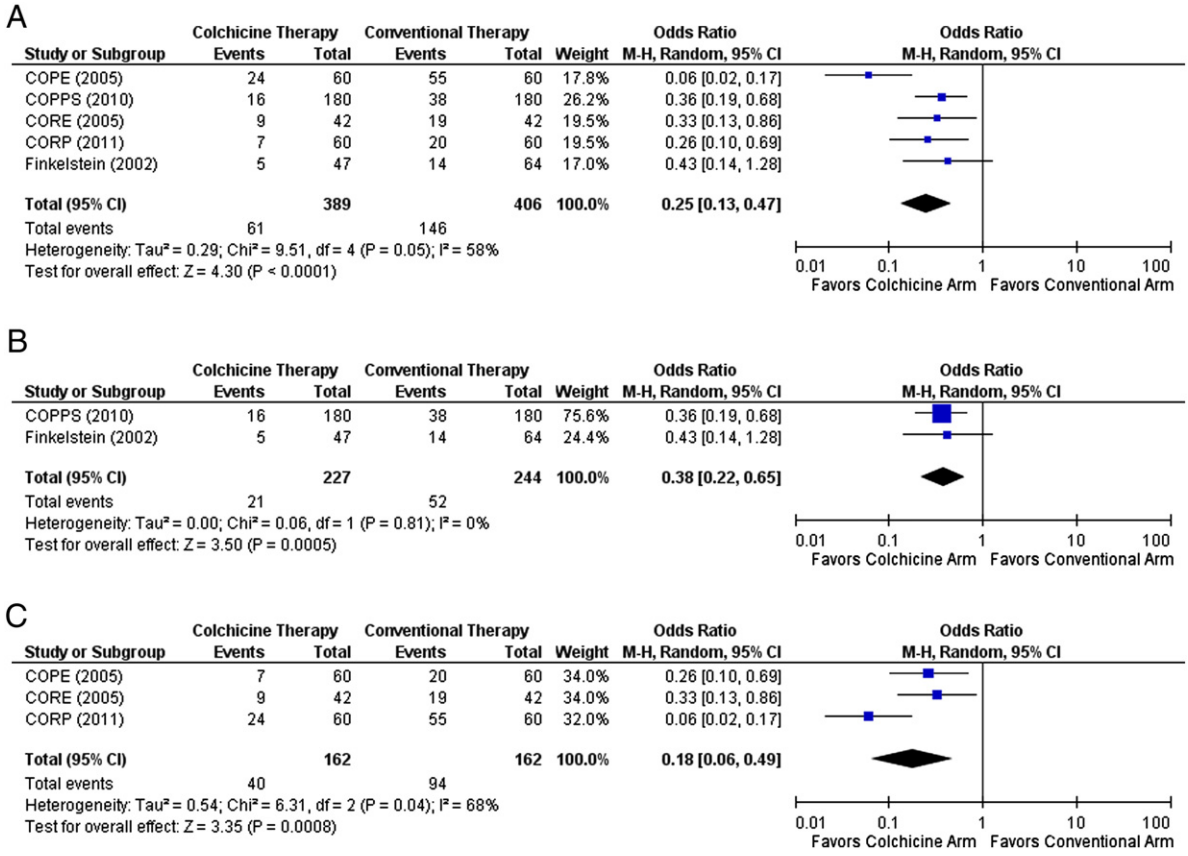

Fig. 1. (A): Forest plot showing impact of Colchicine on the recurrence of acute pericarditis or the incidence of post-pericardiotomy syndrome. (B): Forest plot showing impact of Colchicine on post-pericardiotomy syndrome. (C): Forest plot showing impact of Colchicine on recurrent pericarditis.