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Original research

Efficacy and safety of colchicine for the treatment of myopericarditis

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Received 22 September 2023
Accepted 18 December 2023

ABSTRACT

Objective Clinical trials have evaluated the efficacy and safety of colchicine only in simple pericarditis, excluding cases of concomitant myocarditis. The aim of this paper is to evaluate the efficacy and safety of colchicine for the treatment of the first attack of acute pericarditis with concomitant myocardial involvement.

Methods Double-centre retrospective cohort study analysing consecutive patients admitted for first attack of pericarditis with myocarditis and treated with or without colchicine. The primary efficacy end point was the time to the first recurrence. Propensity score matching was used to generate two groups of patients with similar baseline characteristics. Colchicine-associated side effects were analysed as safety end-point.

Results A total of 175 patients (mean age 46.2±20.1 years, 25.1% females, 88.6% with idiopathic/viral aetiology) were included. Seventy-nine (45.1%) patients were treated with colchicine. After a median follow-up of 25.3 (IQR 8.3–45.6) months, 58 (33.1%) patients had recurrences. The propensity score generated two groups of 73 patients with similar baseline characteristics but the use of colchicine. Patients treated with colchicine had a lower incidence of recurrences (respectively, 19.2% vs 43.8%; p=0.001) and a longer event-free survival (p=0.005). In multivariable analysis, women (HR 1.97, 95% CI 1.04 to 3.73; p=0.037) and corticosteroid use (HR 2.27, 95% CI 1.15 to 4.47; p=0.018) were independent risk factors for recurrences. Colchicine-associated side effects were mild and occurred in 3 (1.7%) patients.

Conclusion In patients with first attack of pericarditis associated with myocardial involvement, colchicine was safe and efficacious for the reduction of recurrences.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Colchicine is recommended for the treatment of pericarditis and the prevention of its recurrences. In colchicine clinical trials, patients with concomitant myocarditis have been excluded.

WHAT THIS STUDY ADDS

⇒ This observation studies with the use of propensity score matching provides evidence for the first time that colchicine is safe and efficacious also for the treatment of pericarditis with myocarditis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may provide evidence to support further clinical trials on the use of colchicine in the setting of myocarditis and gives evidence to update current guidelines' indications on the use of colchicine for pericarditis with concomitant myocarditis.

INTRODUCTION

Pericarditis and myocarditis share common aetiologies, and overlapping forms may be encountered in clinical practice.[1 2]

Colchicine is effective and safe for the treatment of acute and recurrent pericarditis,[3–5] but data are lacking regarding its efficacy and safety in the setting of pericarditis with concomitant myocarditis because these patients were excluded in previous studies.

The aim of the present work is to explore the possible efficacy and safety of colchicine in reducing recurrences in patients with first attack of pericarditis with concomitant myocarditis.

METHODS

Population and study design

This retrospective observational cohort study included all patients referred for a first episode of pericarditis with myocardial involvement to two tertiary centres for pericardial diseases in Northern Italy (University Hospital Santa Maria della Misericordia, Udine and Azienda Ospedaliera Universitaria Città della Salute e della Scienza, Torino) from January 2016 to June 2021. Only adult patients (>18 years old) suffering from a first episode of pericarditis with concomitant myocardial involvement were eligible for inclusion in the study. According to 2015 European Society of Cardiology (ESC) guidelines, myopericarditis was established if patients with definite criteria for acute pericarditis showed elevated biomarkers of myocardial damage (troponin I or T, creatine kinase (CK)-MB fraction) without new focal or diffuse impairment of left ventricular function on echocardiography or cardiac magnetic resanance (CMR).

Study procedures

History and clinical examination, laboratory tests, and electrocardiographic and multimodal imaging

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To cite: Collini V, De Martino M, Andreis A, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2023-323484

(echocardiography and CMR) assessments were routinely performed in all patients at first diagnosis and during follow-up according to local practice and guidelines. Coronary artery disease was excluded by coronary CT or coronary angiography in patients with cardiovascular risk factors or a presentation requiring a differential diagnosis with an acute coronary syndrome. Colchicine administration was based on the clinical judgement of the individual physician. Treatment length was 3 months as recommended for the first episode of pericarditis. The criteria for administration did not change during the study period because the entire observation took place after the 2015 ESC guidelines[5] were published. We used a propensity score matching (PSM) to correct possible imbalances in the study groups.

End points

The efficacy endpoint was recurrence of disease, defined as a new onset of pericardial chest pain after a symptom-free period of at least 4–6 weeks, according to the 2015 ESC guidelines.[5] Side effects associated with colchicine were analysed as a safety endpoint. Follow-up visits were scheduled at 10–14 days after discharge, 1 month, 6 months, 12 months and then yearly for 2 years if uncomplicated.

The study was conducted in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement, the Declaration of Helsinki as amended, and approved by the pertinent Ethical Committee.

Table 1 Baseline features of the studied population according to the use of colchicine

	Colchicine (–) (n=96)	Colchicine (+) (n=79)	P value
Gender, n (%)			
Female	23 (24)	21 (27)	0.69
Male	73 (76)	58 (73)	
Age, mean (SD)	45.1 (19.4)	47.6 (20.8)	0.40
Cardiovascular risk factors, n (%)	63 (66)	41 (52)	0.066
Idiopathic/viral aetiology, n (%)	88 (92)	67 (85)	0.16
Fever, n (%)	53 (56)	36 (46)	0.18
Heart rate ≥70, n (%)	63 (66)	48 (61)	0.51
ST-segment elevation, n (%)	54 (56)	22 (28)	<0.001
EF>55%, n (%)	79 (82)	65 (82)	1.00
Pericardial effusion, n (%)	27 (28)	41 (52)	0.001
Leukocytosis, n (%)	30 (32)	46 (58)	<0.001
Baseline troponin (ratio to 99° percentile)	88±163	59±133	0.81
CRP (mg/dL), mean (SD)	48.7 (49.9)	68.9 (68.8)	0.026
CRP>5, n (%)	84 (88)	68 (86)	0.78
Myocardial oedema on CMR, n (%)	28 (29)	16 (20)	0.18
Myocardial LGE on CMR, n (%)	44 (46)	36 (46)	0.97
NSAIDs, n (%)	90 (94)	68 (86)	0.088
Corticosteroids, n (%)	18 (19)	17 (22)	0.65

CMR, cardiac magnetic resonance; CRP, C reactive protein; EF, ejection fraction; LGE, late gadolinium enhancement; NSAIDs, non-steroidal anti-inflammatory drugs.

Statistical analysis

Continuous variables were expressed as mean±SD or median and IQR, according to the data distribution. The data were analysed using the Shapiro-Wilk test to verify the normal distribution. Categorical variables were presented as absolute numbers and percentages. The Student t-test or the Mann-Whitney U test was used to compare continuous variables between groups, as appropriate. Comparison of categorical variables was performed by χ^2 analysis or the Fisher exact test, as appropriate. Due to imbalances in baseline characteristics between the colchicine and the no-colchicine group, a PSM analysis was performed. PSM was generated from a multivariable logistic regression model in which colchicine/no-colchicine status regressed on the baseline variables (cardiovascular risk factors, ST-segment elevation, pericardial effusion (PE) and C reactive protein (CRP) values) .[6 7] The matching method used to generate balanced cohorts was the single nearest neighbour, without replacement. A region of common support was considered; hence, the observations in the treatment group whose propensity score were higher than the maximum or less than the minimum propensity score of the controls were dropped.

Paired t-test and McNemar test were used to evaluate the balance of the variable between the two groups after PSM.[8 9] Event-free survival was defined as freedom from recurrence. Event-free survival was determined using the Kaplan-Meier approach for matched colchicine and no-colchicine groups. Comparisons between survival distributions were performed using the log-rank test, with estimation of the HR from a Cox regression model, after the proportional hazards assumption had been verified. Univariable and multivariable Cox regression analyses were also performed to determine the effect of each variable on survival. Multivariable regression included all the significant variables with a p value <0.10 in the univariable analysis. Results are presented as HRs and 95% CIs. The proportional hazard assumption was tested using the Schoenfeld residual test. Analyses were performed using Stata V.18.0 (Stata Corp LP).

RESULTS

Baseline data

Baseline characteristics are presented in table 1. A total of 175 patients were included (see figure 1). Patients had a mean age of 46.2±20.1 years, 44 (25.1%) were females and 155 (88.6%) had an idiopathic aetiology. A specific aetiology was detected in 20 cases out of 175 patients (11.4%) and was, respectively, systemic inflammatory disease (12 cases, 6.8%), post-vaccination (4 cases, 2.3%), 2 infectious (leptospirosis), one post-traumatic and one case due to drug hypersensitivity (mesalazine). Transthoracic echocardiography was performed in all patients. CMR was performed in 171 (97.7%) patients (4 patients did not perform the test for claustrophobia). The median ejection fraction was 60% (IQR 55–64) at presentation. Seventy-nine (45.1%) patients were treated with colchicine, while 96 (54.9%) were treated without colchicine. PE was present in 68 cases (38.8%) and was mild in 60 of 68 cases (88.2%). PE was severe in 4 cases with cardiac tamponade. We did not record cases with constrictive pericarditis. CT was performed in 9 of 175 (5.1%) and coronary angiography was performed in 46 of 175 (26.3%) to rule out an acute coronary syndrome. No studied patients had significant coronary artery disease.

As reported in table 1, baseline characteristics were similar between the two groups, except for a higher frequency of PE, CRP and leukocytosis in patients receiving colchicine and a higher percentage of patients with ST-segment elevation in patients not receiving colchicine. Table 2 shows the baseline characteristics after PSM.

Follow-up data

During a median follow-up of 25.3 (IQR 8.3–45.6) months, 58 (33.1%) patients had recurrences. After PSM, a lower incidence

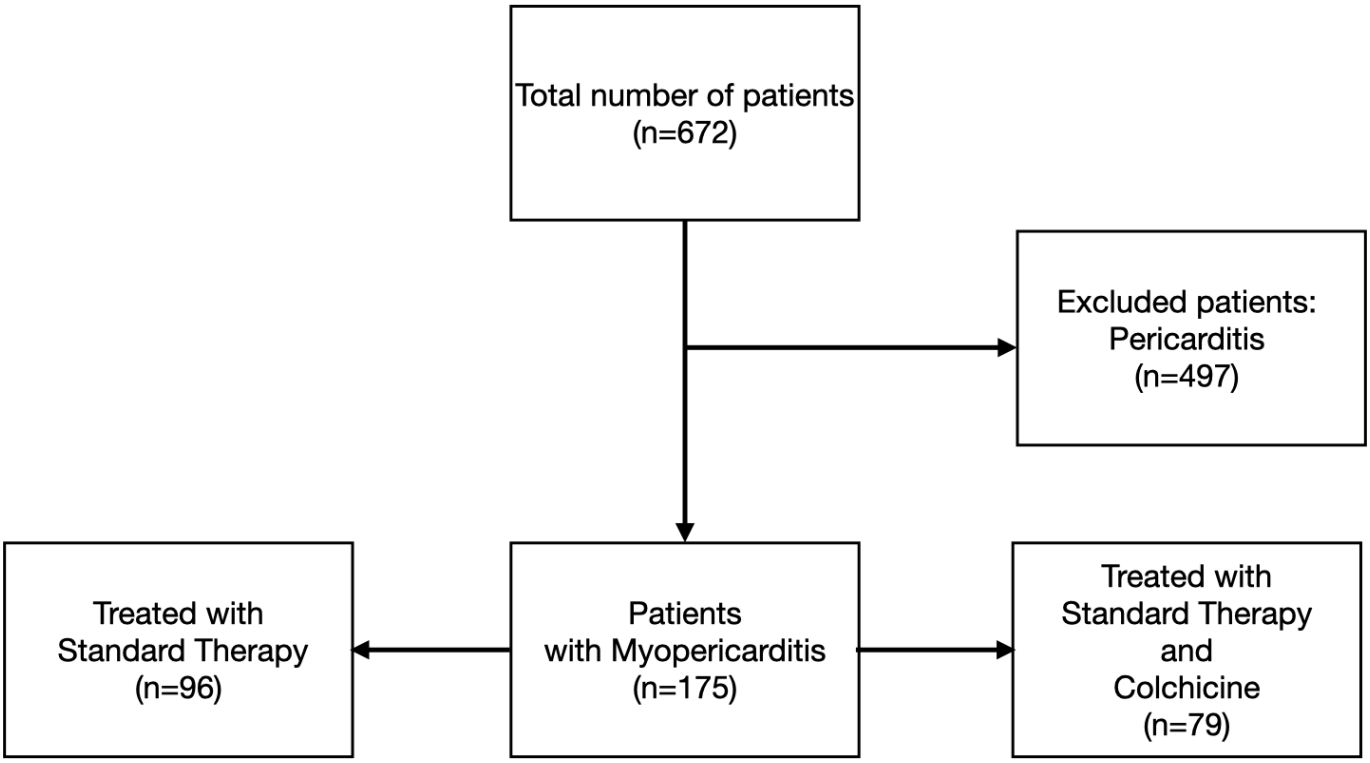

Figure 1 Flow diagram of study population. No patients were lost during follow-up.

of recurrence was observed among patients receiving colchicine with a longer event-free survival (figure 2, p value=0.05).

In multivariable Cox regression analysis (table 3), women (HR 1.97, 95% CI 1.04 to 3.73; p=0.037) and corticosteroid use (HR 2.27, 95% CI 1.15 to 4.47; p=0.018) were independent risk factors for time to recurrence, and colchicine use prevented recurrences (HR 0.39, 95% CI 0.21 to 0.76; p=0.005).

Table 2 Study population with two balanced study groups after propensity score matching

	Colchicine (–) (N=73)	Colchicine (+) (N=73)	P value
Gender, n (%)			
Female	19 (26)	19 (26)	1.00
Male	54 (74)	54 (74)	
Age, mean (SD)	46.7 (20.2)	48.0 (21.2)	0.62
Cardiovascular risk factors, n (%)	42 (58)	40 (55)	0.74
Idiopathic/viral, n (%)	66 (90)	62 (85)	0.35
Fever, n (%)	39 (54)	31 (42)	0.15
HR≥70, n (%)	52 (71)	45 (62)	0.25
ST-segment elevation, n (%)	31 (42)	22 (30)	0.08
EF>55%, n (%)	59 (81)	60 (82)	0.83
PE, n (%)	24 (33)	35 (48)	0.07
CRP (mg/dL), mean (SD)	55.4 (53.8)	59.7 (61.9)	0.87
CRP>5, n (%)	67 (92)	62 (85)	0.13
Myocardial oedema on CMR, n (%)	16 (22)	16 (22)	1.00
Myocardial LGE on CMR, n (%)	28 (38)	35 (48)	0.22
NSAIDs, n (%)	68 (93)	63 (86)	0.16
Corticosteroids, n (%)	15 (21%)	16 (22%)	0.83

CMR, cardiac magnetic resonance; CRP, C reactive protein; EF, ejection fraction; HR, heart rate; LGE, late gadolinium enhancement; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pericardial effusion.

Colchicine-associated side effects were recorded in three cases (1.7%) and were represented by gastrointestinal intolerance of mild intensity not requiring drug discontinuation.

DISCUSSION

To date, this observational study is the largest study evaluating the use of colchicine in patients with myopericarditis. Two previous smaller retrospective observational studies with, respectively, 27 cases[10] and 33 cases[11] reported the successful use of colchicine in the acute phase of the disease without reporting detailed outcomes on recurrences.

In this study, the use of colchicine was efficacious and safe also in cases of pericarditis associated with myocarditis. In the study population, colchicine use prevented recurrences (HR 0.39, 95% CI 0.21 to 0.76; p=0.005) as previously reported in patients with pericarditis without myocardial involvement.[2 3]

In the real world, pericarditis and myocarditis can coexist being caused by common aetiological agents.[1 12] Historically, these patients have been treated with non-steroidal anti-inflammatory drugs and/or corticosteroids. However, in some old animal models, the use of these drugs in this context had a detrimental effect, increasing mortality rates and worsening the clearance of the viral agent. This occurs mainly in post-viral myocarditis.[13] Colchicine is a non-selective inhibitor of the inflammasome and thus reduces the generation of pro-inflammatory cytokines, especially interleukin-1.[13–16] Colchicine is able to prevent microtubule assembly in immune system cells, particularly in neutrophils, where its peak concentration can be more than 16 times higher than the peak concentration in plasma. Interference with microtubules leads to inhibition of a large number of cellular functions, including neutrophil activation, endothelial cell adhesion, migration to injured tissues and cytokine production, resulting in a sustained anti-inflammatory effect.[15 16] Furthermore, even in animal models of

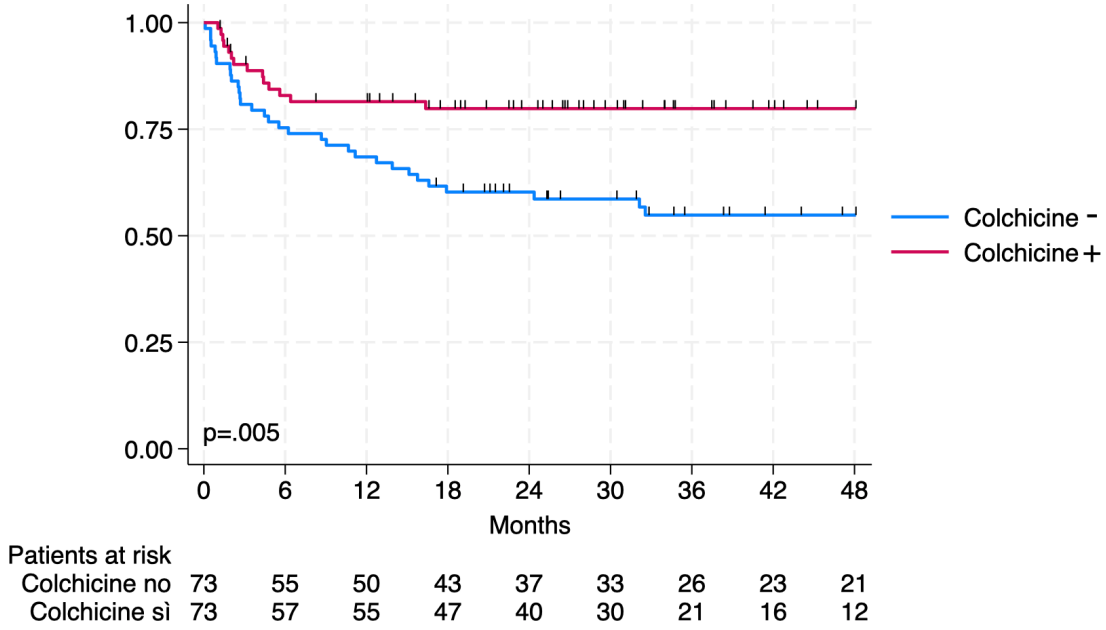

Figure 2 Event-free survival according to colchicine use in the two cohorts after propensity score matching.

Table 3 Univariable and multivariable Cox regression analysis to assess risk factors for time to recurrence in the studied population, after propensity score matching

	Univariable analysis		
	HR	**95% CI**	**P value**
Colchicine	0.40	0.21 to 0.75	0.005
Female gender	2.28	1.23 to 4.24	0.009
Age	1.01	0.99 to 1.02	0.417
BMI	1.03	0.97 to 1.08	0.339
High blood pressure	0.59	0.27 to 1.30	0.192
Dyslipidaemia	0.79	0.35 to 1.78	0.579
Diabetes mellitus	0.50	0.07 to 3.69	0.494
Smoke	1.17	0.60 to 2.28	0.641
Idiopathic/viral aetiology	0.73	0.32 to 1.64	0.449
Pericardial pain	1.09	0.56 to 2.13	0.790
Fever	0.90	0.50 to 1.64	0.742
Sinus rhythm	0.92	0.32 to 2.64	0.876
HR≥70	1.25	0.66 to 2.34	0.490
EF>55%	0.98	0.45 to 2.12	0.951
WBC	1.00	0.99 to 1.00	0.721
Leukocytosis	0.90	0.49 to 1.66	0.734
Baseline troponin (ratio to 99° percentile)	1.00	0.99 to 1.00	0.682
Myocardial oedema	1.12	0.57 to 2.22	0.745
Myocardial LGE	1.10	0.61 to 1.99	0.749
NSAIDs	0.51	0.22 to 1.20	0.122
Corticosteroids	2.17	1.12 to 4.19	0.021
	Multivariable analysis		
	HR	**95% CI**	**P value**
Colchicine	0.39	0.21 to 0.76	0.005
Female gender	1.97	1.04 to 3.73	0.037
Corticosteroids	2.27	1.15 to 4.47	0.018

BMI, body mass index; EF, ejection fraction; HR, heart rate; LGE, late gadolinium enhancement; NSAIDs, non-steroidal anti-inflammatory drugs; WBC, white blood cell.

viral myocarditis, colchicine has been shown to reduce inflammatory and myocardial lesion markers, as well as the apoptosis of cardiomyocytes. In particular, it appears to reduce NLRP3 inflammasome activity, which is associated with reduced release of IL-1, as well as reduced infiltration of immune cells into the myocardium. This allows attenuation of fibro-inflammatory mechanisms, reduced Tn levels, and improved left ventricular function. Colchicine also does not appear deleterious during concomitant viral infection, without impairment of the clearance of viral agents.[17–19]

Regarding clinical trials conducted in humans, this drug has been found to be safe and efficacious in preventing the rate of recurrence in acute and recurrent pericarditis, but patients with myocarditis were excluded.[3 4] In our study, colchicine was able to reduce the rate of recurrences after propensity score matching. As reported in figure 1, a marked reduction in recurrence was also evident immediately after the first 3–6 months of treatment, and the difference persisted until the end of our observation. Colchicine was relatively well tolerated, with mild gastrointestinal side effects in 2% of cases, and no patients experienced severe adverse events that led to the discontinuation of colchicine therapy.

Study limitations

First, this study has an observational retrospective design, however, we used a PSM to adjust for baseline differences between patients treated with or without colchicine. Second, the sample size is relatively small for a propensity score analysis, however, this is a hypothesis-generating study that will allow further research on the topic with the subsequent development of clinical trials. Third, the population was enrolled in two tertiary referral centres, where concomitant therapies were selected at the discretion of local physicians according to current guidelines. The absence of cardiovascular events and the impressive benign natural history of our population did not allow us to apply any prognostic statistical analysis for cardiovascular outcomes.

CONCLUSIONS

This study reports the first and largest evidence for the efficacy and safety of colchicine to prevent recurrences in cases of pericarditis with concomitant myocarditis and provides evidence to use this drug also in patients with myopericarditis and to test this drug in future studies also in the setting of myocarditis.

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Contributors MImazio and VC contributed for the conception of the study. MDM and MIsola were responsible for statistical analysis. All authors contributed to the collection of data, writing, critical revision and final approval of the manuscript. VC is responsible for the overall content as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Comitato Etico Unico Regionale, CEUR. Prot. N. 0005329/P/GEN/ARCS 6 February 2023. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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