

Pericardial Disease

Colchicine in Addition to Conventional Therapy for Acute Pericarditis

Results of the COLchicine for acute PERicarditis (COPE) Trial

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Background—Colchicine is effective and safe for the treatment and prevention of recurrent pericarditis and might ultimately serve as the initial mode of treatment, especially in idiopathic cases. The aim of this work was to verify the safety and efficacy of colchicine as an adjunct to conventional therapy for the treatment of the first episode of acute pericarditis.

Methods and Results—A prospective, randomized, open-label design was used. A total of 120 patients (mean age 56.9 ± 18.8 years, 54 males) with a first episode of acute pericarditis (idiopathic, viral, postpericardiotomy syndromes, and connective tissue diseases) were randomly assigned to conventional treatment with aspirin (group I) or conventional treatment plus colchicine 1.0 to 2.0 mg for the first day and then 0.5 to 1.0 mg/d for 3 months (group II). Corticosteroid therapy was restricted to patients with aspirin contraindications or intolerance. The primary end point was recurrence rate. During the 2873 patient-month follow-up, colchicine significantly reduced the recurrence rate (recurrence rates at 18 months were, respectively, 10.7% versus 32.3%; $P=0.004$; number needed to treat=5) and symptom persistence at 72 hours (respectively, 11.7% versus 36.7%; $P=0.003$). After multivariate analysis, corticosteroid use (OR 4.30, 95% CI 1.21 to 15.25; $P=0.024$) was an independent risk factor for recurrences. Colchicine was discontinued in 5 cases (8.3%) because of diarrhea. No serious adverse effects were observed.

Conclusions—Colchicine plus conventional therapy led to a clinically important and statistically significant benefit over conventional treatment, decreasing the recurrence rate in patients with a first episode of acute pericarditis. Corticosteroid therapy given in the index attack can favor the occurrence of recurrences. (*Circulation*. 2005;112:2012-2016.)

Key Words: colchicine ■ pericarditis ■ survival ■ recurrence ■ prevention

Colchicine has been used for hundreds of years as an antiinflammatory agent for acute arthritis and is the most specific known treatment for acute attacks of gout.¹⁻³ More recently, the drug has been used successfully for the prophylaxis of familial Mediterranean fever attacks^{4,5} and the treatment of recurrent pericarditis.⁶⁻¹³

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Recurrent pericarditis is the most troublesome complication of the disease, occurring in from 15% to 50% of cases.^{6,14-22} It is generally accepted that recurrence is an autoimmune process.^{6,16,22-24} The optimal management for preventing recurrences has not been established.^{6,16,22,24} Colchicine appears to be effective and safe for the treatment and prevention of recurrent pericarditis⁶⁻¹³; moreover, it might be a promising adjunct to the conventional treatment of recurrent pericarditis and might ultimately serve as the initial mode of treatment, especially in idiopathic cases.^{16,24-26} This indication

has not been evaluated extensively in clinical trials, and randomized trials are lacking to guide the evaluation and management of acute pericarditis.^{20,22} A preliminary small French study without a control group²⁷ tested the use of colchicine in 19 patients with a first episode of acute pericarditis. After a mean follow-up of 5 months, a recurrence rate of 10.5% was found. To the best of our knowledge, no prospective, randomized studies have been published to test this intriguing hypothesis.

The aim of the present study was to verify the safety and efficacy of colchicine as an adjunct to conventional therapy for treatment of the first episode of acute pericarditis and for prevention of recurrences.

Methods

Study Design

A prospective, randomized, open-label, parallel-group study was conducted in 2 Italian centers. Validation of clinical events was ensured by an ad-hoc committee of expert cardiologists blinded to patients' treat-

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ment assignment. The study was conceived and managed by the Coordinating Center. Data analyses were performed by an external data analysis committee, which was blinded to treatment assignment. We obtained approval of the study protocol by the institutional review board, and subjects gave informed consent.

Subjects

All consecutive patients with a first episode of acute pericarditis were enrolled. Eligible patients had no contraindication to colchicine, were able to provide informed consent, and had no unfavorable short-term outlook. Inclusion criteria were definite diagnosis of acute pericarditis (idiopathic, viral, and autoimmune causes, including postpericardiotomy syndromes and connective tissue diseases), age ≥ 18 years, and provision of informed consent. Exclusion criteria were tuberculous, neoplastic, or purulent causes; known severe liver disease or current transaminases >1.5 times the upper normal limit; current serum creatinine above 2.5 mg/dL; known myopathy or current serum creatine kinase above the upper normal limit; known blood dyscrasias or gastrointestinal disease; pregnant and lactating women or women of childbearing potential not protected by a contraception method; known hypersensitivity to colchicine; and current treatment with colchicine for any indication. Acute pericarditis was diagnosed when at least 2 of the following criteria were present: typical chest pain, pericardial friction rub, and widespread ST-segment elevation on the ECG.^{14,17,18,25,28}

Randomization and Treatment Plan

Patients were randomized to receive a conventional treatment with aspirin 800 mg orally every 6 or 8 hours for 7 to 10 days with gradual tapering over 3 to 4 weeks (group I) or a treatment with aspirin at the same dose combined with colchicine 1.0 to 2.0 mg for the first day and then a maintenance dose of 0.5 to 1.0 mg daily for 3 months (group II). The lower dose (initial dose 1.0 mg and maintenance dose 0.5 mg daily) was given to patients who weighed <70 kg or who were intolerant to the highest dose (initial dose 1.0 mg BID and maintenance dose of 0.5 mg BID). Randomization was based on permuted blocks, with a block size of 4.

As the preferred nonsteroidal antiinflammatory drug, we used aspirin according to our previously published experience.^{17,18} For the choice for colchicine dose, we considered previous experiences in the treatment of recurrent pericarditis,^{2,6–13} as well as our own previous experience.^{13,24} It was decided to assign patients to the lowest effective dose, thus reducing side effects and improving drug tolerability. Corticosteroid therapy (prednisone at a dose of 1.0 to 1.5 mg $\cdot$ kg⁻¹ $\cdot$ d⁻¹ for 2 to 4 weeks with a gradual tapering off) was restricted to patients with aspirin contraindications (oral anticoagulant therapy, allergy, or history of peptic ulcer or gastrointestinal bleeding) or intolerance. In every case, a gastroduodenal prophylaxis was adopted with omeprazole 20 mg/d, also without initial evidence of gastrointestinal intolerance, as previously published.^{17,18}

We planned the trial procedures to mimic our previous routine care of acute pericarditis.¹⁸ All patients had M-mode, 2D, and Doppler echocardiographic studies performed with a Hewlett-Packard SONOS 2500 or 5500 machine. A clinical and echocardiographic follow-up was performed at 48 to 72 hours, 10 days, 1 month, 3 months, 6 months, and 1 year and then yearly in uncomplicated cases.

End Points

The primary end point was recurrence rate. Criteria for the diagnosis of recurrence were (1) documented first attack of acute pericarditis according to definite diagnostic criteria and (2) evidence of either recurrence or continued activity of pericarditis. Recurrence was documented by recurrent pain and 1 or more of the following signs: fever, pericardial friction rub, ECG changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count, erythrocyte sedimentation rate, or C-reactive protein.^{6,22,28,29}

We included as recurrent pericarditis both the incessant type (patients in whom discontinuation or attempts to wean from treatment ensured a recurrence in a period of less than 6 weeks) and the intermittent type (patients with a symptom-free interval longer than 6 weeks).^{22,29} The secondary end point was the rate of symptom persistence at 72 hours from treatment onset.

Patients were considered to have remission when they were free of symptoms, with disappearance of clinical, ECG, and echocardiographic signs.¹⁰ Conversely, we considered treatment failure to be an unfavorable clinical reaction with persistence of fever, pericardial effusion appearance or worsening, and general illness lasting more than 7 days or if the patient showed an incessant or recurrent course.

Safety

During follow-up, monitoring and recording of all adverse events were performed. A severe adverse event was considered an untoward event that was fatal, life-threatening, or required hospitalization or that was significantly or permanently disabling or medically significant (may jeopardize the patient and may require medical or surgical intervention to prevent an adverse outcome). A Safety Monitoring Committee performed 1 interim analysis, blinded to treatment assignment.

Statistical Analysis

A total of 120 patients, 60 in each treatment arm, were needed to detect a difference in recurrence rates of 32.5% and 10.5% between these 2 treatment arms with a power of 80% using a 2-sided $P=0.05$ level test. The estimated recurrence rate of 32.5% in the control group was based on previous studies (recurrence rate from 15% to 50%).^{6,13,16,18,21,28} The estimated recurrence rate of 10.5% in the colchicine group was based on the results of a small preliminary French study (reported recurrence rate 10.5%).²⁷ Analysis was performed by intention to treat.

Data are expressed as mean $\pm$ SD. Comparisons between patient groups were performed with unpaired t test for continuous variables and a χ^2 analysis for categorical variables. A probability value <0.05 was considered to show statistical significance. Time-to-event distributions were estimated by the Kaplan-Meier method and compared with the log-rank test. To evaluate possible risk factors for recurrence, a logistic regression multivariate analysis was performed. All analyses were performed with the software package SPSS 13.0. The number of patients needed to treat was estimated with its CI using GraphPad Software QuickCalcs.

Results

Between January 2002 and August 2004, 120 patients were randomized. Information on vital status and clinical follow-up data were available in all patients for a mean follow-up of 24 months (range 8 to 39 months). Sixty patients (mean age 57.2 ± 19.6 ; 26 males) were randomly assigned to aspirin alone (group I), and 60 patients (mean age 56.5 ± 18.2 ; 28 males) were assigned to aspirin and colchicine (group II). A detailed trial profile is reported in Figure 1. Baseline demographic and clinical characteristics were well balanced across the groups (Table 1). Corticosteroid therapy was prescribed in 19 patients (15.8%) because of aspirin contraindication or intolerance, according to the study protocol. The overall efficacy profile of the 2 treatments is summarized in Table 2. All 60 patients treated by colchicine responded favorably to therapy.

Primary End Point

During the 2873 patient-months of follow-up, a higher recurrence rate was recorded in patients treated only by aspirin (group I) than in patients treated with colchicine plus conventional treatment (group II; respectively, 33.3% versus 11.7%; $P=0.009$). Nearly all of the recurrences occurred within 18 months. Recurrence rates in group I and group II at 18 months were 32.3% and 10.7%, respectively ($P=0.004$; number of patients needed to treat=5 [95% CI 3.1 to 10.0]). Patients in group II had a longer symptom-free interval (22.9 ± 10.3 versus 17.2 ± 12.3 months; $P=0.007$). Event-free survival in the study groups is reported in Figure 2. An exploratory analysis was done by subgroups according to treatment (aspirin, aspirin plus

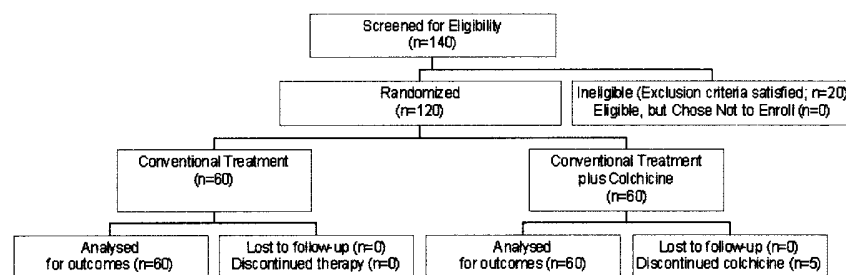


Figure 1. Trial profile.

colchicine, prednisone, and prednisone plus colchicine). Recurrence rates at 18 months were 23.5% in the aspirin subgroup, 8.8% in the aspirin plus colchicine subgroup, 86.7% in the prednisone subgroup, and 11.1% in the prednisone plus colchicine subgroup (log-rank $P<0.001$).

Secondary End Point and Risk Factors for Recurrences

A lower incidence of symptom persistence at 72 hours was recorded in group II than in group I (respectively, 11.7% versus 36.7%; $P=0.003$). Baseline clinical features of patients with and without recurrences during follow-up are reported in Table 3. Patients with recurrences during follow-up had a higher rate of corticosteroid use in the index attack (33.3% versus 10.7%; $P=0.011$). After logistic regression multivariate analysis that introduced age, gender, pericardial effusion, severe pericardial effusion, cardiac tamponade, etiology, corticosteroid use, and colchicine therapy as independent variables, corticosteroid use remained an independent risk factor for the subsequent development of recurrences (OR 4.30, 95% CI 1.21 to 15.25; $P=0.024$), whereas the use of colchicine was found to be protective (OR 0.17, 95% CI 0.05 to 0.53; $P=0.003$).

Safety

Safety profiles of the studied treatments are summarized in Table 2. Overall drug tolerability was good for aspirin and colchicine; no serious adverse drug effects were recorded in the study groups. Colchicine-treated patients had 5 cases of diarrhea (8.3%), which was promptly reversible after drug withdrawal. Side effects were reported as a reason for discontinuing therapy

for 5 patients (8.3%) in the colchicine group (group II) and 0 patients in group I. Minor side effects (including abdominal pain and dyspepsia) were recorded in 4 (6.7%) of 60 cases in group I without need for drug withdrawal.

Discussion

Major Findings

The COPE study provides evidence that colchicine in combination therapy with aspirin or prednisone is safe and efficacious in the treatment of the first episode of acute pericarditis, as well as in the prevention of recurrences. Previous reports^{6–13,22} have shown that colchicine is effective and safe as an adjunct for the treatment of recurrent pericarditis and the prevention of further recurrences after conventional treatment failure. In these studies, patients treated with colchicine after previous recurrences showed a reduced recurrence rate: from 0% to 26%, with a mean value of 14%.¹⁶ A small French study²⁷ in 19 patients with acute pericarditis suggested that colchicine may also be effective in the treatment of the first episode of acute pericarditis; however, this hypothesis was tested in only 19 patients without a control group. After a mean follow-up of 5 months, a recurrence rate of 10.5% was found, whereas the recurrence rate may be as high as 15% to 50%^{16,21} with conventional treatment.

On the basis of cumulative anecdotal evidence and the opinion of experts, colchicine (0.5 to 0.6 mg BID) is suggested as a possible therapy for the first episode of acute pericarditis,^{16,25,26} whereas nonsteroidal antiinflammatory drugs are the mainstay of treatment. The threshold of prescription of the drug has been lowered, because at low doses, the drug is well tolerated, with few side effects;

TABLE 1. Baseline Clinical Characteristics of Randomized Patients

Feature	Group I: No Colchicine (n=60)	Group II: Colchicine (n=60)	P
Age, y	57.2±19.6	56.5±18.2	NS
Male gender	26 (43.3)	28 (46.7)	NS
Pericarditic chest pain	60 (100.0)	60 (100.0)	NS
Pericardial rub	19 (31.7)	21 (35.0)	NS
ST-segment elevation	53 (88.3)	52 (86.7)	NS
Pericardial effusion	38 (63.3)	41 (68.3)	NS
Cardiac tamponade	1 (1.6)	1 (1.6)	NS
Idiopathic pericarditis	51 (85.0)	50 (83.3)	NS
Autoimmune causes*	9 (15.0)	10 (16.7)	NS

Values are n (%) or mean±SD.

*Autoimmune causes include connective tissue diseases and postpericardiotomy syndromes.

TABLE 2. Follow-Up Data of Randomized Patients

Feature	Group I: No Colchicine (n=60)	Group II: Colchicine (n=60)	P
Mean follow-up, mo	23.7±8.8	24.2±8.7	NS
Corticosteroid use,* n (%)	10 (16.6)	9 (15.0)	NS
Recurrence, n (%)	20 (33.3)	7 (11.7)	0.009
Recurrence rate at 18 mo, %	32.3	10.7	0.004†
Symptom persistence at 72 h, n (%)	22 (36.7)	7 (11.7)	0.003
Side effects, n (%)	4 (6.7)	5 (8.3)	NS
Severe adverse effects, n (%)	0 (0.0)	0 (0.0)	NS
Cardiac tamponade, n (%)	0 (0.0)	0 (0.0)	NS
Constrictive pericarditis, n (%)	0 (0.0)	0 (0.0)	NS

*Steroid prescribed for the index attack because of aspirin contraindications or intolerance.

†P value from log-rank test.

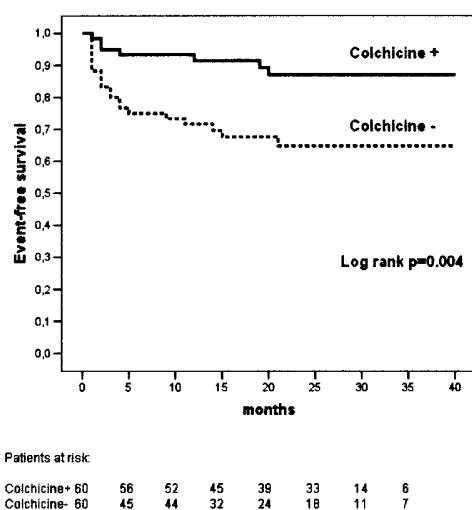


Figure 2. Kaplan-Meier event-free survival curves according to treatment groups (see text for details).

however, evidence for this use comes from a small study on 19 patients and consensus opinion of the experts. This opinion is derived mainly from studies in which colchicine was used in the treatment of patients with recurrences after failure of conventional treatment but not after a first event. The 2 populations may be quite different given that it is generally accepted that recurrence is an autoimmune process,^{6,16,23} whereas the first episode generally has an infectious cause (ie, viral).^{6,14–18,20,28} The use of colchicine in any acute pericarditis as “primary” prevention of recurrences may represent an important step in the management of acute pericarditis if controlled trials confirm the initial positive results.²² However, there are no clinical studies to guide the evaluation and management of acute pericarditis, and strategies to prevent recurrences require further study.^{20,22}

The present study was designed to address whether colchicine is a useful addition to conventional treatment either in therapy of the first episode or in prevention of recurrences. Colchicine may be a way to cope with this complication.

TABLE 3. Baseline Clinical Features of Patients With and Without Recurrences During Follow-Up

Feature	Patients With Recurrence (n=27)	Patients Without Recurrence (n=93)	P
Age, y	57.3±18.8	56.7±18.9	NS
Female gender	19 (70.4)	47 (50.5)	NS
Pericardial effusion	20 (74.1)	59 (63.4)	NS
Severe pericardial effusion	5 (18.5)	5 (5.4)	NS
Cardiac tamponade	1 (3.7)	1 (1.1)	NS
Idiopathic etiology	21 (77.8)	80 (86.0)	NS
Autoimmune causes*	6 (22.2)	13 (14.0)	NS
Corticosteroid use†	9 (33.3)	10 (10.7)	0.011
Colchicine use	7 (3.7)	53 (56.9)	<0.001

Values are n (%) or mean±SD.

*Autoimmune causes include connective tissue diseases and postpericardiotomy syndromes.

†Steroid prescribed for the index attack because of aspirin contraindications or intolerance.

Colchicine proved useful to control symptoms within 72 hours faster than aspirin or prednisone alone (Table 2). These data are similar to what has been described in patients with gouty attack. Most patients who receive colchicine respond within 18 hours, and joint inflammation subsides in 75% to 80% of patients within 48 hours.¹ Moreover, colchicine was able to reduce the subsequent recurrence rate by ≈3-fold (recurrence rates at 18 months were 10.7% versus 32.3% with and without colchicine, respectively; $P=0.004$), and thus the number of patients with a first episode of acute pericarditis who need to be treated to prevent a recurrence is only 5.

The exact mechanism of colchicine action is not fully understood. Most of the pharmacological effects of colchicine on cells involved in inflammation appear to be related to its capacity to disrupt microtubules. Colchicine inhibits the process of microtubule self-assembly by binding β -tubulin with the formation of tubulin-colchicine complexes. This action takes place either in the mitotic spindle or in the interphase stage, and thus, colchicine inhibits the movement of intercellular granules and the secretion of various substances.^{1,2} By this mechanism, colchicine is able to inhibit various leukocyte functions, and this effect should be the most significant for its antiinflammatory action. Moreover, colchicine shows a preferential concentration in leukocytes, and the peak concentration of colchicine may be >16 times the peak concentration in plasma. This appears to be related to its therapeutic effect.^{1,2}

Risk Factors for Recurrences

As already reported,^{6,14,15,28} in previous studies, no characteristics of the first episode of acute pericarditis were able to predict the likelihood of recurrences; however, concern has been raised that treatment of acute pericarditis with prednisone may increase the risk of recurrence.^{6,20,22,24,28–30} The present study appears to support this fear, because patients with recurrences during follow-up had a higher rate of previous corticosteroid use in the index attack (Table 3). After multivariate analysis, prednisone use was an independent risk factor for the subsequent development of recurrences (OR 4.30, 95% CI 1.21 to 15.25; $P=0.024$).

Animal studies have shown that corticosteroids may exacerbate virally induced pericardial injury.²⁰ Corticosteroid therapy given in the index attack can favor the occurrence of recurrences, probably because of its deleterious effect on viral replication. Corticosteroids may perpetuate pericardial inflammation instead of resolving it; moreover, frequent and prolonged administration may lead to serious complications.^{6,20,22,28,30} These data argue against the routine administration of corticosteroids during a first episode of acute pericarditis.

Safety

At doses of 1 to 2 mg per day, colchicine has been found to be safe even when given continuously over decades.^{1,2,16} Gastrointestinal side effects are not uncommon, occurring in up to 10% of cases, although they are generally mild and may resolve with dose reduction.^{31,32} In studies in which colchicine was used to treat recurrences, temporary discontinuation of the drug or a reduction of its dose was needed in ≈10% to 14% of cases.¹⁶ These side effects may limit its therapeutic applicability.

In the present study, on the basis of previous experiences,^{13,24} we used the lowest effective dose while also taking into account the weight of the treated patients. With these doses, we recorded

5 cases of diarrhea (8.3%), which were promptly reversible after drug withdrawal. Two (40.0%) of these patients experienced recurrences after drug discontinuation. No serious adverse effects were observed. In the largest prospective multicenter study on recurrent pericarditis and colchicine,¹¹ the drug (≥ 1 mg/d) was discontinued in 39 patients (76.5%), and 14 of them (35.9%) experienced relapses.

Other concerns are related to bone marrow suppression and fertility. After a cumulative 15 000 years of follow-up in patients with familial Mediterranean fever, no interference of colchicine treatment was recorded with regard to either growth rate or fertility.³³

Study Limitations

A possible study limitation is the open-label design. This work was designed as a preliminary study to test the hypothesis that early treatment of the first recurrence with colchicine as an adjunct to conventional therapy may reduce the subsequent recurrence rate. Moreover, the measured end points, including symptom status at 72 hours and symptom recurrence over time, are subjectively determined by the patient and physician. These limitations would have been avoided by the use of a double-blind study design. However, validation of clinical events was ensured by an ad hoc committee of expert cardiologists blinded to patients' treatment assignment, whereas data analyses were performed by an external data analysis committee masked to treatment assignment. Moreover, strict adherence to the intention-to-treat principle ensures that the effects seen correspond closely to what is achievable in clinical practice. At present, this study is the first randomized trial in this area. The present study provides good evidence that colchicine as an adjunct to conventional therapy is safe and effective in treatment of the first episode of acute pericarditis, and it shows that colchicine plus conventional therapy might be considered as first-choice treatment for acute pericarditis.

Appendix

Investigators of the COPE Trial

Coordinating Center: Cardiology Department, Maria Vittoria Hospital, Turin, Italy. Ad Hoc Committee for the Validation of Clinical Events: E. Cecchi, D. Demarie. Safety Monitoring Committee: R. Trinchero, M. Imazio. External Data Analysis Committee: M. Bobbio, A. Brusca (deceased). COPE trial centers: Maria Vittoria Hospital, Amedeo di Savoia Hospital, Turin, Italy.

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