Clinical Study

Heart*Drug*

The Efficacy of Colchicine in the Treatment of Recurrent Pericarditis Related to Postcardiac Injury (Postpericardiotomy and Postinfarcted) Syndrome: A Multicenter Analysis

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Abstract

Background: Pericarditis related to the postcardiac injury syndrome (PCIS) following myocardial infarction or cardiac surgery is a troublesome and often recurrent clinical entity resistant to therapeutic interventions. The usefulness of colchicine in the prevention of recurrent PCIS has not been evaluated. ***Objective:*** We performed a cumulative analysis of available multicenter data with the aim of evaluating the efficacy of colchicine in the treatment of recurrent PCIS. ***Methods and Results:*** The study was designed as a multicenter all-cases analysis. Researchers who had published studies and case reports on colchicine treatment in recurrent pericarditis related to PCIS during the last 15 years were approached and asked to contribute all available cases to the database. There were 28 patients, 18 male (64%) and 10 female (36%), ranging in age from 21 to 82 years (mean 53 ± 15 years). PCIS pericarditis was secondary to pericardiotomy in 19 patients and infarction in 9. In 21 patients (75%), colchicine therapy was discontinued during follow-up and renewed only in the case of relapse. In these patients, the total period of treatment was summed up for analysis. 7 patients (25%) were taking colchicine as a permanent treatment, and no colchicine-free follow-up was documented. In total, 130 recurrences (mean 4.64 ± 3.7 per patient, range 2–16) were noted before colchicine therapy was initiated. During colchicine treatment (mean duration of treatment 16.6 ± 13.5 months), a significant reduction in the number of recurrences was observed. Only 5 of 28 patients (18%) presented with new recurrences (mean 0.25 ± 0.59 vs. 4.64 ± 3.7 per patient in the precolchicine period, p < 0.001). The mean follow-up period after colchicine discontinuation (data were available for 21 patients) was 31.9 ± 28 months; during follow-up, 13 patients (62%) remained recurrence free and 8 of them (38%) experienced relapses (mean 0.43 ± 0.6

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per patient, p < 0.001 vs. precolchicine). ***Conclusions:*** It seems that colchicine may be effective in preventing new relapses in patients with recurrent pericarditis related to postcardiac injury both during active therapy and after its discontinuation.

Introduction

Late pericarditis following myocardial infarction (Dressler's syndrome) or cardiac surgery (Dressler's-like syndrome) is referred to as postmyocardial infarction syndrome (PMIS) or postpericardiotomy syndrome, respectively [1, 2]. The term postcardiac injury syndrome (PCIS) is used to encompass both these entities [3, 4]. PCIS is characterized by fever, pleuropericardial pain, pericarditis and pulmonary involvement. Evidence supports an immunopathic etiology of this syndrome. Currently, the classical postmyocardial infarction Dressler's syndrome has been rendered a rare phenomenon among patients who benefit from early revascularization [5]. In contrast, the incidence of postpericardiotomy syndrome is high and varies from 13% [6] to 47% [7].

Postpericardiotomy syndrome is a troublesome and often recurrent clinical entity [6–10]. Accepted modalities of PMIS treatment have traditionally included nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressive agents and, in unremitting cases, pericardiectomy (usually unsuccessful), while relapses may occur during attempts to reduce drug dose. Unfortunately, recurrent pericarditis may be a debilitating disease resistant to therapeutic interventions [6–11].

Recently, the first study to demonstrate the benefits of colchicine for the *primary prevention* of postpericardiotomy syndrome in patients after cardiac surgery was published [12]. However, the usefulness of colchicine in the prevention of recurrent PMIS has not been evaluated.

Therefore, we decided to perform a cumulative analysis of all available multicenter data in order to evaluate the efficacy of colchicine in treatment of recurrent PCIS.

Methods

The study was designed as a multicenter all-cases analysis. Researchers who had published studies and case reports on colchicine treatment in recurrent pericarditis of any etiology during the last 15 years were approached and asked to contribute all available cases to the database. Patient data were obtained from Italy (n = 44), Spain (n = 33), France (n = 37), Israel (n = 20), Lebanon (n = 3), Turkey (n = 2) and Denmark (n = 1).

A total of 140 cases were screened initially to investigate the following inclusion criteria:

(1) PCIS etiology of pericarditis (postpericardiotomy or postinfarction);

(2) clinical diagnosis of two or more relapses of acute pericarditis before institution of colchicine therapy;

(3) therapeutic trial of colchicine beyond its use during the tapering period of corticosteroids or NSAIDs;

(4) complete documented follow-up since the first episode of acute pericarditis including reports on therapeutic trials with corticosteroids, and continuing for at least 1 month following initiation of colchicine therapy, and

(5) colchicine dose of 1 mg/day for a prolonged period to achieve homogeneity of treatment.

In particular, data were considered complete only in patients with a methodical follow-up since the first episode of acute pericarditis, including precise information about the following predefined clinically relevant variables: age, sex, etiology of pericarditis, duration of follow-up since the first episode of pericarditis, use of corticosteroid therapy, number of relapses before initiation of colchicine treatment, duration of colchicine treatment and duration of follow-up after discontinuation of colchicine treatment. In addition, precise information needed to be documented about the number of relapses during colchicine treatment as well as during follow-up after discontinuation of colchicine treatment (postcolchicine). Twenty-one patients had to be excluded due to the lack of definitive age data or a colchicine dose different from 1 mg/day. In 91 patients, the etiology of pericarditis was other than PCIS (mainly idiopathic); these patients were also excluded. Therefore, the final study sample comprised 28 patients with PCIS pericarditis who met the inclusion criteria.

Results are expressed as mean values ± SD for continuous variables and as frequency and percentage for categorical variables. Comparison of categorical characteristics was performed by χ^2 analysis and Fisher's exact test. A t test was performed for continuous variables. A p value <0.05 was considered significant. Correlations between all continuous variables were conducted by Pearson correlation.

Results

In this study, there were 28 patients, 18 male (64%) and 10 female (36%), ranging in age from 21 to 82 years (mean 53 ± 15 years). PCIS pericarditis was secondary to pericardiotomy in 19 patients and infarction in 9. In 21 patients (75%), colchicine therapy was discontinued during follow-up and renewed only in the case of relapse. In these patients, the total length of treatment was summed up for analysis. Seven patients (25%) were taking colchicine as a permanent treatment, and no colchicine-free follow-up was documented.

Despite treatment with NSAIDs, corticosteroids, pericardiocentesis or some combination thereof, all patients (100%) experienced relapses before inclusion in this study, representing statistics arising from the definition. In total, 130 recurrences (mean 4.64 ± 3.7 per patient,

Table 1. Follow-up duration and number of relapses in study patients

Variable	Before colchicine treatment	During active treatment with colchicine	Follow-up after colchicine treatment[1]
Follow-up duration, months	17.4 ± 29	16.6 ± 13.5	31.9 ± 28
Number of relapses per patient	4.64 ± 3.7	0.25 ± 0.59	0.43 ± 0.6
Number of patients with relapse	28 (100)	5 (18)	8 (38)

Figures in parentheses represent percentages.
[1] Available for only 21 patients.

Table 2. Pearson correlation coefficients between duration of follow-up, number of relapses and age of patients with PCIS

	Age	Follow-up before	Number of relapses before	Duration of treatment	Number of relapses during	Follow-up after	Number of relapses after
Age	1.0	−0.46*	−0.48*	−0.13	−0.17	−0.21	−0.15
Follow-up before		1.0	0.49*	−0.10	−0.16	−0.12	0.16
Number of relapses before			1.0	0.07	−0.13	0.13	0.05
Duration of treatment				1.0	0.32	−0.35	0.52*
Number of relapses during					1.0	−0.23	0.25
Follow-up after						1.0	−0.34
Number of relapses after							1.0

'Before', 'during' and 'after' refer to the periods before, during and after colchicine treatment. * $p < 0.05$.

range 2–16) were noted before colchicine therapy was initiated. During colchicine treatment (mean duration of treatment 16.6 ± 13.5 months), a significant reduction in the number of recurrences was observed (table 1). Only 5 of 28 patients (18%) presented with new recurrences (mean 0.25 ± 0.59 vs. 4.64 ± 3.7 per patient in the pre-colchicine period, $p < 0.001$). The mean length of follow-up after colchicine discontinuation (data were available for 21 patients) was 31.9 ± 28 months; during follow-up, 13 of these patients (62%) remained recurrence free and 8 of them (38%) experienced relapses (mean 0.43 ± 0.6 per patient, $p < 0.001$ vs. precolchicine). The recurrences after colchicine discontinuation were generally minor and were effectively controlled in all patients by the reinstitution of colchicine therapy. Gastrointestinal side effects were minor (diarrhea and nausea) and resolved in all patients.

Table 2 details the correlations between age, number of relapses in each period and the duration of follow-up and treatment. As expected, there was a significant correlation between the duration of follow-up and number of relapses before colchicine treatment ($r = 0.49$, $p = 0.008$). No correlation was found between the duration of colchicine treatment and number of relapses before colchicine treatment. There was no correlation between the numbers of relapses in each period of follow-up; in particular, there was no connection between the number of relapses before colchicine treatment and the number of relapses under colchicine treatment or after its discontinuation.

Discussion

Colchicine has traditionally been used for the treatment of gout. The complex actions of this substance, which are mainly attributable to its stabilizing action on the cytoskeleton and cell membranes, and its special pattern of distribution form the basis for the results presented here regarding the prophylactic or therapeutic actions of colchicine in a whole range of other diseases. This is all the more significant in that in several instances it concerns diseases that have so far been unsatisfactorily con-

trolled by other treatments [13]. The present multicenter analysis demonstrates that colchicine is effective in preventing recurrences of pericarditis in PCIS. These results are especially important, since the study included patients with a high risk of recurrence (on average, more than 4 previous relapses per patient).

Considering the natural course of the disease, which is characterized by periodical relapses [14], it might have been expected that patients would experience new recurrences after discontinuation of therapy. However, during a mean follow-up period of more than 2 years, 62% of the patients in whom colchicine was discontinued remained free from new relapses. The absence of a correlation between the numbers of relapses per patient in the different periods of follow-up (before, during and after colchicine) indeed supports the concept that colchicine therapy provides sustained benefit even after discontinuation of the drug.

Study Limitations

The present study is an analysis of patients with recurrent PCIS with substantial variation in the number of previous relapses and the timing of instituting colchicine therapy as well as treatment duration. Eventually, only a randomized placebo-controlled double-blind trial may provide a definitive conclusion regarding optimal therapy for recurrent PCIS. However, in the absence of these data, the analysis of the present database provides an important source of information to guide the treatment of this problematic patient group.

Conclusions

It seems that colchicine may be effective in preventing new relapses in patients with recurrent pericarditis related to postcardiac injury both during active therapy and after its discontinuation.

Acknowledgments

References

1 Dressler W: A post-myocardial infarction syndrome; preliminary report of a complication resembling idiopathic, recurrent, benign pericarditis. JAMA 1956;160:1379–1383.
2 Nishimura RA, Fuster V, Burgert SL, Puga FJ: Clinical features and long-term natural history of the postpericardiotomy syndrome. Int J Cardiol 1983;4:443–454.
3 Khan AH: The postcardiac injury syndromes. Clin Cardiol 1992;15:67–72.
4 Kim S, Sahn SA: Postcardiac injury syndrome. An immunologic pleural fluid analysis. Chest 1996;109:570–572.
5 Shahar A, Hod H, Barabash GM, Kaplinsky E, Motro M: Disappearance of a syndrome: Dressler's syndrome in the era of thrombolysis. Cardiology 1994;85:255–258.
6 Fowler NO, Harbin AD III: Recurrent acute pericarditis: Follow-up study of 31 patients. J Am Coll Cardiol 1986;7:300–305.
7 Adler Y, Finkelstein Y, Guindo J, Rodriguez de la Serna A, Shoenfeld Y, Bayes-Genis A, Sagie A, Bayes de Luna A, Spodick DH: Colchicine treatment for recurrent pericarditis. A decade of experience. Circulation 1998;97:2183–2185.
8 Adler Y, Zandman-Goddard G, Ravid M, Avidan B, Zemer D, Ehrenfeld M, Shemesh J, Tomer Y, Shoenfeld Y: Usefulness of colchicine in preventing recurrences of pericarditis. Am J Cardiol 1994;73:916–917.
9 Maning WJ: Diseases of the pericardium; in Bennet JC, Goldman L (eds): Cecil Textbook of Medicine, ed 20. Philadelphia, WB Saunders, 1996, pp 336–342.
10 Spodick DH: Pericardial diseases; in Braunwald E, Zipes DP, Libby P (eds): Heart Disease, ed 6. Philadelphia, WB Saunders, 2001, pp 823–1866.
11 Spodick DH: Acute pericarditis: Current concepts and practice. JAMA 2003;289:1150–1153.
12 Finkelstein Y, Shemesh J, Mahlab K, Abramov D, Bar-El Y, Sagie A, Sharoni E, Sahar G, Smolinsky AK, Schechter T, Vidne BA, Adler Y: Colchicine for the prevention of postpericardiotomy syndrome. Herz 2002;27:791–794.
13 Lange U, Schumann C, Schmidt KL: Current aspects of colchicine therapy – classical indications and new therapeutic uses. Eur J Med Res 2001;6:150–160.
14 Adolph RJ: Old drugs with new uses. Colchicine for the treatment of recurrent pericarditis. Circulation 1990;82:1505–1506.