Colchicine Treatment for Recurrent Pericarditis

A Decade of Experience

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Background—The most troublesome complication of acute pericarditis is recurrent episodes of pericardial inflammation, occurring in 15% to 32% of cases. The cause of the recurrence is usually unknown, although in some cases it may be traced to viral infection or may be a consequence of coronary artery bypass grafting. The optimal method for prevention has not been fully established; accepted modalities include nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy.

Methods and Results—Based on the proven efficacy of colchicine therapy for familial Mediterranean fever (recurrent polyserositis), several small studies have used colchicine successfully to prevent recurrence of acute pericarditis after failure of conventional treatment. Recently, we reported the results from the largest multicenter international study on 51 patients who were treated with colchicine to prevent further relapses and who were followed up for ≤10 years.

Conclusions—In light of new trial data that have accumulated in the past decade, we review the evidence for the efficacy and safety of colchicine for the prevention of recurrent episodes of pericarditis. Clinical and personal experience shows that colchicine may be an extremely promising adjunct to conventional treatment and may ultimately serve as the initial mode of treatment, especially in idiopathic cases. (Circulation. 1998;97:2183-2185.)

Key Words: pericarditis ■ colchicine

Acute inflammation of the pericardium is usually of idiopathic etiology, but it may also be secondary to systemic infection, acute myocardial infarction, cardiac contusion, and autoimmune diseases.

The most troublesome complication of acute pericarditis is the development of recurrent episodes of pericardial inflammation, occurring in 15% to 32% of cases. Recurrent pericarditis is, in most cases, idiopathic. The pathophysiological process may involve the immune system: high titer of anti-myocardial antibodies have been found in post–open heart surgery patients with acute pericarditis. The optimal method for preventing recurrences has not been established. Therapeutic modalities are nonspecific and include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressive agents, and pericardiectomy. Relapses may also occur during reduction of drug doses (incessant pericarditis) or at varying intervals after discontinuation of treatment (recurrent pericarditis). Because treatment is often difficult and recurrences may occur over a period of many years, constant efforts are being directed toward establishing better means for prevention. In light of recent trial data, we will review the evidence supporting the use of colchicine in preventing recurrent episodes of pericarditis.

On the basis of proven efficacy of colchicine in preventing relapses of systemic inflammatory processes in familial Mediterranean fever (recurrent polyserositis), Rodriguez de la Serna and colleagues suggested in 1987 that colchicine be used to prevent recurrences of acute pericarditis. They reported on 3 patients who had recurrent pericarditis (2 idiopathic and 1 with systemic lupus erythematosus), despite adequate treatment with corticosteroids. All were treated with colchicine (1 mg/d) with tapering of the corticosteroids within 2 months. There were no relapses throughout the follow-up period of 15 to 35 months.

In a later prospective study, Guindo and colleagues reported on 9 patients (5 idiopathic, 2 post–open heart surgery, 1 with Dressler’s syndrome, and 1 with systemic lupus erythematosus) in whom NSAIDs and corticosteroids failed to prevent relapses of pericarditis (mean of 4.3 episodes per patient). All were treated with combined prednisone (20 to 60 mg/d), which was tapered and discontinued within 6 weeks, and colchicine (1 mg/d). Chest pain was effectively relieved, and no recurrences of pericarditis were noted within a 10- to 54-month follow-up period.

Adler and coworkers reported on 8 patients with recurrent pericarditis (5 idiopathic, 2 post–open heart surgery, 1 post chest trauma) who had not responded to NSAIDs (6 patients), corticosteroids (7 patients), and pericardiocentesis (3 patients). All responded to colchicine (1 mg/d) and corticosteroids. The corticosteroids were discontinued within 2 to 6 months.
months, and no recurrences were noted during the 18 to 34 months of follow-up. This result contrasts with a total of 26 relapses in these 8 patients before the introduction of colchicine. Four patients in whom colchicine had been withdrawn because of noncompliance or mild gastrointestinal side effects experienced a relapse within 1 to 12 weeks. With reinstitution of colchicine therapy, they remained symptom-free for the 15 to 24 months of follow-up.

Millaire and coworkers\textsuperscript{15} reported on 19 patients who had recurrent pericarditis and were treated with colchicine (loading dose of 3 mg/d, reduced to 1 mg/d). Fourteen had no recurrences during a follow-up period of 32 to 44 months. In 4 others, relapses were successfully treated with NSAIDs, and these patients remained symptom-free for an additional 11 to 37 months. Only 1 patient had multiple relapses and needed corticosteroids. The authors concluded that colchicine was an effective alternative therapy for recurrent pericarditis and might even replace corticosteroids. In another report by Adler et al.,\textsuperscript{16} colchicine totally prevented relapses in 56% of patients with previous episodes (range, 2 to 15 attacks) in a long-term follow-up (mean, 36 months per patient) study, and when relapses did occur, they were usually mild and easily controlled without steroids. These researchers suggested that colchicine might even serve as the initial mode of therapy for recurrent pericarditis, because most of the patients who experienced relapses after the institution of colchicine or its withdrawal were those who had previously been treated with corticosteroids.\textsuperscript{17} Indeed, several studies have found that corticosteroids may have severe side effects and lead to new recurrences of pericarditis or prolong disease duration.\textsuperscript{17–20} Thus, colchicine may also have a role in facilitating their tapering-off process.\textsuperscript{9} Still, some authors doubt the efficacy of colchicine because a double-blind, controlled study on the subject is difficult to perform.\textsuperscript{21} It was for this reason that Fowler and Harbin\textsuperscript{22} examined the natural history of recurrent pericarditis to determine the frequency of spontaneous remissions. Of the 31 patients included in their study, only 8 had a remission period that exceeded 1 year; in 5 of the 8, remission exceeded 2 years.

A partial answer to these doubts may be found in the largest multicenter study on recurrent pericarditis and colchicine published to date.\textsuperscript{23} Fifty-one affected patients (36 men and 15 women; mean±SD age, 40.8±18.7 years) who were treated with colchicine to prevent further relapses were followed up for ≤10 years (range, 6 to 128 months; mean, 36.0 months). The pericarditis was idiopathic in 33 patients and secondary in 18. Despite treatment with NSAIDs (n=47), corticosteroids (n=29), pericardiectomy (n=8), or some combination thereof, 187 recurrences (mean, 3.58±3.64; range, 2 to 15) were noted before colchicine therapy was initiated, with a mean interval between crises of 2.0 months (range, 0.5 to 19 months). During 1004 patient-months of colchicine treatment, only 7 of 51 patients (13.7%) presented with new recurrences. Colchicine was discontinued in 39 patients, and 14 of them (35.8%) experienced relapses. These recurrences were generally minor and were effectively controlled in all patients by the reinstitution of colchicine therapy, sometimes with a dose adjustment of the drug (≤2 mg/d). Gastrointestinal side effects were mild (diarrhea and nausea) and resolved in all patients. During the 2333 patient-months of follow-up, 31 patients (60.7%) remained recurrence-free. Comparison of the symptom-free periods before and after colchicine treatment yielded significant statistical differences (3.1±3.3 versus 43.0±35.0 months, P<0.0001). The authors concluded that colchicine was effective and safe for the long-term prevention of recurrent pericarditis.

The exact mechanism whereby colchicine prevents recurrences of pericarditis is still not fully understood. Colchicine has been used for several centuries as an anti-inflammatory agent for acute arthritis and is the most specific known treatment for acute attacks of gout. Colchicine binds to tubulin, blocks mitosis,\textsuperscript{9} and inhibits a variety of functions of polymorphonuclear leukocytes both in vivo and in vitro.\textsuperscript{24} Colchicine also interferes with the transcellular movement of collagen.\textsuperscript{25} The close proximity of lymphoid components and fibroblasts at inflammatory sites and the production of lym- phokines, which influence fibroblast chemotaxis, proliferation, and protein synthesis, are now well recognized.\textsuperscript{26} Thus, colchicine may reduce immunopathic antifibroblastic properties. The peak concentration of colchicine in white blood cells may be ≥16 times the peak concentration in plasma. This preferential concentration of colchicine in lymphocytes is related to its observed therapeutic effect.\textsuperscript{27}

Cumulative anecdotal evidence indicates that colchicine may also be effective in the treatment of the initial episodes of acute pericarditis. Millaire and Durlaux,\textsuperscript{28} in a study of 19 patients, described the efficacy of colchicine for the first episode of acute pericarditis, especially when it was idiopathic, viral, or post–open heart surgery. Colchicine effectively controlled the acute phase of pericarditis in almost all cases. Only two relapses were noted in a mean follow-up period of 5 months (range, 1 to 12 months), one due to discontinuation of treatment after 8 days and the other due to noncompliance.

Recently, we examined the usefulness of colchicine for the treatment of large pericardial effusions as complications of idiopathic pericarditis.\textsuperscript{29} Colchicine (1 mg/d) was administered to two patients (26 and 2 years old) with large acute or chronic pericardial effusions who did not respond well to therapy with NSAIDs, corticosteroids, and pericardiectomy. Response was immediate and dramatic in both cases, with disappearance of the pericardial effusion on echocardiography. Neither patient suffered a relapse during the respective 24 and 6 months of follow-up.

In addition to its apparently greater efficacy compared with corticosteroids,\textsuperscript{9,26} colchicine may also have a sparing effect on steroids, which have severe systemic side effects over time and may prolong disease duration.\textsuperscript{17–20} Furthermore, immunosuppressive drugs and pericardiectomy are generally not appropriate and may even be life threatening,\textsuperscript{23} whereas colchicine is usually well tolerated, with only minor side effects. During a total of 1004 patient-months of colchicine treatment (mean, 12 months per patient), temporary discontinuation of the drug or a reduction of its dose was needed in only 7 of 51 patients (13.7%).\textsuperscript{23} This was due to mild gastrointestinal side effects (diarrhea and nausea) in all cases, which are the common drawbacks of colchicine therapy. Drug toxicity with respect to long-term administration of
colchicine might be estimated from familial Mediterranean fever or gout patients. Azoospermia and chromosomal abnormalities have been reported with long-term treatment, but these findings are debatable.

In conclusion, colchicine seems to be an effective and safe agent for the prevention of recurrent episodes of pericarditis. Colchicine is an extremely promising adjunct to the conventional treatment of recurrent pericarditis and may ultimately serve as the initial mode of treatment, especially in idiopathic cases. Considering that recurrent pericarditis is not life threatening and that long-term treatment is aimed at improving the quality of life, we suggest that corticosteroids should be limited to very severe cases. Milder cases may initially be treated with colchicine as well as with NSAIDs (ibuprofen).

The recommended dose of colchicine according to most studies is 1 mg/d for at least 1 year, with a gradual tapering off. The need for a loading dose of 2 to 3 mg/d at the beginning of treatment is unclear. The drug is well tolerated. Gastrointestinal side effects develop in only a small proportion of patients, are usually minor, and do not require discontinuation of treatment in most cases.

Despite the promising data on the efficacy and safety of colchicine for recurrent pericarditis that have accumulated in the past decade, large, controlled, prospective studies are required to provide definitive answers on the subject.

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References
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