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Original article

Does colchicine decrease the rate of recurrence of acute idiopathic pericarditis treated with glucocorticoids?

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ABSTRACT

Background: The traditional treatment of acute pericarditis includes non-steroidal anti-inflammatory agents (NSAIDs) or glucocorticoids. The addition of colchicine has been found to reduce the rate of recurrences. Glucocorticoids, however, may attenuate this effect, although the available data are limited. We examined the impact of colchicine on the rate of recurrence of acute idiopathic pericarditis pretreated with prednisone.

Methods: The frequency of recurrence in patients hospitalized for acute idiopathic pericarditis in a tertiary medical center in 2004–2014 who were treated with glucocorticoids or with non-steroidal therapy was assessed from the computerized hospital database. A retrospective design was used.

Results: The cohort included 199 patients aged 18–86 years. Sixty-two (31%) were treated with prednisone, 42 with colchicine and 20 without, and 133 with non-steroidal therapy; in 4 patients, therapy was not detailed. Follow-up ranged from 13 to 147 months (median, 48 months). Fifty-three patients (26.6%) experienced at least one recurrence of pericarditis. The recurrence rate was significantly higher in patients who received prednisone and colchicine (17/42, 40.5%) than in patients who received NSAIDs or aspirin and colchicine (8/44, 18.2%, $p = 0.03$) or any non-steroidal therapy (30/133, 22.6%, $p = 0.03$). There was no difference between the rate of recurrence in patients who were treated with prednisone alone (5/20, 25%) and those treated with NSAIDs or aspirin and colchicine or with any non-steroidal therapy (p = NS). Baseline characteristics and duration of follow-up were similar in patients with and without recurrence. Hospital stay was longer in patients treated with prednisone alone as compared to patients treated with prednisone and colchicine. There were no other differences in baseline characteristics between these groups.

Conclusions: The addition of colchicine to prednisone in patients admitted for acute idiopathic pericarditis does not reduce the risk of recurrence. This finding suggests that prednisone blunts the salutary effects of colchicine.

Introduction

Acute pericarditis is diagnosed in 5% of patients admitted to the emergency department with chest pain not associated with acute myocardial infarction [1,2]. It accounts for 0.2% of all cardiovascular admissions [3]. In developed countries, 80–90% of all cases of pericarditis are idiopathic [2], presumably complicating the course of a viral infection. The remaining 10% to 20% of cases are related mostly to post-pericardial injury, connective tissue disease, tuberculosis, genetic diseases such as familial Mediterranean fever, and malignancy [2]. A recurrence of idiopathic pericarditis is seen in 15–30% of patients [2,4] and may portend significant morbidity and disability. The mechanism predisposing patients to recurrence is not well established; autoimmune as well as infectious etiologies have been proposed [4,5]. The conventional therapy for acute pericarditis includes steroids or non-steroidal anti-inflammatory agents (NSAIDs) [2,4]. Prednisone has been associated with a higher recurrence rate and more side effects than NSAIDs [4]. In recent years, the addition of colchicine to the treatment regimen has been

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found significantly to lower the incidence of recurrences and reduce the severity of symptoms [5–12]. However, most of the relevant prospective trials included only patients who were treated with NSAIDs for the acute episode. One study suggested that steroids may attenuate the efficacy of colchicine in preventing recurrence [12], but this has not been confirmed. Additionally, some of the studies on preventing recurrence of pericarditis evaluated heterogeneous groups of patients with pericarditis of varying etiologies, including post-pericardiotomy syndrome and rheumatoid arthritis.

The aim of the present study was to examine the impact of adding colchicine to prednisone on the rate of recurrence of acute idiopathic pericarditis.

Methods

The computerized database of a tertiary, university-affiliated, hospital was searched for all the patients admitted with a first episode of acute pericarditis between January 1, 2004 and December 31, 2014. Patients for whom an etiology for the pericarditis was identified (rheumatoid arthritis, systemic lupus erythematosus, familial Mediterranean fever, tuberculosis, post-pericardiotomy syndrome, chronic renal failure, or purulent pericarditis) were excluded, as were patients with severe systemic disease, active malignancy, or pneumonia, and pregnant patients. Other exclusion criteria were follow-up of less than 12 months and failure to meet current diagnostic criteria for acute pericarditis [4]. The final study group consisted of 199 patients with idiopathic acute pericarditis, defined as pericarditis for which no known specific cause was present. Demographic, clinical, electrocardiographic, radiological, biochemical, and echocardiographic data obtained during the acute phase were extracted from the files, in addition to data on complications, in-hospital course, and medications.

The diagnosis of acute pericarditis was based on the presence of at least 2 of the following 4 criteria: typical pleuritic chest pain, characteristic electrocardiographic changes, pericardial friction rub, and demonstration of new pericardial effusion [4]. The diagnosis of pericardial effusion was based on echocardiography, computed tomography, or magnetic resonance imaging findings. The criteria for recurrent pericarditis included a documented first attack of acute pericarditis, a symptom-free interval of 4 weeks or longer, patient complaints of recurrent pain, and one or more of the following signs: a pericardial friction rub, electrocardiographic changes suggestive of pericarditis, imaging evidence of new or worsening pericardial effusion, and elevation in C-reactive protein level or erythrocyte sedimentation rate [6,7,9,10,12]. Recurrence was recorded only if there was evidence of a hospital readmission or emergency room examination. These data appeared in the computerized database of our medical center, which includes information on these events from other hospitals in Israel as well.

Peak values of plasma C-reactive protein level and body temperature were recorded. White blood cell count was recorded at admission. The length of the prodromal period was defined as the time from symptom onset to hospital admission. The size of the pericardial effusion, when present, was semi-quantitatively assessed by the echocardiographer and dichotomously categorized as large or non-large. An elevated plasma troponin (cTn-T) level was defined according to the criteria used at the time of measurement.

The study was approved by the local institutional ethics committee.

Statistical analysis

Differences in mean continuous variables between groups were calculated with Student's t test, and differences in discrete variables, with chi-square or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

Age of the cohort ranged from 18 to 86 years [mean (SD) 50 (18) years]; 73.9% were male. The vast majority of patients (97%) presented with pleuritic chest pain. Pericardial effusion was found in 134 patients (67%), 9 with cardiac tamponade; 52 patients (26%) had concomitant pleural effusion. Eight patients (4%) needed interventions (pericardiotomy or pericardiocentesis). Sixty-two patients (31%) were treated with prednisone, and 133 patients with non-steroidal therapy: 25 (13%) with aspirin, 89 (45%) with other NSAIDs (ibuprofen or naproxen), 6 patients with colchicine alone, and 13 who were not given any anti-inflammatory medications. In 4 patients, information on medications was not provided. Plasma C-reactive protein level was increased in all but 3 of the 179 patients in whom it was measured.

The duration of follow-up ranged from 13 to 147 months (median, 48 months). During this period, 53 patients (26.6%) experienced a recurrence of pericarditis. In all but one patient, the pericarditis recurred during the first year after the initial episode. Eighteen patients had one recurrence, 14 had 2 recurrences, and 8 patients had more than 2 recurrences.

Table 1 shows the characteristics of the patients with and without recurrence. Baseline variables were not predictive of recurrence. The duration of follow-up was similar in the two groups (61.7 ± 36.5 months and 54.6 ± 31.5 months, respectively, $p = 0.21$).

Table 2 depicts the recurrence rates according to the choice of therapy for the first episode of pericarditis. Rates were similar in patients treated with prednisone alone or with NSAIDs or aspirin (NS/AS) alone (25.0% and 28.6%, respectively, p = NS). The addition of colchicine to NS/AS was associated with a 37% lower recurrence rate than NS/AS alone, but the difference did not reach statistical significance (18.2% vs 28.6%, p = NS). The rate of recurrence was significantly higher in patients treated with prednisone and colchicine than in patients treated with NS/AS and colchicine (40.5% vs 18.2%, $p = 0.03$), or any non-steroidal therapy (30/133, 22.6%, $p = 0.03$). There was no difference in the rate of recurrence between patients treated with prednisone alone (5/20, 25%) and patients treated with NS/AS or any non-steroidal therapy. There were no differences in clinical characteristics between patients who received prednisone and colchicine and those who received prednisone alone, except for a shorter hospital stay in the patients given colchicine (Table 3). To identify possible causes of bias in therapy selection, we compared the findings between patients given prednisone with or without colchicine and patients given non-prednisone therapy. As shown in Table 4, the patients who received prednisone were characterized by older age, longer hospitalization time, longer interval between onset of prodromal symptoms and admission, higher plasma C-reactive protein levels, and higher white blood cell count than patients who received non-prednisone treatment. They also had a higher frequency of large pericardial effusion, dyspnea, elevated troponin levels, pleural effusion, and symptoms of upper respiratory tract infection. However, none of these variables was significantly associated with recurrence.

Discussion

The addition of colchicine to the treatment regimen has been found previously to lower significantly the incidence of recurrences in patients with acute pericarditis who were treated mainly with NSAIDs [5–12]. The results of the present retrospective analysis show that in patients with acute idiopathic pericarditis treated with prednisone, as opposed to NSAIDs, the addition of colchicine does not reduce, and may even increase, the risk of recurrence. Our search of the literature yielded no studies that specifically examined the benefit of colchicine in preventing the

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