Do Colchicine and Prednisone Affect the Rate of Recurrence of Post-Pericardiotomy Syndrome

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ABSTRACT: **Background:** Post-pericardiotomy syndrome (PPS) is a major cause of pericarditis, yet data on the risk of recurrence are limited, and the impact of steroids and colchicine in this context is unknown.

Objectives: To examine the effect of prednisone and colchicine on the rate of recurrence of PPS.

Methods: Medical files of patients diagnosed with PPS were reviewed to extract demographic, echocardiographic, X-ray imaging, and follow-up data.

Results: The study comprised 132 patients (57% men), aged 27–86 years. Medical treatment included prednisone in 80 patients, non-steroidal anti-inflammatory agents in 41 patients, colchicine monotherapy in 2 patients, and no anti-inflammatory therapy in 9 patients. Fifty-nine patients were given colchicine for prevention of recurrence. The patients were followed for 5–110 months (median 64 months). Recurrent episodes occurred in 15 patients (11.4%), 10 patients had a single episode, 4 patients had two episodes, and one patient had three episodes. The rate of recurrence was lower in patients receiving colchicine compared to patients who did not (8.5% vs. 13.7%), and in patients not receiving vs. receiving prednisone (7.7% vs. 13.8%) but the differences were non-significant. Twenty-three patients died and there were no recurrence-related deaths.

Conclusions: The rate of recurrence after PPS is low and multiple recurrences are rare. The survival of patients with recurrent PPS is excellent. Prednisone pre-treatment was associated with a numerically higher rate of recurrence and colchicine treatment with a numerically lower rate, but the differences were non-significant.

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Post-pericardiotomy syndrome (PPS) occurs in up to 40% of the patients who undergo cardiac surgery [1-10], and may result in considerable morbidity and frequent need for invasive interventions [5,11]. PPS is believed to have an autoimmune pathogenesis triggered by damage to the pericardium or pleura. PPS is diagnosed when at least two of the following criteria are observed in patients after cardiac injury: fever without alternative cause, pericarditic or pleuritic chest pain, pericardial or pleural rubs, evidence of pericardial effusion, or pleural effusion with elevated C-reactive protein (CRP) levels [1].

Acute idiopathic pericarditis is often complicated by recurrence, observed in 15%–50% of the patients [1,12-15]. The underlying mechanism of recurrence is believed to be autoimmune, although re-infection has been shown to be the mechanism in approximately 23% of the patients [16]. Recurrence after idiopathic pericarditis may lead to significant morbidity and disability with prolonged courses of prednisone therapy, steroid-sparing agents, or interleukin blocking agents. Multiple recurrences are of particular concern and may necessitate a very long and aggressive therapy. Colchicine reduces the risk of recurrence after acute pericarditis [1,7,13,14,17,18], whereas steroid therapy is associated with increased risk [1] and may attenuate the preventive effect of colchicine [15].

Data on the risk of recurrence after PPS are very limited and based on small studies, which used divergent criteria for the diagnosis of PPS and recurrence, with conflicting results [2,4,5,18]. Moreover, the possible impact of prednisone pre-treatment and of colchicine in this context, and the frequency of multiple recurrences after PPS, are unknown. We examined the rate and number of recurrent episodes after PPS and whether treatment by colchicine and prednisone affected the recurrent episodes.

PATIENTS AND METHODS

The study was approved by the local institutional ethics committee.

This retrospective study comprised patients hospitalized at our medical center between 1 May 2009 and 1 May 2014 with a diagnosis of PPS. The medical files were reviewed for data on use of medications, as well as clinical, laboratory, and imaging findings. Data on follow-up including hospital re-admissions, emergency room attendance, recurrent episodes, and death were also gathered. The diagnosis of PPS was based on the presence of at least two of the following criteria: fever

without alternative cause, pericarditic or pleuritic chest pain, pericardial or pleural rubs, evidence of pericardial effusion, or pleural effusion with elevated CRP levels [1]. The criteria for the diagnosis of recurrence were the same as for the initial episode of PPS; however, patients had to be symptom-free for at least 1 month. Pericardial effusion was diagnosed by echocardiography or cardiac computed tomography (CT). Pleural effusion was diagnosed using plain chest roentgenography, or chest CT. Peak CRP levels was also recorded.

STATISTICAL ANALYSIS

Categorical variables were described as numbers and percentages and were compared among groups using the Chi-square test or Fisher's exact test. Continuous variables were compared using Student's *t*-test. A *P* value of < 0.05 was considered significant.

RESULTS

The study group comprised 132 patients (57% men) aged 27–86 years (mean ± standard deviation 64.9 ± 12.1 years). Coronary artery bypass graft surgery (CABG) was performed on 50 patients, 49 had valve surgery, 23 had both, and 10 had surgery for aortic or congenital heart disease. Medical treatment for the initial episode included steroids for 80 patients, non-steroidal anti-inflammatory agents (NSAIDs) for 41 patients, and colchicine monotherapy for 2 patients. Nine patients did not receive anti-inflammatory therapy. Colchicine was administered to 59 patients for prevention of recurrence. The patients were followed for 5–110 months (median 64 months). Fifteen patients (11.4%) had recurrent episodes: 10 patients had a single recurrence, 4 patients had two recurrences, and 1 patient had three recurrent episodes. The time range to first recurrence was 1–21 months. There were no differences in age (62.13 ± 12.37 years vs. 65.17 ± 12.23 years, $P = 0.363$), high-sensitivity CRP (hs-CRP) levels (9.26 ± 7.35 mg/dl vs. 10.41 ± 6.87 mg/dl, $P = 0.559$), time from surgery to PPS (30.71 ± 40.29 days vs. 22.65 ± 39.07 days, $P = 0.468$), or follow-up duration (68.67 ± 22.08 months vs. 62.26 ± 22.84 months, $P = 0.307$) among patients with or without recurrence. Table 1 shows the frequency of recurrence according to baseline characteristics and medications. There were no differences between patients with or without recurrence in terms of age, sex, type of surgery, frequency of pleural and pericardial effusion, follow-up duration, or medications. The levels of hs-CRP were measured in 123 patients. The rate of recurrence in patients with hs-CRP level above and below median (9.3 mg/dl) was similar (11.3% vs. 11.5%, P = non-significant). The rate of recurrence in patients who were treated with colchicine (8.5%) was numerically lower than the rate in patients not treated (13.7%), although the difference was not statistically significant. The rate of recurrence in patients treated with prednisone (13.8%) was numerically higher than the rate in patients not treated with prednisone (7.7%), but the difference was not statistically significant. Anticoagulants and diabetes did not affect the rate of recurrence. Twenty-three patients died during follow-up, which was 6–68 months after PPS. There were no recurrence-related deaths.

Table 1. Frequency of recurrence by medications and baseline characteristics

	Yes number (%)	No number (%)	*P* value
Male gender	8 (10.7)	7 (12.3)	0.788
Diabetes mellitus	6 (11.3)	8 (10.1)	› 0.999
CABG	5 (10.0)	10 (12.2)	0.738
Valve	6 (12.2)	9 (10.8)	0.785
CABG + valve	1 (4.3)	14 (12.8)	0.468
Other chest surgery	3 (30.0)	12 (9.8)	0.088
Pericardial effusion	14 (13.2)	1 (4.8)	0.698
Pleural effusion	13 (10.7)	2 (22.2)	0.278
LV dysfunction	1 (7.4)	13 (11.1)	0.298
Prednisone	11 (13.8)	4 (7.7)	0.402
Colchicine	5 (8.5)	10 (13.7)	0.416
Anticoagulants	3 (5.7)	12 (15.2)	0.095

CABG = coronary artery bypass graft surgery, LV = left ventricular

DISCUSSION

To the best of our knowledge, this is the first report on the impact of colchicine and prednisone therapy on the recurrence of PPS. The results show that the rate of recurrence in patients with PPS diagnosed according to current guidelines is low, multiple recurrences are rare, and the survival of patients with recurrent PPS is excellent. The rate of recurrence in patients treated with colchicine was substantially lower than in patients not treated but the difference was not statistically significant. The rate of recurrence in patients pretreated with prednisone was numerically higher than those who did not receive prednisone but the difference was nonsignificant.

The rate of recurrence of PPS in previous trials varied remarkably. In the COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial, the rate of recurrence was 0% in patients with PPS who received colchicine after cardiac surgery for primary prevention of PPS and 5% in the control group ($P = 0.485$) [19]. The mean follow-up duration was 18.5 months in the placebo group and 20.2 months in the colchicine group. The diagnosis of PPS was based on the presence of at least two of the following in patients after cardiac surgery: fever lasting beyond the first postoperative week, pleuritic chest pain, friction rub, pleural effusion, and new or worsening pericardial effusion. The criteria for the diagnosis of recurrence were not detailed. By contrast, Imazio et al. [7] reported on recurrence in 3 of 35 patients (8.6%) who developed PPS despite

colchicine pre-treatment and in 3 of 53 patients (5.7%) with PPS who were not treated with colchicine. A recurrence rate of 3.7% has been reported in a trial that included 54 patients with PPS [4]. Mean follow-up duration was 19.8 months. Most recurrences occurred during the first 2 months. CRP elevation was not required for the diagnosis of PPS in this trial and unlike other studies, chest pain was a prerequisite for the diagnosis of recurrence. Lehto and colleagues [5] reported a recurrence rate of 38% (23 of 61 patients). However, they defined a relapse as worsening of pericardial or pleural effusion while on medication or after withdrawal of medication, whereas in our patients the diagnosis of PPS was made when 2 of the 5 criteria recommended by current guidelines existed.

The criteria for diagnosis of a relapse in our patients were the same as for the initial episode. However, to exclude patients with a persistent course, we included only patients who were symptom-free for at least 1 month. As the results show, use of these strict diagnostic criteria yielded an intermediate rate of recurrence of PPS as compared to previous reports. As our data show, recurrence in our patients was not influenced by age, type of surgery, or left ventricular function.

The lack of impact of prednisone pretreatment on recurrence in our patients is not surprising. Two possible mechanisms for recurrence after viral pericarditis have been suggested: an immune response, possibly in genetically predisposed patients, or re-infection. In PPS, infection has not been shown to play an important role. Since prednisone is thought to promote recurrence due to its effect on viral replication and clearance, it is not surprising that prednisone pre-treatment was not associated with recurrence in our patients. By contrast, the lack of effect of colchicine on recurrence in our patients is surprising given the non-specific mechanism of the anti-inflammatory effect of colchicine and its value in prevention of recurrence after idiopathic pericarditis [1,9,13,14,17]. The rate of recurrence among our patients who were not given colchicine, 13.7%, was almost twice the rate among patients who were given colchicine. The difference was not statistically significant but our study might have been underpowered to detect a therapeutic effect, particularly of colchicine. Considering the low event rate, randomized trials or larger observational ones are necessary and the current study cannot be considered definitive regarding this issue.

Many risk factors for PPS have been identified such as low body mass index, younger age, female gender, history of prednisone use, past history of pericarditis, preoperative treatment of pulmonary disease, aortic valve replacement, pleura incision, enflurane or halothane anesthesia, higher postoperative complement conversion products, lower preoperative interleukin-8 levels, transfusion of red blood cells, and lower preoperative platelet and hemoglobin levels [3,4,20]. Postoperative colchicine reduced the risk of PPS [9,19]. Diabetes and metformin use appear to protect from PPS [5]. The role of these factors on the risk of recurrence is unclear. In our patients, halothane and enflurane were not used and diabetes was not protective from recurrence. Genetic background may predispose to idiopathic recurrent pericarditis [21]. However, the role of genetic background in PPS has not been elucidated. Carriage of a Mediterranean Fever (MEFV) gene mutation may protect against severe PPS [22], although its role in PPS recurrence has not been examined.

The number of recurrences has a clinical importance. Recurrence can be associated with significant morbidity, including episodes of pain, need for hospital readmission, impairment of everyday activities, need to avoid exertion, adverse effects of medical therapy, absence from work, and occasionally need for pleural drainage and other interventions. Prednisone therapy may be necessary for long periods of time, and, in some patients, steroid-sparing medications or daily subcutaneous injections of interleukin blocking agents. In patients with multiple recurrences, the periods of treatment and inconvenience are longer. Our group previously reported a rate of 4% of multiple recurrences in patients with acute idiopathic pericarditis and 15% of the patients with recurrence had more than two episodes [15]. In the present study, only one patient had more than two recurrences, and no patients had more than three. This, together with the excellent survival rate in patients with recurrence, emphasizes the good prognosis of patients with recurrent PPS, and suggests that recurrent PPS is a self-terminating disease.

LIMITATIONS

The study was retrospective. However, because the patients were consecutive and all had follow-up, the likelihood of a bias was low. Since we did not have data on compliance or dosage of medications, assessment of the effect of prednisone and colchicine on recurrence was conducted on an intention-to-treat basis. Both initial and recurrent episodes were recorded only if patients visited the emergency department. Thus, it is possible that we missed mild cases treated in the community. However, given current local medical practice, the likelihood of non-attendance of a patient with clinically significant morbidity after cardiac surgery is very low. In addition, because of the low recurrence rate, our study may be underpowered to detect the therapeutic effect of colchicine in this context.

CONCLUSIONS

Our results show that the rate of recurrence in this relatively large series of patients with PPS diagnosed according to current guidelines is low. Moreover, they show that multiple recurrences are uncommon and the survival of patients with recurrence is excellent. As expected, the rate of recurrence in our patients treated with colchicine was lower than in patients who did not receive colchicine and the rate of recurrence in patients pretreated with prednisone was higher than those who did not receive prednisone but the differences were not significant.

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Capsule

IL-17a promotes sociability in mouse models of neurodevelopmental disorders

A subset of children with autism spectrum disorders appear to show an improvement in their behavioral symptoms during the course of a fever, a sign of systemic inflammation. **Reed** et al. elucidated the molecular and neural mechanisms that underlie the beneficial effects of inflammation on social behavior deficits in mice. They compared an environmental model of neurodevelopmental disorders in which mice were exposed to maternal immune activation (MIA) during embryogenesis with mouse models that are genetically deficient for contactin-associated protein-like 2 (*Cntnap2*), fragile X mental retardation-1 (*Fmr1*), or Sh3 and multiple ankyrin repeat domains 3 (*Shank3*). The authors established that the social behavior deficits in offspring exposed to MIA can be temporarily rescued by the inflammatory response elicited by the administration of lipopolysaccharide (LPS). This behavioral rescue was accompanied by a reduction in neuronal activity in the primary somatosensory cortex dysgranular zone (S1DZ), the hyperactivity of which was previously implicated in the manifestation of behavioral phenotypes associated with offspring exposed to MIA. By contrast, the authors did not observe an LPS-induced rescue of social deficits in the monogenic models. They demonstrated that the differences in responsiveness to the LPS treatment between the MIA and the monogenic models emerge from differences in the levels of cytokine production. LPS treatment in monogenic mutant mice did not induce amounts of interleukin-17a (IL-17a) comparable to those induced in MIA offspring; bypassing this difference by directly delivering IL-17a into S1DZ was sufficient to promote sociability in monogenic mutant mice as well as in MIA offspring. Conversely, abrogating the expression of IL-17 receptor subunit a (IL-17Ra) in the neurons of the S1DZ eliminated the ability of LPS to reverse the sociability phenotypes in MIA offspring. These data support a neuroimmune mechanism that underlies neurodevelopmental disorders in which the production of IL-17a during inflammation can ameliorate the expression of social behavior deficits by directly affecting neuronal activity in the central nervous system.

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