Colchicine for the Prevention of Postpericardiotomy Syndrome

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Background: Postpericardiotomy syndrome (PPS) is a troublesome complication of cardiac surgery, occurring in 10–45% of cases. Accepted modalities of treatment include nonsteroidal anti-inflammatory drugs, corticosteroids, and pericardiectomy in severe cases. The optimal method for prevention of PPS has not been established. Recent trial data have shown that colchicine is efficient in the secondary prevention of recurrent episodes of pericarditis. The aim of the present study was to evaluate the possible benefit of colchicine for the primary prevention of PPS in patients after cardiac surgery. To the best of our knowledge, this is the first study addressing this issue.
Patients and Methods: A prospective, randomized, double-blind design was used. The initial study group included 163 patients who underwent cardiac surgery in two centers in Israel between October 1997 and September 1998. On the 3rd postoperative day, the patients were randomly assigned to receive colchicine (1.5 mg/day) or placebo for 1 month. All were evaluated monthly for the first 3 postoperative months for development of PPS.
Results: 52 of the 163 patients were excluded because of postoperative complications, noncompliance, or gastrointestinal side effects of treatment. Of the 111 patients who completed the study, 47 (42.3%) received colchicine and 64 (57.7%) placebo. There was no statistically significant difference between the groups in clinical or surgical characteristics. PPS was diagnosed in 19 patients (17.1%), 5/47 cases (10.6%) in the colchicine group and 14/64 (21.9%) in the placebo group. The difference showed a trend toward statistical significance ($p < 0.135$).
Conclusions: Colchicine may be efficacious for the prevention of PPS in patients after cardiac surgery. Further evaluations in larger clinical trials are warranted.

Key Words: Colchicine · Postpericardiotomy syndrome · Recurrent pericarditis

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Colchicin zur Verhinderung des Postperikardiotomie-Syndroms

Hintergrund: Das Postperikardiotomie-Syndrom (PPS) ist eine Folgeerscheinung nach Herzoperationen und tritt bei 10–45% der Patienten auf. Die Behandlung kann mit nichtsteroidalen Entzündungshemmern, Kortikosteroiden und in schweren Fällen durch eine Perikardektomie erfolgen. Ein optimales Verfahren zur Vermeidung des PPS gibt es noch nicht. Neuere klinische Studien zeigten, dass Colchicin bei der Sekundärprävention einer wiederauftretenden Perikarditis wirksam ist. Es war das Ziel der vorliegenden Untersuchung, die Wirkung von Colchicin bei der Primärprävention des PPS zu überprüfen. Eine vergleichbare Untersuchung gibt es unseres Wissens noch nicht.

Patienten und Methoden: Die Untersuchung erfolgte prospektiv, randomisiert und doppelblind. In der ursprünglichen Studiengruppe wurden 163 Patienten mit geplanter Herzoperation in zwei Zentren in Israel zwischen Oktober 1997 und September 1998 eingeschlossen. Am 3. postoperativen Tag erhielten die Patienten randomisiert über 1 Monat entweder täglich 1,5 mg Colchicin oder Plazebo. Bei allen Patienten wurde das Auftreten des PPS nach 1, 2 und 3 Monaten überprüft.
Ergebnisse: 52 der 163 Patienten wurden wegen postoperativer Komplikationen, Non-Compliance oder gastrointestinalen Nebenwirkungen von der Studie ausgeschlossen. Von den 111

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verbliebenen Patienten erhielten 47 (42,3%) Colchicin und 64 (57,7%) Plazebo. Es gab keinen statistisch signifikanten Unterschied in klinischen oder operativen Parametern. Das PPS trat bei insgesamt 19 Patienten (17,1%) auf. In der Colchicin-Gruppe trat es bei 10.6% (5/47) und in der Plazebo-Gruppe bei 21.9% (14/64) der Patienten auf. Der Unterschied war aber nicht statistisch signifikant ($p < 0{,}135$).

Schlussfolgerung: Weitere klinische Studien sind erforderlich um die Wirksamkeit von Colchicin bei der Verhinderung des PPS bei Patienten nach Herzoperationen zu sichern.

Schlüsselwörter: Colchicin · Postperikardiotomie-Syndrom · Perikarditis · Herzoperation · Entzündliche Herzerkrankungen

Introduction

Postpericardiotomy syndrome (PPS) is a common complication of cardiac surgery, occurring in 10–45% of patients [6, 10, 21]. It develops days to months after cardiac and pericardial injury, and can often be prolonged and disabling [23].

Treatment usually consists of nonsteroidal anti-inflammatory drugs (NSAIDs), with corticosteroids and pericardiectomy reserved for severe, unresponsive cases [19, 22]. Recurrences are often worse than the index attack and managed similarly [16, 23].

The optimal method for prevention of PPS in patients after cardiac surgery is not established. Several measures have been proposed, such as administration of NSAIDs and steroids [23], all with limited success.

Colchicine is an effective anti-inflammatory drug, which has been used for centuries to treat acute gouty arthritis [14], and more recently for familial Mediterranean fever (FMF) [24, 26]. Data accumulated over the past 15 years, including our own experience, have indicated that colchicine is efficient in the secondary prevention of recurrent episodes of pericarditis and large pericardial effusions [1, 2, 4, 5, 7, 13, 18].

The aim of the present study was to evaluate the possible benefit of colchicine in preventing PPS in patients after cardiac surgery. To the best of our knowledge, this is the first study addressing this important issue.

Patients and Methods

A multicenter, prospective, randomized, double-blind design was used. The study was approved by the national and local ethics committees, and an informed consent was signed by each participant. The study included 163 consecutive patients (mean age 64 ± 11 years, range 32–83 years) who had undergone cardiac surgery between October 1997 and September 1998: 90 (55.2%) at Sheba Medical Center, Tel-Hashomer, and 73 (44.8%) at Rabin Medical Center, Petah-Tiqva, Israel. On the 3rd postoperative day patients were randomly assigned to a course of either colchicine (1.5 mg/day divided into three doses) or placebo for 1 month. Diagnostic measures and other medical treatment were provided according to regular departmental policy. Patients who received corticosteroids at the perioperative period, had a complicated postoperative course of recovery with prolonged hospitalization (> 3 days) in the cardiac intensive care unit or withdrew from treatment because of gastrointestinal side effects, and those who did not attend the follow-up visits were excluded from the analyses.

Since there is no single or group of findings that are pathognomonic for PPS, the diagnosis was based on the presence of two of the following five parameters: fever lasting beyond the 1st postoperative week without any other signs of systemic or focal infection; pleuritic chest pain; friction rub; radiologic evidence of pericardial or pleural involvement; and echocardiographic evidence of a new pericardial effusion or enlargement of the known one [23]. Elevated erythrocyte sedimentation rate (ESR) and electrocardiographic changes were used to help establish the diagnosis but were not considered independent measures. Patients found to have PPS were treated with NSAIDs in combination with the study medication.

Patients were evaluated monthly for the first 3 postoperative months, including complete physical examination, electrocardiography, echocardiography and laboratory work-up (complete blood count, blood chemistry, ESR), when needed.

Statistical Analysis

Statistical analysis was performed with Pearson χ^2 test, Leaven's test, or Fisher's exact test, as appropriate.

Results

Of the initial study group of 163 patients, 52 were excluded because of gastrointestinal side effects (11.7%),

noncompliance (10.4%), corticosteroid therapy (5.5%), stroke (1.8%), renal failure (1.2%), allergic reaction (0.6%), and acute pancreatitis (0.6%). Of the 111 patients who completed the study, 47 (42.3%) received colchicine and 64 (57.7%) placebo. The colchicine group consisted of 36 men and eleven women with a mean age of 62 ± 12 years (range 32–80 years), and the placebo group included 45 men and 19 women with a mean age of 65 ± 10 years (range 43–83 years; p = NS).

The clinical characteristics of the two groups, respectively, were as follows: diabetes mellitus, 27.7% and 26.6%; hypertension, 48.9% and 43.8%; smoking, 46.8% and 48.4%; hyperlipidemia, 36.2% and 46.8%; previous myocardial infarction (the operation was performed at an appropiate interval of time after the infarction), 42.5% and 37.5%; stable angina pectoris preoperatively, 34.0% and 28.1%; and unstable angina, 48.9% and 54.7%. There were no statistically significant differences between the groups for any of these factors. Cardiac surgery consisted of coronary bypass grafting in 38 patients in the colchicine group and 52 in the placebo group, valve replacement in six and ten patients respectively, and combined surgery in three and two patients, respectively (p = NS for all). The average number of bypass grafts was 2.7 in the colchicine group and 2.5 in the placebo group (p = NS). The average time patients were attached to the cardiopulmonary bypass machine amounted to 1.6 h and 1.7 h, respectively (p = NS). The average duration of hospitalization after surgery was 7.8 days in both groups.

PPS was diagnosed in 19 of the 111 patients (17.1%) during the study period, 5/47 cases (10.6%) in the colchicine group and 14/64 cases (21.9%) in the placebo group ($p < 0.135$, trend level). The colchicine group had a total of six events of pericarditis (four patients had one event, and one patient two), and the placebo group 17 events (twelve patients had one event, one patient two, and one patient three). They were successfully treated with acetylsalicylic acid (1.5–2 g/day, n = 19), with corticosteroids (prednisone 40–60 mg/day) reserved for three unresponsive cases.

Discussion

The present study shows that colchicine may be a promising agent for primary prevention of PPS in patients after cardiac surgery. Although not usually severe in terms of tissue damage, PPS can cause disabling pain and malaise which may considerably reduce quality of life.

The underlying mechanism of PPS is still unclear [21], although the immune system apparently plays a major role in its pathogenesis. Elevated levels of anti cardiac muscle antibodies [10], antimyosin antibodies [20], circulating immune complexes [8], and complement and C3 breakdown products [17] have been reported in patients with PPS. These findings and the generally good response of affected patients to NSAIDS and corticosteroids [23] suggest that an anti-inflammatory drug such as colchicine may be useful also in the prevention of PPS.

Colchicine binds to tubulin, blocks mitosis [23], and inhibits a variety of polymorphonuclear leukocyte functions [9]. It also interferes with the transcellular movement of collagen [15]. The close proximity of lymphoid components and fibroblasts at inflammatory sites, and the induced production of lymphokines, which influence fibroblast chemotaxis, proliferation and protein synthesis, are well recognized [25]. Thus, colchicine may reduce immunopathic antifibroblastic properties. Colchicine's preferential concentration in lymphocytes, where peak levels may reach > 16 times those in plasma, is related to its observed therapeutic and preventive effects [11].

Recently, we reported our successful experience with colchicine for prevention of recurrent pericarditis [2, 3, 12]. In a large international study, 51 patients (36 men and 15 women) with recurrent pericarditis were given colchicine and followed for up to 10 years (2,333 patient-months) [2, 12]. In all cases, previous treatment with NSAIDS, corticosteroids, pericardiocentesis, or some combination thereof, failed to reduce recurrences; the mean interval between crises was 2.0 months. Results indicated that 31 patients (60.7%) remained recurrence-free throughout follow-up, with statistically significant differences in the duration of the symptom-free period before and after colchicine treatment (3.1 ± 3.0 vs. 43.0 ± 35.0 months; $p < 0.0001$). We have also shown that colchicine is beneficial in the treatment of large pericardial effusions [4].

Prompted by these data, we prospectively examined the efficacy of colchicine in the primary prevention of PPS in post-cardiac surgery patients. Preventive treatment with colchicine reduced the rate of occurrence of PPS from 21.9% in the placebo group to 10.6% in the colchicine group. This difference reached only trend level and was not statistically significant. The rates for both groups were compatible with other reports [6, 10, 21].

The safety and toxicity of colchicine may be extrapolated from findings in patients with FMF or gout. After a cumulative 15,000 years of follow-up in patients with FMF, Zemer et al [26] noted no interference of colchicine treatment in either growth rate or fertility. Up to 80% of treated patients complained of mild gastrointestinal side effects (diarrhea and nausea), a result of the drug's action on dividing cells in the gastrointestinal tract. These effects were, however, dose-dependent and could be reduced by dose adjustment. Moreover, for PPS unlike for FMF, the course of treatment is short. In the present study, 19 of 163 patients (11.7%) were excluded from the analyses because of gastrointestinal side effects. This high rate can be partly explained by the patients' general condition after cardiac surgery in intensive care units. Additional 33 patients were excluded for other reasons, including severe complications (e.g., stroke), which were probably not related to the study.

In conclusion, colchicine may be beneficial for the primary prevention of PPS. Larger clinical trials are warranted to address this issue. If findings are persistent, the use of colchicine in this setting could considerably improve patients' quality of life. Owing to the drug's low cost, it could also spare cardiac intensive care units large expenditures of diagnosis and treatment.

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