Original Investigation

Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation
The COPPS-2 Randomized Clinical Trial

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IMPORTANCE Postpericardiotomy syndrome, postoperative atrial fibrillation (AF), and postoperative effusions may be responsible for increased morbidity and health care costs after cardiac surgery. Postoperative use of colchicine prevented these complications in a single trial.

OBJECTIVE To determine the efficacy and safety of perioperative use of oral colchicine in reducing postpericardiotomy syndrome, postoperative AF, and postoperative pericardial or pleural effusions.

DESIGN, SETTING, AND PARTICIPANTS Investigator-initiated, double-blind, placebo-controlled, randomized clinical trial among 360 consecutive candidates for cardiac surgery enrolled in 11 Italian centers between March 2012 and March 2014. At enrollment, mean age of the trial participants was 67.5 years (SD, 10.6 years), 69% were men, and 36% had planned valvular surgery. Main exclusion criteria were absence of sinus rhythm at enrollment, cardiac transplantation, and contraindications to colchicine.

INTERVENTIONS Patients were randomized to receive placebo (n=180) or colchicine (0.5 mg twice daily in patients ≥70 kg or 0.5 mg once daily in patients <70 kg; n=180) starting between 48 and 72 hours before surgery and continued for 1 month after surgery.

MAIN OUTCOMES AND MEASURES Occurrence of postpericardiotomy syndrome within 3 months; main secondary study end points were postoperative AF and pericardial or pleural effusion.

RESULTS The primary end point of postpericardiotomy syndrome occurred in 35 patients (19.4%) assigned to colchicine and in 53 (29.4%) assigned to placebo (absolute difference, 10.0%; 95% CI, 1.1%-18.7%; number needed to treat = 10). There were no significant differences between the colchicine and placebo groups for the secondary end points of postoperative AF (colchicine, 61 patients [33.9%]; placebo, 75 patients [41.7%]; absolute difference, 7.8%; 95% CI, −2.2% to 17.6%) or postoperative pericardial/pleural effusion (colchicine, 103 patients [57.2%]; placebo, 106 patients [58.9%]; absolute difference, 1.7%; 95% CI, −8.5% to 11.7%), although there was a reduction in postoperative AF in the prespecified on-treatment analysis (placebo, 61/148 patients [41.2%]; colchicine, 38/141 patients [27.0%]; absolute difference, 14.2%; 95% CI, 3.3%-24.7%). Adverse events occurred in 21 patients (11.7%) in the placebo group vs 36 (20.0%) in the colchicine group (absolute difference, 8.3%; 95% CI; 0.76%-15.9%; number needed to harm = 12), but discontinuation rates were similar. No serious adverse events were observed.

CONCLUSIONS AND RELEVANCE Among patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion. The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.

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Postpericardiotomy syndrome, postoperative atrial fibrillation (AF), and postoperative pericardial/pleural effusions are common complications after cardiac surgery, affecting more than one-third of patients, an incidence largely unchanged despite advances in surgical techniques, anesthetic procedures, and perioperative care.[1-6]

These complications may have minor effect on management (mild fever and effusions) but may also lead to prolonged hospital stay, readmissions, and need for invasive interventions; moreover, postoperative AF may increase long-term mortality.[7] Colchicine monotherapy has been recently suggested to prevent these complications.[8-10]

Although preliminary data from the Colchicine for Prevention of the Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation (COPPS) trial for 1-month postoperative treatment with colchicine were promising,[10] additional data will be helpful in determining if colchicine should be used routinely for the prevention of several relevant perioperative complications (including postpericardiotomy syndrome, postoperative AF, and postoperative effusions). Both efficacy and safety should be evaluated, especially in the perioperative period, preferably with administration of the drug before cardiac surgery to assess its full beneficial effect in the immediate perioperative period, when most of the studied complications are more likely to occur. In addition, a limitation of the COPPS trial was that colchicine was begun on postoperative day 3; whether its beneficial effects may be further optimized when colchicine is started before surgery is uncertain. Moreover, with preoperative treatment, a loading dose may be unnecessary; this may further improve adherence, similar to pericarditis.[11-13]

We conducted the COPPS-2 trial to determine the efficacy and safety of perioperative administration of oral colchicine to reduce postpericardiotomy syndrome, postoperative AF, and postoperative pericardial/pleural effusions.

Methods

Study Design and Patients

The COPPS-2 trial is an investigator-initiated, double-blind, placebo-controlled, randomized clinical trial conducted in 11 centers in Italy to test the primary hypothesis that perioperative use of oral colchicine reduces the occurrence of postpericardiotomy syndrome, postoperative AF, and postoperative pericardial/pleural effusions in patients undergoing cardiac surgery for any reason excluding cardiac transplantation. Detailed methods have been previously published[11] and are available in Supplement 1 (trial protocol). The main differences in the study methods of the COPPS and COPPS-2 trials are described in the eTable in Supplement 2. The design of the study was simple and pragmatic to maximize a possible practical application that can be generalized to real-world patients. The data were gathered by all authors and were received, checked, and analyzed at the Cardiology Department of Maria Vittoria Hospital, Torino, Italy, after blinded adjudication of events.

The study was approved by the human subjects committees of all participating institutions and conducted according to international standards of good clinical practice. All participants provided written informed consent.

Intervention

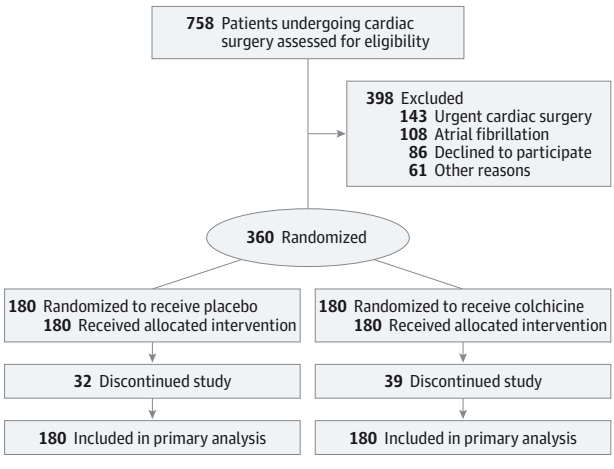
Patients were randomly assigned to receive placebo or colchicine, starting between 48 and 72 hours before surgery and continued for 1 month after surgery (**Figure 1**). Random assignment to treatment groups was performed by a central computer-based automated sequence. Randomization was based on permuted blocks with a block size of 4. The random allocation sequence was implemented using sequentially numbered study drug containers. Allocation concealment was achieved by using opaque sealed envelopes, sequentially numbered containers, and central randomization. Colchicine was administered orally as 0.5 mg twice daily to patients weighing 70 kg or more or as 0.5 mg once daily to patients weighing less than 70 kg, without a loading dose. Colchicine was provided by gastric tube in unconscious postoperative patients. Adherence to study drug therapy was assessed on the basis of counts of pills in dispensed boxes, with a target of at least 80% adherence.

The dosing was selected to balance potential efficacy vs patient intolerance, especially gastrointestinal intolerance.[12,13] The duration of colchicine therapy was based on prior studies suggesting a 1-month length of treatment.[8,14]

Additional medical therapy was provided according to individual patient comorbidities and based on existing practice guidelines.

Centers were encouraged to use continuous electrocardiographic (ECG) monitoring for at least 5 days after surgery. Twelve-lead ECGs were recommended daily and more frequently at the discretion of the treating physicians for symptoms or clinically suspected arrhythmia. Clinical data and confirmatory ECG strips or 12-lead ECGs were recorded for all postoperative arrhythmias of at least 30-second duration. Current best practice guidelines for prevention of postoperative AF were strongly recommended to all centers.

Figure 1. Screening, Enrollment, Randomization, and Follow-up of Study Participants in the COPPS-2 Trial



End Points

The primary study end point was incidence of postpericardiotomy syndrome within 3 months. Secondary study end points were postoperative AF and postoperative effusions within 3 months after cardiac surgery, incidence of cardiac tamponade, need for pericardiocentesis or thoracentesis, recurrences of postpericardiotomy syndrome, disease-related readmissions (related to the 3 main outcomes of postpericardiotomy syndrome, postoperative AF, and postoperative pericardial/pleural effusions), stroke incidence, and overall mortality.

The 3-month time frame was selected because almost all such events in the COPPS trial occurred in the first 3 months after cardiac surgery.[15]

Diagnostic criteria for postpericardiotomy syndrome included the following (2 of 5 criteria were required for the diagnosis): (1) fever without alternative causes; (2) pleuritic chest pain; (3) friction rub; and evidence of new or worsening (4) pericardial effusion and/or (5) pleural effusion with evidence of systemic inflammation by C-reactive protein elevation.[11,14,16]

Postoperative AF was defined as AF lasting for more than 30 seconds. Continuous electrocardiographic monitoring was adopted for at least 5 days after surgery. Twelve-lead ECGs were recommended daily and more frequently at the discretion of the treating physicians for symptoms or clinically suspected arrhythmia. Clinical data (eg, postoperative AF onset time, symptoms, treatments, and duration) and confirmatory rhythm strips or 12-lead ECGs were collected for all postoperative arrhythmias of at least 30-second duration. Use of long-term or prophylactic antiarrhythmic drugs, history of AF, and planned AF ablation were not exclusions, given the similar or higher risk of postoperative AF in these patients and no known biological interaction that might reduce the efficacy of colchicine in such patients.[11]

Data Management and Safety Evaluation

Data were collected using standardized case report and clinical events forms by investigators who were masked to treatment assignments. A clinical end point committee, also masked to treatment, adjudicated all events. During follow-up, all adverse events were monitored and recorded. Potential adverse events were recorded and reported to the steering committee and a data and safety monitoring committee. An adverse event was considered severe if the event was fatal, was life-threatening, required hospitalization, was significantly or permanently disabling, or was medically significant (ie, an event that was life-threatening or required medical or surgical intervention to prevent an adverse outcome). An adverse event was filed according to whether it was discovered by patient-reported symptoms or blood chemistry monitoring during follow-up visits. Unmasking of the randomization code was allowed only in the case of a severe adverse event.

The steering committee monitored the progress of the trial, and the data and safety monitoring committee monitored both scientific integrity and patient safety throughout the trial and could recommend termination or other trial modifications at any time. After enrollment of 50% of patients, the data and safety monitoring committee reviewed an interim analysis and recommended study continuation.

Follow-up and Covariates

Standardized data were collected on demographics, risk factors, medical and surgical history, major comorbid conditions, medications, and laboratory measures. Postoperative follow-up visits were scheduled at 1 day, 3 days, day of discharge after cardiac surgery, weekly during rehabilitation, 1 month, and 3 months. Each follow-up visit included physical examination, blood chemistry, ECG, echocardiography aimed at identification and semiquantitative assessment of pericardial effusion, and thoracic ultrasound to assess presence of pleural effusion. At least 1 chest x-ray was performed during cardiac surgery stay before discharge and then as clinically indicated. Incidence of postoperative AF was assessed by means of ECG monitoring during intensive care and overall cardiac surgery stay, ECG at the time of follow-up visits, or symptomatic AF recorded by ECG.

Statistical Analysis

All analyses were prespecified prior to closing of the study database. Sample size calculations were based on previous data from the COPPS trial.[8] Assuming a postpericardiotomy syndrome rate of 22% in the placebo group at 3 months and a 2-sided test at the α=.05 level, a total enrollment of 360 patients was needed to attain a power of 80% to detect a reduction in the recurrence rate to 11% in the colchicine group. The study hypothesis was that colchicine would reduce the postpericardiotomy syndrome rate by 50%. Assuming similar event rates for postoperative AF and postoperative pericardial/pleural effusions such as in COPPS and the COPPS postoperative AF substudy, the study was adequately powered to assess the effects of colchicine on these outcomes.[8-10]

The main analysis was by intention to treat, including all patients according to treatment assigned at randomization. An additional on-treatment analysis was planned based on patients who were both tolerant of and adherent to colchicine (including patients with at least 80% adherence over the course of the study until the onset of the primary end point or the end of the assigned treatment, whichever occurred first).

The clinical effect of colchicine was further evaluated in different prespecified subgroups including age (<65 years vs ≥65 years), sex, serum C-reactive protein (nonelevated or elevated), and presence or absence of pericardial effusion assessed at 1 to 3 days and at day of discharge after cardiac surgery.

Quantitative variables are expressed as mean (standard deviation) or median (range and interquartile range [IQR]) as appropriate. Qualitative variables are expressed as number (percentage). Descriptive statistics and χ^2 or Fisher exact tests were performed on dichotomous categorical variables in both the on-treatment and intention-to-treat analyses. Outcomes are reported as absolute differences with 95% confidence intervals. Time-to-event distributions were estimated by the Kaplan-Meier method and compared by the log-rank test. Logistic regression was used to determine odds ratios (ORs) and 95% confidence intervals for the effect of treatment in each subgroup. Analyses were performed with SPSS, version 13.0 (SPSS Inc) and MedCalc, version 12.7.2 (MedCalc Software).

Results

Study Cohort

Enrollment started in March 2012 and ended in March 2014. Follow-up continued through June 2014, a predetermined stopping point for the completion of follow-up for the primary outcome. Participants were followed up for a median of 95 days (IQR, 15 days).

Study enrollment, randomization, and retention are shown in Figure 1. Of the 758 patients who were screened, 360 (47.5%) were enrolled. Ineligible patients were most often excluded because they required urgent cardiac surgery (36%), were not in sinus rhythm (27%), or declined consent (22%).

At the end of the enrollment phase, 180 patients were randomly assigned to each of the 2 treatment groups. No patients were lost to follow-up and all were analyzed for outcomes. The baseline demographic and clinical characteristics of study groups were similar and are reported in **Table 1**. At baseline, mean age of the trial participants was 67.5 years (SD, 10.6 years) (median, 70 years; range, 19-89 years), and 248 patients (68.9%) were men. Heart valve surgery was performed in 131 patients (36.4%), coronary artery bypass graft surgery in 122 patients (33.9%), aorta surgery in 22 patients (6.1%), and mixed cardiac surgery in 85 patients (23.6%). Perioperative medications were similar in the study groups and included β-blockers in 204 patients (56.7%), angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers in 188 patients (52.2%), and amiodarone in 31 patients (8.6%).

All patients who tolerated treatment with colchicine or placebo discontinued therapy at 1 month, as planned.

Outcomes

The main outcome results are reported in **Table 2**. The primary outcome of postpericardiotomy syndrome occurred in 35 of 180 patients (19.4%) in the colchicine group and in 53 of 180 patients (29.4%) in the placebo group (absolute difference, 10.0%; 95% CI, 1.1%-18.7%; number needed to treat [NNT] = 10). The Kaplan-Meier incidence of postpericardiotomy syndrome by treatment group is shown in **Figure 2**. Postoperative AF occurred in 61 patients (33.9%) assigned to colchicine and in 75 (41.7%) assigned to placebo (absolute difference, 7.8%; 95% CI, −2.2% to 17.6%); postoperative pericardial/pleural effusions occurred in 103 patients (57.2%) assigned to colchicine and in 106 (58.9%) assigned to placebo (absolute difference, 1.7%; 95% CI, −8.5% to 11.7%). However, a reduction of the incidence of postoperative AF was recorded at the prespecified on-treatment analysis: postoperative AF was found in 61 (41.2%) of 148 patients assigned to placebo and 38 (27.0%) of 141 assigned to colchicine (absolute difference, 14.2%; 95% CI, 3.3%-24.7%; NNT = 7) because a significant number of patients experienced gastrointestinal adverse effects resulting in drug discontinuation. Most postoperative AF events occurred between postoperative days 1 to 5, peaking on day 2. Among all 101 episodes, 44 lasted 1 day or less. Two patients in the placebo group and 2 patients in the colchicine group were discharged with persistent AF.

Table 1. Baseline Characteristics of COPPS-2 Participants According to Treatment Assignment[a]

Characteristics	Placebo (n = 180)	Colchicine (n = 180)
Age, mean (SD), y	68.0 (10.0)	67.0 (11.1)
Men	115 (63.9)	133 (73.9)
Selected coronary risk factors		
Current smoker	54 (30.0)	49 (27.2)
Systemic arterial hypertension	122 (67.8)	121 (67.2)
Diabetes mellitus	42 (23.3)	38 (21.1)
Medical and surgical history		
Cardiac surgery	10 (5.6)	10 (5.6)
Pericarditis	1 (0.6)	4 (2.2)
Atrial fibrillation	15 (8.3)	18 (10.0)
Comorbid conditions		
COPD	15 (8.3)	15 (8.3)
Hypothyrodism	12 (6.7)	8 (4.4)
Chronic renal failure	13 (7.2)	13 (7.2)
Preoperative pericardial effusion	2 (1.1)	3 (1.7)
Ejection fraction, mean (SD), %	55.5 (10.1)	55.3 (9.6)
NYHA class		
I	42 (23.3)	58 (32.2)
II	109 (60.6)	95 (52.8)
III	26 (14.4)	23 (12.8)
IV	3 (1.7)	4 (2.2)
Perioperative medications		
β-Blockers	101 (56.1)	103 (57.2)
Amiodarone	18 (10.0)	13 (7.2)
ACE inhibitors/ARBs	100 (55.6)	88 (48.9)
Other antiarrhytmic drugs	5 (2.8)	4 (2.2)
Cardiac surgery		
CABG surgery	59 (32.8)	63 (35.0)
Valvular diseases	69 (38.3)	62 (34.4)
Aortic disease	11 (6.1)	11 (6.1)
Combined[b]	41 (22.8)	44 (24.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blockers; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Any combination of the 3 types of cardiac surgery (CABG, cardiac surgery for valvular disease, and cardiac surgery aortic disease).

No significant differences were recorded in other secondary end points, including cardiac tamponade, need for pericardiocentesis, thoracentesis, or both, recurrences, postpericardiotomy syndrome and postoperative AF-related readmissions, stroke, and overall mortality. Effects of colchicine on the primary end point did not differ significantly among the prespecified subgroups (age <65 years vs age ≥65 years, sex, and presence/absence of pericardial effusion) except in the subgroup with elevation of elevated serum C-reactive protein (eFigure in Supplement 2).

Adverse Events

Adverse event rates occurred in 21 patients (11.7%) in the placebo group and 36 (20.0%) in the colchicine group (absolute

Table 2. Primary and Secondary Study Outcomes at 3-Month Follow-up According to Treatment Assignment

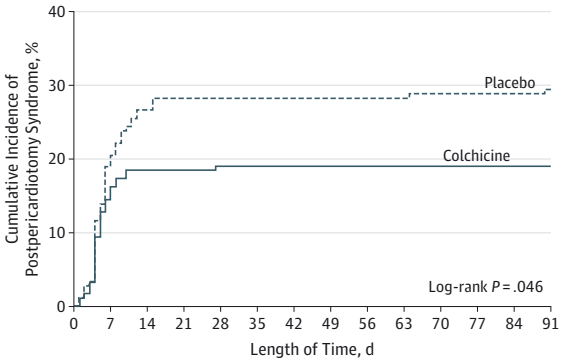
Outcomes	No. (%) of Participants		Absolute Difference (95% CI), %
	Placebo (n = 180)	Colchicine (n = 180)	
Primary end point (postpericardiotomy syndrome) within 3 mo	53 (29.4)	35 (19.4)	10.0 (1.1 to 18.7)
Main secondary end points			
Postoperative atrial fibrillation[a]	75 (41.7)	61 (33.9)	7.8 (−2.2 to 17.6)
Postoperative pericardial/pleural effusions	106 (58.9)	103 (57.2)	1.7 (−8.5 to 11.7)
Cardiac tamponade	3 (1.7)	1 (0.6)	1.1 (−1.6 to 4.3)
Pericardiocentesis or thoracentesis	13 (7.2)	13 (7.2)	0.0 (−5.6 to 5.6)
Postpericardiotomy syndrome recurrence	3 (1.7)	3 (1.7)	0.0 (−3.3 to 3.3)
Disease-related readmissions[b]	2 (1.1)	2 (1.1)	0.0 (−2.7 to 2.7)
Overall mortality[c]	2 (1.1)	6 (3.3)	2.2 (−1.6 to 6.1)
Stroke	1 (0.6)	2 (1.1)	0.50 (−2.1 to 3.4)

[a] Postoperative atrial fibrillation at the prespecified on-treatment analysis was recorded in 61 of 148 patients (41.2%) assigned to placebo and 38 of 141 patients (27.0%) assigned to colchicine (absolute difference, 14.2%; 95% CI, 3.3%-24.7%).

[b] Disease-related readmissions were those related to postpericardiotomy syndrome, postoperative atrial fibrillation, or postoperative effusions.

[c] All deaths were in-hospital deaths related to cardiac surgery and not related to experimental treatments.

Figure 2. Results of Kaplan-Meier Analysis of the Primary Outcome (Incidence of Postpericardiotomy Syndrome)



No. at risk

Placebo	180	143	131	128	128	128	128	128	128	127	126	126	125	81
Colchicine	180	147	141	141	139	139	139	139	139	139	139	139	139	91

difference, 8.3%; 95% CI, 0.76%-15.9%; number needed to harm = 12), primarily because of an increased incidence of gastrointestinal intolerance in 12 patients (6.7%) in the placebo group and 26 (14.4%) in the colchicine group (absolute difference, 7.7%; 95% CI, 1.4%-14.3%; number needed to harm = 13). Discontinuation rates were similar at 32 patients (17.8%) in the placebo group and 39 (21.7%) in the colchicine group (absolute difference, 3.9%; 95% CI, −4.4% to 12.5%). No serious adverse events were observed (**Table 3**).

Discussion

In this multicenter trial, perioperative administration of colchicine significantly reduced the incidence of postpericardiotomy syndrome after cardiac surgery but did not reduce the risk of postoperative AF and postoperative pericardial/pleural effusions by intention-to-treat analysis. Patients receiving colchicine treatment had more frequent adverse effects, especially gastrointestinal intolerance generally leading to study drug discontinuation. About 20% of all patients enrolled in the trial discontinued study drug; this relatively high rate may have affected the overall efficacy of the drug, especially for postoperative AF prevention.

Postpericardiotomy syndrome with low-grade fever, often associated with pericardial/pleural effusion, is relatively common after cardiac surgery, and it is generally related to the amount of pericardial/pleural manipulation.[1,8,14]

Different strategies have been considered for postpericardiotomy syndrome prevention, including aspirin, corticosteroids, and colchicine. In a meta-analysis of 894 patients,[8,14,17,18] colchicine was protective against postpericardiotomy syndrome (OR, 0.38; 95% CI, 0.22-0.65), whereas study findings for methylprednisolone (OR, 1.13; 95% CI, 0.57-2.25) and aspirin (OR, 1.00; 95% CI, 0.16-6.11) were negative.[19] In a single-center post hoc analysis of 822 patients who underwent valvular surgery and received a single intraoperative dose of 1 mg/kg of dexamethasone or placebo in the DECS trial, corticosteroids failed to reduce the incidence of postpericardiotomy syndrome (OR, 0.88; 95% CI, 0.63-1.22).[20]

In the largest trial, COPPS,[8] 360 consecutive patients (mean age, 66 years; 66% men, n=180 in each treatment group) were randomized on the third postoperative day to receive either placebo or colchicine for 1 month (1.0 mg twice daily on the first day followed by a maintenance dose of 0.5 mg twice daily in patients weighing ≥70 kg and halved doses for patients weighing <70 kg). Colchicine significantly reduced the incidence of postpericardiotomy syndrome at 12 months compared with placebo (8.9% vs 21.1%, respectively; P = .002; NNT=8) and the incidence of postoperative pericardial effusions (relative risk reduction, 43.9%; NNT=10) and pleural effusions (relative risk reduction, 52.3%; NNT=8).[9] The incidence of adverse effects (primarily gastrointestinal intolerance) and study drug discontinuation was similar between the study groups, with a nonsignificantly increased rate of both events in patients receiving colchicine.[8,9]

In COPPS-2, colchicine was given 48 to 72 hours before cardiac surgery to pretreat patients and improve the efficacy of the drug in the prevention of postoperative systemic inflammation and its complications, especially postpericardiotomy syndrome and postoperative AF. We also avoided a loading dose and used weight-adjusted doses with the aim of improving adherence. However, we observed a 2-fold increase of adverse effects and study drug discontinuations compared with those

Table 3. Adverse Events in COPPS-2 According to Treatment Assignment at 3-Month Follow-up According to Treatment Assignment[a]

Adverse Events	No. (%) of Participants[b] Placebo (n = 180)	Colchicine (n = 180)	Absolute Difference (95% CI), %
Any adverse events	21 (11.7)	36 (20.0)	8.3 (0.76 to 15.9)
Gastrointestinal intolerance[c]	12 (6.7)	26 (14.4)	7.7 (1.4 to 14.3)
Hepatotoxicity[d]	2 (1.1)	1 (0.6)	0.50 (−2.1 to 3.4)
Drug discontinuation	32 (17.8)	39 (21.7)	3.9 (−4.4 to 12.5)

[a] No serious adverse events (any fatal or life-threatening event requiring hospitalization or any event that was significantly or permanently disabling or medically significant; ie, life-threatening or requiring medical or surgical intervention to prevent an adverse outcome) were reported, as well as myotoxicity, alopecia, or other adverse effects beyond those reported in the table.

[b] Data represent the number of affected individuals.

[c] Diarrhea, nausea, cramping, abdominal pain, or vomiting.

[d] Any elevation of aminotransferase levels above the normal reference range.

reported in the COPPS trial, likely due to significant vulnerability of patients in the perioperative phase, when the use of antibiotics and proton pump inhibitors is common and also increases the risk of gastrointestinal adverse effects (eg, diarrhea). Nevertheless, efficacy for prevention of postpericardiotomy syndrome was maintained, and colchicine was especially efficacious in the setting of systemic inflammation with C-reactive protein elevation as suggested by subgroup analysis. Probably for the same reason, as well as because of the recording of all postoperative effusions regardless of their size, hemodynamic importance, and association with systemic inflammation, colchicine failed to prevent all postoperative effusions.

The high rate of adverse effects is a reason for concern and suggests that colchicine should be considered only in well-selected patients. A longer pretreatment time or initiation 2 to 3 days after surgery may reduce the occurrence of adverse effects and improve adherence as reported in the COPPS trial.[8] However, the overall prognosis of postpericardiotomy syndrome reported in the trial was good; therefore, its preoperative prevention may be unnecessary given the high rate of adverse effects of colchicine. Early prevention after cardiac surgery or early specific treatment of the syndrome seems to warrant better tolerability and similar or better outcomes.[8-10]

Postoperative AF is the most common complication after cardiac surgery because of the increasing number of cardiac surgery operations and the advanced age of the patient population. Postoperative AF increases morbidity, length of hospital stay, and health care costs.[5-7]

The pathophysiologic basis for the development of postoperative AF is likely multifactorial, including pericardial inflammation, autonomic imbalance in the postoperative period, excessive production of catecholamines, and fluid shifts.[21-23] Inflammation, inhomogeneity of atrial conduction, and incidence of postoperative AF are significantly decreased by corticosteroid use,[24] suggesting that anti-inflammatory therapy may be beneficial for its prevention.

Microtubules have a significant role in numerous cellular cytoskeletal and intracellular transport activities. Colchicine blocks microtubule assembly and can actively disrupt microtubules. Microtubules regulate the localization and interaction of adrenergic receptors and adenylate cyclase and may modulate the phosphorylation of calcium channels and, as a result, the response of the atria to autonomic stimulation. Because autonomic balance is altered in the postoperative state, agents that attenuate sympathetic activity (eg, adrenergic receptor blockers) or the response to sympathetic activity (eg, colchicine) increase parasympathetic activity, which may decrease the risk of calcium overload–induced ectopy. In addition, colchicine attenuates neutrophil activation, endothelial cell adhesion, and migration to injured tissues.[23] In the COPPS postoperative AF substudy, patients receiving colchicine had a reduced incidence of postoperative AF (relative risk reduction, 45%; NNT=11) with a shorter in-hospital and rehabilitation stay.[10]

These experimental and pathophysiologic findings supported the COPPS-2 trial hypothesis that colchicine could prevent postoperative AF. However, in COPPS-2, colchicine failed to reduce the incidence of postoperative AF in the intention-to-treat analysis; the high frequency of adverse effects and drug discontinuation were probably major causes since the prespecified on-treatment analysis documented a significant reduction of the arrhythmia, indicating that colchicine reduced the incidence of postoperative AF in patients who tolerated the drug. Ongoing studies will better clarify the potential of this drug using lower doses (ie, 0.5-0.6 mg/d) that may be better tolerated.

Several study limitations should be considered in interpreting these findings. We excluded pediatric patients, pregnant or lactating women, patients with potential contraindications or at higher risk of complications following the administration of colchicine, and patients who had urgent cardiac surgery. Thus, the results of COPPS-2 should be properly interpreted and applied to populations who were eligible for the study. Despite a highly selected population, a relatively high rate of adverse effects, especially gastrointestinal adverse effects and drug discontinuation, may limit the clinical applicability of colchicine in perioperative care. While the efficacy of colchicine for postpericardiotomy syndrome prevention is confirmed, the extent of efficacy for postoperative AF needs to be further investigated in future trials. At present, colchicine is not approved for the prevention of postpericardiotomy syndrome in North America or Europe, and its use as such is off label. Moreover, our limited sample size and follow-up might have precluded the identification of rare adverse effects.

Conclusions

Among patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusions. The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.

ARTICLE INFORMATION

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