The Role of Colchicine in Treating Postoperative and Post-catheter Ablation Atrial Fibrillation

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ABSTRACT

Purpose: The goal of this review was to summarize, analyze, and compare trials studying the efficacy of colchicine in the prevention of atrial fibrillation (AF) post-operatively (POAF) and post–catheter ablation. Ongoing studies and current guidelines are also presented and reviewed.

Methods: Published studies on the field were identified through a literature search of the PubMed and clinicaltrials.gov databases.

Findings: Four original studies regarding POAF, two original studies regarding post–catheter ablation AF, and six meta-analyses were identified. In addition, the 3 most recent guidelines/expert consensus documents were scrutinized.

Implications: AF occurs frequently after cardiac surgery (POAF) and catheter pulmonary vein isolation (postablation AF) and is associated with increased cardiovascular morbidity. A number of trials over the last few years have investigated the role of colchicine in the prevention of POAF and postablation AF targeting the local and systemic inflammatory process that leads to initiation and maintenance of AF. Available data imply that colchicine may have a preventive role in POAF and/or postablation AF. However, certain limitations of these studies underline the need for further investigation. (*Clin Ther.* 2019;41:21–29) © 2018 Elsevier Inc. All rights reserved.

Key words: cardiac surgery, catheter ablation, cryoablation, cryoballoon, POAF, radiofrequency.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is a frequent complication in patients undergoing cardiothoracic surgery, with an incidence varying from 16% to 50% depending on patient population, type of surgery, and use of perioperative prophylactic medication such as antiarrhythmic or anti-inflammatory agents.[1] Early recurrence of AF occurs in at least 20% to 40% of patients after catheter pulmonary vein isolation (PVI).[2] POAF is associated with increased risk for thromboembolism, stroke, cardiac decompensation, hospitalization duration, and health costs.[3]

The pathophysiology of POAF is not fully elucidated. Inflammation seems to plays an important role in the initiation and maintenance of AF. Previous studies have shown that markers of inflammatory reactivity (eg, C-reactive protein [CRP] complex levels, number of white blood cells) are increased in patients who develop AF.[4] Similarly, recurrence of AF within the first weeks after a PV ablation procedure seems to be mediated by an inflammatory process triggered by the ablation per se as implied by increased early CRP levels in AF ablation patients.[2] Moreover, AF can further induce and maintain a cascade of inflammatory events leading to electrical and structural atrial remodeling, which contributes to the clinical phenomenon of "AF begets AF."[5]

Thus, in the last few years, many trials have investigated the role of anti-inflammatory agents in

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preventing POAF or post–PV ablation AF, using various treatment regimens such as corticosteroid therapy,[6] intravenous magnesium,[7] atorvastatin,[4] and colchicine.

Colchicine is an alkaloid with potent anti-inflammatory properties and a unique mechanism of action that does not involve the arachidonic acid pathway affected by NSAIDs and glucocorticosteroids.[8] Colchicine exerts its anti-inflammatory role by inhibiting microtubule depolymerization, which at the same time negatively affects the phosphorylation of calcium channels, further decreasing the possibility of calcium overload–induced tachyarrythmia.[9]

The present review article summarizes the existing literature on the role of colchicine in preventing postoperative and post–PV ablation AF. Although postoperative and post–PV ablation AF are, expectedly, distinct entities, they are attributed to common pathophysiologic pathways. Therefore, some of the available meta-analyses have analyzed overall data. Under this scope, data for both entities are presented hereafter.

MATERIALS AND METHODS

Data were collected by thorough searches in PubMed to identify randomized controlled trials (RCTs) and meta-analyses. The following queries were used: "post-operative atrial fibrillation AND/OR colchicine," "cardiac surgery AND/OR atrial fibrillation AND/OR colchicine," "atrial fibrillation AND/OR pulmonary vein isolation AND/OR colchicine," and "atrial fibrillation AND/OR catheter ablation AND/OR colchicine." Original articles and/or meta-analyses published in English were considered eligible. Finally, the aforementioned search queries were used in www.clinicaltrials.gov to identify any ongoing studies. Time frame for literature search was from 1950 until March 2018.

RESULTS

The literature research identified the following: (1) four original studies that evaluated POAF[10–13]; (2) two studies that assessed the effects of colchicine treatment in AF post-PVI under catheter ablation[14,15]; (3) six meta-analyses[16–21]; and (4) ongoing studies. Those studies are outlined in Table I and are summarized in the next 2 sections.

POSTOPERATIVE (CARDIAC-THORACIC SURGERY) AF

Randomized Controlled Trials

A literature research revealed 4 original articles reporting colchicine administration for the prevention of AF following cardiac-thoracic surgery (Table I).

The first RCT was published by Imazio et al[10] in 2011 ("Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postcardiotomy Syndrome [COPPS] Atrial Fibrillation Substudy''). For the COPPS-POAF (Colchicine for the Prevention of the Post-Pericardiotomy Syndrome Atrial Fibrillation POAF) substudy, all patients in sinus rhythm on day 3 from the total COPPS trial population were included for analysis of colchicine effects. (The COPPS trial was a randomized, double-blind, placebo-controlled, multicenter study [6 centers in Italy] that was designed to test the role of colchicine in the prevention of postpericardiotomy syndrome in a 12-month follow-up.) Of a total population of 336 patients, one half of those who presented with no contraindication to colchicine were included and treated with a 1mg loading dose at day 3 postoperatively, followed by 0.5 mg BID. The duration of treatment was 1 month (dose reduction at one half of the initial one was used for patients <70 kg or intolerant to the highest dose). The primary end point was the incidence of POAF for patients on intervention at 1 month. The substudy revealed a reduced incidence of POAF (12% vs 22%; $P = 0.021$), shorter duration of POAF (3 vs 8 days; $P < 0.001$), shorter hospitalization time (9.4 vs 10.3 days; $P = 0.040$), and shorter overall hospital stay (cardiac surgery plus rehabilitation stay, 21 vs 24 days; $P = 0.030$) in patients treated with colchicine. Conversely, the incidence of death and stroke was similar in the study groups. In patients in whom POAF was reported, the perioperative use of a beta-blocker was lower (33% vs 56%; $P = 0.003$), whereas the use of amiodarone was comparable between study groups ($P = 0.830$). The beneficial effect of colchicine was independent of beta-blocker administration and left atrial diameter >45 mm.

After those initial positive results, a second RCT ("COPPS-2 trial") was designed and published in

Table I. Original trials estimating the role of colchicine on postoperative and postablation atrial fibrillation.

Study	No. of Patients	Population	Colchicine Dose	Start of Treatment, d	End of Treatment, d	Follow-up, mo	*P**	Deduction
Post cardiac surgery								
Imazio et al,[10] 2011	336	Cardiac surgery	Ld: 1 mg BID Md: 0.5 mg BID	3 postoperative	30	12	0.021	Positive
Imazio et al,[11] 2014	360	Cardiac surgery	Ld: None Md: 0.5 mg BID	2−3 preoperative	30	3	0.21	Neutral
Tabbalat et al,[13] 2016	360	Elective cardiac surgery	Ld: 2 mg 1 mg (4 h preoperative) Md: 0.5 mg BID	1−2 preoperative	Hospital discharge		0.14	Neutral
Zarpelon et al,[12] 2016	140	Elective CABG	Ld:1.0 mg BID Md: 0.5 mg BID	1 postoperative	Hospital discharge		0.271	Neutral
Post PVI via RF catheter ablation								
Deftereos et al,[14] 2012	170	PVI with RF	Ld: None Md: 0.5 mg BID	0	90	3	0.01	Positive
Deftereos et al,[15] 2014	206	PVI with RF	Ld: None Md: 0.5 mg BID	0	90	12	0.01	Positive

CABG = coronary artery bypass grafting; Ld = loading dose; Md = maintenance dose; PVI = pulmonary vein isolation; RF = radiofrequency.
P values for reduction of atrial fibrillation incidence in the colchicine group.

2014 by Imazio et al.[11] The trial was a prospective, multicenter (11 Italian centers), randomized, double-blind, placebo-controlled study. The study population comprised 360 patients who underwent elective cardiac surgery. It differed from the COPPS-POAF trial on 2 points. The first was timing of treatment initiation: patients were started on colchicine 48 to 72 hours before cardiac surgery and continued for 1 month postsurgery. The second difference was the dose regimen: patients on colchicine received no loading dose and were started on colchicine 0.5 mg BID for 1 month (or 0.5 mg once a day if the patient was <70 kg or intolerant to the higher dose). Follow-up extended up to 3 months. The primary end point was postpericardiotomy syndrome at 3 months; postoperative effusions and POAF at 3 months were set as secondary end points. Although there were significant differences between the colchicine and placebo groups for the primary end point of postpericardiotomy syndrome (19.4% vs 29.4%), POAF and postoperative effusion levels were equivalent (34% vs 42%; absolute difference CI, −2.2 to 17.6). In a prespecified on-treatment analysis, there was a reduction in POAF at 3 months (placebo group, 41.2%; colchicine group, 27%; absolute difference, 14.2% [95% CI, 3.3 to 24.7).

Zarpelon et al[12] published a study in 2016 entitled "Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization." The primary end point of the study was the effectiveness of colchicine to prevent AF in the period after myocardial revascularization surgery. Secondary end points included death, hospitalization, and postoperative infection. It was a single-center, randomized, open-label study in which 140 patients were evaluated. Inclusion criteria comprised a minimum age of 18 years, indication for elective myocardial revascularization surgery, and sinus rhythm on the day before surgery; patients had a mean age of 61 years. Patients with the following were excluded: a history of AF or atrial flutter; need for heart valve surgery at the same time; and co-administration of antiarrhythmic drugs except for beta-blockers, calcium channel blockers, and digoxin. The colchicine group received a loading dose of 1 mg BID 24 hours before surgery and a maintenance dose of 0.5 mg BID until hospital discharge. The colchicine group reported no statistically significant reduction in AF incidence compared with the control group (7% vs 13%; $P = 0.271$). In addition, the results were comparable for the secondary end point, except the rate of infection, which was higher in the colchicine group (27% vs 9%; $P = 0.007$).

In 2016, Tabbalat et al[13] published a study entitled "Effect of colchicine on the incidence of atrial fibrillation in open heart surgery patients: END-AF trial." The aim of this multicenter (5 centers in Jordan), randomized, open-label study was the incidence of POAF in patients with no history of AF or supraventricular tachycardia, undergoing cardiac surgery and who received colchicine preoperatively. The primary end point was recorded AF with a duration >5 minutes. The colchicine group (179 of the total 360 patients) received 2 mg 12 to 24 hours before the surgery, 1 mg 4 hours before or immediately postsurgery, and a maintenance dose of 0.5 mg BID during the hospitalization (mean duration, 8 days). POAF and duration of AF were comparable between the colchicine and the control groups (15% vs 21%; $P = 0.14$).

Meta-analyses

A large number of meta-analyses in relation to the number of original studies are available. Although the data overlap (mainly due to the COPPS and COPPS-2 studies), each meta-analysis included a different subset of patients, whereas mixed POAF and postablation AF populations were frequently analyzed.

Five of the identified meta-analyses[16–20] indicate the protective role of colchicine in POAF after cardiac surgery, recurrent pericarditis, and postpericardiotomy syndrome, except for one,[21] in which the role of colchicine was neutral. The most recent meta-analysis by Salih et al[16] (published in 2017) is the only one that distinguished and studied the patients who underwent cardiac surgery (n = 912) from those who underwent PVI (n = 345). The main finding for these distinct patient populations was that colchicine is an effective drug for the prevention of postoperative and postablation AF, with some risk of discontinuation of therapy due to gastrointestinal intolerance.

In contrast, earlier meta-analyses by Trivedi et al (2014; n = 584),[20] Verma et al (2015; n = 1118),[18] and Papageorgiou et al (2016; n = 1118)[17] studied cardiac surgery and PVI populations together, without separate subanalysis. They suggested that colchicine treatment might have clinical and cost benefits in AF prevention.

In 2017, a meta-analysis by Lennerz et al[19] focused on 1412 patients undergoing cardiac surgery. The primary end point was POAF after treatment with colchicine; secondary end points included hospitalization length and side effects after colchicine treatment. A decrease in POAF, as well as a reduction in hospital stay by 1 day with an increase in incidence of gastrointestinal disturbances in patients receiving colchicine, was detected.

Finally, in 2016, a meta-analysis by Wang et al,[21] incorporating only data from POAF studies, was published. This meta-analysis was the only one with neutral results. The primary end points were pericardial effusion and POAF, and the secondary end points included pericarditis symptoms as well as recurrence, cardiac tamponade, hospitalization due to postoperative pericarditis, and side effects of colchicine. In summary, this meta-analysis found no significant decrease in POAF and postoperative pericardial effusion. Conversely, a significant reduction in recurrence of postoperative pericarditis and duration of hospital stay due to surgery in patients treated with colchicine was observed.

Studies in Progress

Two ongoing studies were identified through www.clinicaltrials.gov and are summarized in Table II. We present here a brief description of each study. The END-AFLD (Effect of Low Dose Colchicine on the Incidence of POAF; NCT03015831) study started recruitment in 2017 with the goal of being completed in 2020 (target sample size, ~1200 patients). The main efficacy end point of this randomized, placebo-controlled trial is the reduction in POAF incidence in patients undergoing cardiac surgery until patient discharge. Gastrointestinal side effects have been set as a primary safety end point. To achieve the study goals, investigators opted for the following regimen: 0.5 mg daily starting from the first postoperative day and until discharge.

The COP-AF (Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery; NCT03310125) study started recruiting patients in January 2018 and will last for 4 years. Patients aged >55 years and undergoing thoracic surgery with general anesthesia will be included (estimated enrollment, 3000 patients). Patients will be randomly assigned to receive colchicine (10-day treatment 0.5 mg BID) versus placebo. The incidence of POAF within 14 days from the index procedure is set as a primary endpoint.

POST-PV ABLATION AF

An article entitled "Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study" was published in 2012 by Deftereos et al[14] and was the first study, to the best of our knowledge, to evaluate the effect of colchicine in the recurrence of AF after PVI via catheter ablation. It was a randomized, double-blind, placebo-controlled trial conducted in 2 Greek tertiary hospitals. A total of 161 patients

Table II. Ongoing studies.

NCT	Investigators	Target Sample, No.	Colchicine Dose	End of Treatment	Follow-up	Study Initiation	Expected Study Completion
03015831	Jordan Collaborating Cardiology Group	1200	LD: 1 mg 1 d preoperative MD: 0.5 mg daily	Hospital discharge	7 d	10/2017	5/2020
03310125	Hamilton Health Sciences Corporation, McMaster University	3000	0.5 mg BID for 10 d within 14 d after surgery	10 days	14 d	1/2018	6/2022

LD = loading dose; MD = maintenance dose; NCT = National Clinical Trial identifier.

experiencing paroxysmal AF (with at least 2 recorded AF episodes within 1 year or at least 1 recorded episode treated with antiarrhythmic drug) were recruited. The primary end point was AF recurrence within a 3-month period after radiofrequency catheter ablation of the pulmonary veins. Patients in the experimental arm (vs placebo) received 0.5 mg BID for 3 months starting from the first day of the ablation procedure without a loading dose. During this period, patients were prohibited from receiving any antiarrhythmic drug class I or III, except for those with heart failure or coronary artery disease. AF recurrence follow-up was conducted with 48-hour Holter recordings bimonthly for the duration of the study. Inflammatory markers (CRP and interleukin-6 [IL-6]) were evaluated at days 1 and 4. During the 3-month follow-up, AF recurrence was recorded in 33.5% of the control group versus 16% of the colchicine group ($P = 0.01$). Mean recurrence-free duration was 69 days in the control group versus 82 days in the colchicine group ($P = 0.006$). On the first postintervention day, levels of inflammatory markers (CRP and IL-6) were comparable in the 2 groups. In contrast, on day 4, significant reductions occurred in CRP and IL-6 levels in the colchicine group compared with the control group ($P < 0.01$).

In 2014, a second study by Deftereos et al[15] entitled "Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life" was published. This study was a 3-center (Greek), randomized, double-blind, placebo-controlled trial, and the primary end point was the reduction of AF recurrence after a single ablation procedure. A total of 223 patients with paroxysmal AF underwent ablation. The colchicine group, which comprised 103 patients, received colchicine 0.5 mg BID with no loading dose. Treatment was continued for 3 months, and patients were clinically followed up for 15 months. The first 3 postintervention months were considered the blanking period (any AF events were therefore ignored). During the follow-up period, each patient was evaluated by using 14 Holter recordings. The recurrence rate was lower in the colchicine group (31%) versus the control group (50%; $P = 0.010$). In addition, recurrence-free time was greater in the colchicine group (548 days) versus in the placebo group (445 days; $P = 0.007$). More, this reduction had a beneficial impact in self-perceived quality of life of the patients.

CLINICAL PRACTICE GUIDELINES: CONSENSUS DOCUMENTS

Colchicine has traditionally been used in the treatment of gout and other rheumatic diseases. Colchicine application, in view of its effects on the cardiovascular system, was limited to the management of acute and recurrent pericarditis and postsurgical pericardial effusion. Moreover, colchicine may be recommended for the management and prevention of post–cardiac injury syndrome.[22]

According to the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for AF management[23] (justified on the results of the COPPS trial substudy), colchicine treatment after cardiac surgery may be suggested (Class IIb, Level of Evidence B) for the reduction of AF. In the most recent (2016) European AF management guidelines (European Society of Cardiology in collaboration with the European Association for Cardio-Thoracic Surgery),[3] colchicine is not reported to pose any benefit. This suggestion was made by using the results of the COPPS-2 study.[11]

In addition, the role of colchicine in the prevention of the AF recurrences postoperatively and postablation is mentioned in the 2017 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society/Asia Pacific Heart Rhythm Society/Latin American Society of Cardiac Stimulation and Electrophysiology (Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología) expert consensus statement on catheter and surgical ablation of AF.[24] This statement suggests that colchicine may be used for the prevention of AF recurrence after cardiac surgery or AF ablation. Interestingly, although no firm recommendation exists, according to a survey among the consensus-writing team, short-course colchicine regimens are already administered at ~6% after PVI.

DISCUSSION

Postoperative AF has been the subject of interest for a series of research over the previous years. AF is a very frequent complication[25] in patients undergoing cardiac surgery, with negative consequences in the duration of hospitalization and survival, while in general, AF aggravates patients' quality of life. A 2018 review and meta-analysis evaluated the incidence of POAF recurrence in patients who underwent cardiac surgery.[26] A population of 1157 patients (66 [10]

years of age; 73% male), monitored for ~4 weeks with noninvasive methods, presented with POAF with an incidence of 28%. The patients who were followed up for 2 years with an implantable loop recorder presented a 61% to 100% incidence rate of AF.

The mechanism of POAF is considered to be reentry. Perioperative factors such as inflammation, operative trauma, myocardial ischemic necrosis, and metabolic and electrolyte disorders may contribute to the occurrence of AF. Both POAF and postablation AF induce acute inflammation in which neutrophils are the predominant immune cells, creating a substrate for the colchicine anti-inflammatory effect.[5]

Colchicine is an alkaloid with anti-inflammatory and antiproliferative characteristics that inhibits mitosis and neutrophil motility. In particular, colchicine is an agent that binds to nonpolymerized tubulin in neutrophils and blocks microtubule depolymerization. Microtubules have an important role in cellular processes, including cell division, intracellular trafficking, cytokine secretion, and neutrophil adhesion. Consequently, colchicine interferes with neutrophil activation and migration to inflamed tissues.[27]

Moreover, microtubules control the localization and the interaction of adrenergic receptors in the cell membrane, regulating the phosphorylation of calcium channels. In this way, colchicine influences the atrial response to autonomic stimulation by reducing sympathetic activity, decreasing the possibility of calcium overload–induced tachyarrhythmia.

Colchicine is easily absorbed after oral administration.[28] Peak concentration is reached in 0.5 to 2 hours, and the plasma $t_{1/2}$ is ~20 minutes. In contrast, the $t_{1/2}$ in leukocytes is estimated to be ~60 hours. The most common side effects of colchicine are gastrointestinal disorders and elevation in liver enzyme levels. Colchicine is considered to be the main treatment for gout. Furthermore, based on its mechanism of action and the clinical results of various randomized trials, colchicine has gained a role in various cardiovascular diseases. According to the 2015 European clinical practice guidelines on the management of pericardial disease, colchicine may be administered (Class IIa, Level of Evidence B) for the treatment of post–cardiac injury syndromes, while it should be noted that it is a first-line drug in the treatment of acute pericarditis (Class I, Level of Evidence A).

Since 2011, a series of studies have evaluated the effect of colchicine in POAF. The COOPS study[10] was the first trial that showed the effectiveness of colchicine in reducing POAF and post–pericardial syndrome, from the third postoperative day. In the COPPS study, treatment with colchicine started the third postoperative day and was continued for 1 month. It should be noted that an increased incidence of POAF (43%) was observed from the first to third day after surgery in the colchicine group. Due to this observation, the same research group organized the COPPS-2 study,[11] in which they modified the initiation of the treatment and colchicine dose. More specifically, colchicine administration onset was 48 to 72 hours before surgery, without a loading dose, for a total duration of 1 month; patients were clinically followed up for 3 months. Although data from the COPPS study were promising, the results of the COPPS-2 study were not confirmatory. The on-treatment subanalysis revealed a beneficial effect of colchicine on POAF, but this finding was not statistically significant for the intention-to-treat population. Possible causes for this outcome might be: (1) the dropout of patients due to gastrointestinal colchicine intolerance (almost double that in the COPPS study); or (2) the wide variety of cardiac interventions in the patient population studied.

Similarly, gastrointestinal disturbances, as a side effect of colchicine, were the reason for dropout for more than one half of the patients in the colchicine group in the END-AF (Effect of Colchicine on the Incidence of Atrial Fibrillation in Open Heart Surgery Patients) trial.[13] This outcome could also be identified as a serious "confounding factor" that should be considered in interpreting the trial's neutral results regarding the efficacy of colchicine. Nevertheless, a nonsignificant 6% reduction in documented AF was recorded in the colchicine group. It should be underlined that the study was powered to detect differences >12%.

According to the expert consensus statement of 2017 on surgical and catheter AF ablation,[24] there is a possibility of AF recurrences after treatment. Recurrences are classified into 3 types, in relation to the period of occurrence: (1) early recurrence (within 3 months); (2) late recurrence (from 3 months to 1 year); and (3) very late recurrence (>1 year). Early recurrences are observed in $\geq$50% of patients, and late recurrences in 25% to 40% of cases. As far as very late recurrences, some studies have reported that the longer the follow-up after ablation, the higher the incidence of AF.

Two studies evaluating the use of colchicine for the prevention of early AF (early recurrences) after PVI

with radiofrequency catheter ablation were by our research group (Deftereos et al).[14,15] The first study, published in 2012, had a 3-month follow-up, which observed a greater reduction in AF incidence (16% colchicine group vs 33.5% control group) and a notable mean recurrence-free time. Moreover, the levels of inflammation markers were decreased from the first to fourth day of treatment in the study group. The second study, published in 2014, had a 15-month follow-up, and all the episodes during the blanking period (first 3 months) were excluded. The results were similar to the previous study. A 31% reduction in the recurrence rate was observed in the colchicine group versus a 50% reduction in the control group. In addition, an improvement in the quality of life of patients who received colchicine was reported.

CONCLUSIONS

Colchicine treatment may have a preventive role in the development of AF after cardiac surgery or catheter ablation for PVI. More trials are needed to determine the proper regimen in terms of onset, dosing, and treatment duration.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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