

The cardiovascular effects and safety of colchicine

Abstract

Colchicine is an alkaloid obtained from the bulb and seed of the Crocus (*Colchicum autumnale* L. (Liliaceae), Autumn Crocus) plant with a history of 2000 years and is currently prescribed for the treatment of rheumatic diseases. In 2015, the European Society of Cardiology supported and recommended colchicine as a first-choice treatment agent that can be added to traditional anti-inflammatory treatments to improve response to treatment, increase remission rates and reduce relapses in acute and recurrent pericarditis in the diagnosis and treatment guidelines of pericardial diseases. In addition, the use of colchicine in the Secondary Prevention of Atherosclerosis is recommended with evidence level A in the European Society of Cardiology Guidelines published in 2021. It was concluded that colchicine is a safe and effective treatment modality to prevent AF recurrence after catheter ablation. It has been noted that colchicine, used secondary to the currently used preventive drugs against CHD, has lower rates of cardiovascular death, MI, stroke, or emergency hospitalization due to angina requiring coronary revascularization, and the risk of acute cardiovascular events compared to placebo. In addition, it has been reported that the use of colchicine in patients with MI reduces the risk of ischemic cardiovascular events. Colchicine is an effective and safe option as a first-choice treatment agent that can be added to conventional anti-inflammatory treatments in patients with recurrent cardiovascular events despite optimal medical therapy and in the secondary prevention of atherosclerotic cardiovascular diseases where other risk factors cannot be adequately controlled.

Keywords: colchicine, pericarditis, secondary cardiovascular protection, coronary artery disease

Volume 10 Issue 2 - 2022

Fatmanur Otmar Ozcan,¹ Kubra Saygisever-Faikoglu,² Gokhan Faikoglu,³ Tugce Uskur,³ Dundar Okan Yillar,³ Barkin Berk,⁴ Pelin Kelicen Ugur⁵

¹Department of Internal Medicine, Okmeydani Training and Research Hospital, Turkey

²Department of Pharmacology, Cerrahpasa Faculty of Medicine, Istanbul University, Turkey

³Department of Medical Pharmacology, Faculty of Medicine, Beykent University, Turkey

⁴Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Istanbul Medipol University, Turkey

⁵Department of Pharmacology, Faculty of Pharmacy, Hacettepe University, Sıhhiye, Ankara Turkey

Correspondence: Gokhan Faikoglu, Department of Medical Pharmacology, Faculty of Medicine, Beykent University, Turkey, Email gokhanfaikoglu@gmail.com

Received: March 08, 2022 | **Published:** March 24, 2022

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; MI, myocardial infarction; FMF, familial Mediterranean fever; HRS, heart rhythm society; EHRA, European heart rhythm association; ECAS, European society of cardiac arrhythmias; APHRS, Asia Pacific heart rhythm society; SOLAEC, Latin American society of cardiac stimulation and electrophysiology; NSAID, non-steroidal anti-inflammatory drugs; IL, interleukin-1; NLRP3, NLR family pyrin domain containing 3; Bcl-2, B cell lymphoma 2; RhoA, Ras homolog family member A; CRP, C-reactive protein; VEGF, vascular endothelial growth factor; TNF- α , tumor necrosis factor- α ; NF- κ B, nuclear factor-kappa B; CRP, C-reactive protein; Lp-PLA₂, lipoprotein-associated phospholipase A2; NO, nitric oxide; IL1- β , interleukin-1 Beta; ACS, acute coronary syndromes; ASKH, effects on atherosclerotic heart diseases; hsCRP, high-sensitivity C-reactive protein; CAD, coronary artery disease; LoDoCo, low-dose colchicine for secondary prevention of cardiovascular disease; COLCOT, colchicine cardiovascular outcomes trial; CLEAR-SYNERGY, colchicine and spironolactone in patients With MI/SYNERGY stent registry; CONVINCE, colchicine for prevention of vascular inflammation in non-cardio embolic stroke; COPE, colchicine in acute pericarditis; CORE, Colchicine for REcurrent pericarditis; CORP, colchicine for recurrent pericarditis; POAF, post-operative atrial fibrillation; COPPS, colchicine for the prevention of the post-pericardiotomy syndrome; COLCORONA, colchicine coronavirus SARS-CoV2 trial

Introduction

Colchicine has been used in medicine for over 2000 years. Colchicine is an alkaloid structure obtained from the plant *Colchicum autumnale*, known as autumn crocus or bitter crocus, and its effectiveness in the treatment of gout has been known for centuries. After determining the effectiveness of colchicine in preventing recurrence of attacks and amyloidosis in patients with Familial Mediterranean Fever (FMF), research focused on its suppressive

functions in inflammasome-related inflammation. Its use in the treatment of Behcet's disease is also well known.¹⁻⁴

Recently, the European Society of Cardiology has added colchicine as a first-line drug to conventional anti-inflammatory treatments for patients with pericardial diseases (acute and recurrent pericarditis).⁵ This review aims to evaluate the effectiveness of colchicine on the cardiovascular system. In 2017, in their common statement of opinion regarding the catheter and surgical ablation of Atrial Fibrillation (AF), the Heart Rhythm Society (HRS), the European Heart Rhythm Society (EHRA), the European Cardiac Arrhythmia Society (ECAS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Society for Cardiac Stimulation and Electrophysiology (SOLAEC) recommend the administration of colchicine to prevent AF recurrence after cardiac surgery or AF ablation.⁶

It has also been noted in other publications that colchicine's specific mechanism of action is quite different from steroid and non-steroidal anti-inflammatory drugs (NSAIDs) and together with an established safety profile, this mechanism makes its use safe in patients with coronary artery disease and chronic heart failure.^{7,8}

The fact that it has been shown that inflammation develops through inflammasome-mediated and increased interleukin-1 (IL-1) activation in both FMF and gout, has accelerated studies to fully understand the mechanisms of action of colchicine. The pathogenesis in both diseases has the same mechanism. Increased caspase 1 activity as a result of uncontrolled stimulation of the NLRP3-related inflammasome complex in the cell causes overproduction of IL-1 beta cytokine. Considering the selective effect of colchicine on inflammation observed in these diseases, it is thought that it blocks caspase 1 activation by inhibiting the formation of the inflammasome complex in the early stages of its mechanism of action.⁹

In addition, it has been known for a long time that the colchicine molecule binds to tubulin monomers, thus preventing the elongation

of microtubules. This feature, which disrupts the cytoskeleton and is effective in metabolic pathways, has caused it to be considered in anticancer studies as well as in the treatment of inflammatory processes.⁹

The most studied therapeutic mechanism of action of colchicine is its tubulin-binding capacity, blocking the assembly and polymerization of microtubules. Colchicine is a classical anti-mitotic drug that blocks mitotic cells in metaphase. It binds to soluble tubulin to form tubulin-colchicine complexes and then binds to the ends of microtubules to prevent elongation of the microtubule polymer. Colchicine at low concentrations inhibits microtubule growth and at higher concentrations promotes microtubule depolymerization. It causes severe toxicity in normal tissues at high doses, which limits its use in cancer treatments.¹⁰

In addition to its use in the treatment of gout and Familial Mediterranean Fever, colchicine is currently used in cardiology for various indications, particularly pericarditis and peri-operative atrial fibrillation.¹¹

Effects of colchicine on atherosclerotic heart diseases (ASHD)

Colchicine has positive effects on atherosclerosis, which is characterized by lipid deposition and atherosclerotic plaque deposition under the intima. Colchicine inhibits leukocyte functions by preventing microtubule polymerization and prevents leukocyte accumulation and leukocyte deformation in inflamed and damaged endothelium by reducing the release of adhesion molecules and chemoattractants from the endothelium and leukocyte surface. It also inhibits NLRP3 inflamasome and IL1- β formation. It exerts an anti-thrombotic effect without the potential risk of bleeding by inhibiting leukocyte-platelet aggregation but not platelet-platelet aggregation.¹² It has been shown to reduce hsCRP concentration in patients with ASCH receiving statins and antiplatelet therapy.¹³ Colchicine has been observed to reduce low-signal plaque volume, a measure of plaque instability, on computed tomography angiography.¹⁴

In a retrospective study of 1288 gout patients with high cardiovascular risk, colchicine reduced the risk of MI by 54%. In a similar retrospective study of 501 patients with gout, it was reported that it reduced the risk of MI, stroke, and ischemic attack by 49%. In a single-center trial in which 532 patients on a statin and antiplatelet therapy were followed for 3 years, daily low-dose (0.5 mg/day) colchicine was reported to reduce the risk of acute coronary syndrome, out-of-hospital cardiac arrest, and non-cardioembolic ischemic stroke.¹⁵

The potential for colchicine to reduce angioplasty and stent-related recurrent events were also examined. In a randomized, double-blind trial of 196 patients with diabetes and percutaneous coronary intervention with metal stent implantation, patients, who received two doses of 0.5 mg colchicine daily for 6 months, were followed up with angiography (16% vs. 33%, $p=0.007$) and intravascular ultrasound (24% vs. 43%, $p=0.006$) and evaluated for re-occlusion at the stent site, and it was observed that the patients receiving colchicine were protected compared to the placebo group.¹⁶

Effects of colchicine on acute coronary syndromes (ACS)

Acute coronary syndromes (ACS) are clinical manifestations of an intracoronary thrombotic event resulting from erosion or rupture of an unstable atherosclerotic plaque that causes platelet aggregation

and partial or complete vascular occlusion, and inflammation that develops during plaque formation and after its rupture, which has been emphasized in recent years.¹⁷⁻¹⁹

In particular, colchicine therapy has a unique anti-inflammatory mechanism and the potential for long-term use; and its lowering of hsCRP, unlike aspirin and atorvastatin, has made it a theoretical candidate drug for stable coronary artery disease (CAD) patients.^{14,20}

In a Comprehensive prospective, randomized trial, the use of low-dose continuous colchicine in 532 patients with stable CAD is reviewed. It has been proven that the risk of ACS, cardiac arrest, or non-cardioembolic ischemic stroke is reduced in patients given 0.5 mg of colchicine daily in addition to standard CAD therapy (5.3% vs. 16%, $p<0.001$). In another trial, it was shown that patients using colchicine for gout prophylaxis have a lower risk of myocardial infarction than those not using colchicines.²¹

Effects of colchicine on hs-CRP in patients with stable coronary artery disease

The effects of colchicine on high-sensitivity C-reactive protein (hs-CRP), an important biomarker of inflammation and a predictor of future vascular events, were investigated in patients with stable coronary artery disease. In the trial, 64 patients with high hs-CRP levels (>2.0 mg/L) despite aspirin and high-dose atorvastatin therapy were divided into two groups. When hs-CRP levels were re-measured 2 weeks later in 20 patients who were not given colchicine, they did not differ significantly from baseline (baseline: 4.28 mg/L; week 2: 3.70 mg/L). Measurements were repeated after 4 weeks in 44 patients who were given 0.5 mg colchicine twice a day, and a statistically significant decrease was found in hs-CRP levels compared to baseline (baseline: 4.58; week 4: 1.78 mg/L; $p<0.001$). In 28 (64%) of these 44 patients, hs-CRP levels decreased by more than 50%, and in 31 patients (70%) hs-CRP levels were found to be less than 2.0 mg/L. The results of the trial showed that colchicine was effective in reducing hs-CRP in stable coronary artery patients whose hs-CRP level did not decrease despite aspirin and atorvastatin therapy.¹³

Effects of colchicine on hs-CRP and plaque morphology in patients with acute coronary syndrome

The effects of colchicine on hs-CRP levels and plaque morphology were prospectively evaluated in patients with the acute coronary syndrome in the last month. 80 patients who received standard treatment (statins, renin-angiotensin inhibitors, beta-blockers, etc.) were included in the trial. While standard treatment and 0.5 mg/day colchicine were given to 40 patients, only standard treatment was applied to the other 40 patients. Plaque instability of all patients was evaluated by computed tomography angiography at 1 month and the following 1 year after acute coronary syndrome. At the end of the follow-up period, the plaque volume decreased 40.9% in the colchicine group, while the plaque volume reduction was 17% in the standard treatment-only group ($p=0.008$). In addition, hs-CRP levels were significantly decreased in the colchicine group (37.3% in the Colchicine group; 14.6% in the Standard treatment group; $p<0.001$).¹⁴

In the same trial, multivariate linear regression analysis showed that colchicine treatment had an independent role in both plaque volume reduction and hs-CRP level reduction. In the correlation analysis, a strong positive correlation was found between plaque volume and hs-CRP level ($r=0.578$, $p<0.001$).¹⁴

The authors showed that improvements in plaque morphology were closely associated with decreases in hs-CRP levels due to the

anti-inflammatory property of colchicine. In conclusion, low-dose colchicine also reduced hs-CRP and regressed atherosclerotic plaque in people with coronary disease and taking statins.^{14,22}

Effects of low-dose colchicine in stable coronary artery disease (LoDoCo trial)

In the LoDoCo (Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease) trial published in 2013, low-dose colchicine (0.5 mg/day) was also well tolerated in patients taking high-dose statins and showed significant benefit in the treatment process. In the same trial, undesirable effects were not found in patients receiving medium- and high-dose statins.²⁰

A Cochrane systematic review evaluating 39 studies and 4992 patients concluded that low-dose colchicine therapy reduced the risk of myocardial infarction and had a very low side-effect profile. In conclusion, people treated with low-dose colchicine for stable coronary artery disease had a lower risk of adverse cardiovascular events and myocardial infarction.²³

Effects of low-dose colchicine in patients with myocardial infarction (COLCOT trial)

In the COLCOT (Colchicine Cardiovascular Outcomes Trial) trial, which included 4745 patients, the efficacy of low-dose colchicine was compared with placebo in patients with myocardial infarction in the last 30 days. The primary endpoints were cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, and hospitalization for angina resulting in coronary revascularization. After a median of 22.6 months, the primary endpoint occurred in 5.5% of patients in the colchicine group and 7.1% in the placebo group (HR 0.77; P=0.02). A significantly lower risk of ischemic cardiovascular events was found with low-dose colchicine in patients with a recent myocardial infarction.²⁴

In an advanced cohort of the COLCOT trial (COLCOT-2), the relationship between the onset of colchicine after myocardial infarction and its benefit to patients was evaluated, and the results of the trial were published in the European Heart Journal in 2020. In the trial, the 30-day period after myocardial infarction was divided into 3 phases (<3 days; 4-7 days; >8 days). The composite primary endpoint was cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or hospitalization for angina requiring coronary revascularization. In this analysis, which included 4661 patients, the mean follow-up was 22.7 months. The primary endpoint event was significantly lower in the group in which colchicine was initiated within the first 3 days after myocardial infarction compared to the 4-7 days and >8 days periods (HR =0.96 and HR=0.82, respectively). In the placebo comparative analysis, it was determined that the highest positive effect of colchicine was in the group in which colchicine was started within the first 3 days after myocardial infarction (HR=0.52 P=0.007). In conclusion, patients treated with low-dose colchicine in patients with a history of myocardial infarction in the past 30 days have a lower risk of adverse cardiovascular events.²⁵

Effects of low-dose colchicine in chronic coronary artery disease (LoDoCo 2 trial)

The effect of low-dose colchicine on the risk of cardiovascular events was examined in the LoDoCo 2 trial. 5522 patients with chronic coronary disease were randomly assigned to low-dose colchicine (0.5 mg/day) and placebo groups and followed for a mean of 28.6 months. Primary endpoints were cardiovascular death, spontaneous myocardial infarction, ischemic stroke, and coronary revascularization

due to ischemia; and secondary endpoints were cardiovascular death, spontaneous myocardial infarction, and ischemic stroke. Any of the primary endpoints occurred at a rate of 6.8% in the colchicine group and 9.6% in the placebo group (HR 0.69; P<0.001). Any of the secondary endpoints were 4.2% in the low-dose colchicine group and 5.7% in the placebo group (HR 0.72; P=0.007). In conclusion, low-dose colchicine significantly reduced primary and secondary outcome events.²⁶

In addition, the efficacy of low-dose colchicine is also being studied in clinical studies of CLEAR-SYNERGY (Colchicine and Spironolactone in Patients With MI / SYNERGY Stent Registry),²⁷ which included 7000 patients, and CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke),²⁸ which included 2623 patients.

In the light of all these studies and data, it is observed that the use of colchicine in the treatment of atherosclerosis with an anti-inflammatory mechanism is evaluated and recommended by the authorities as an inexpensive and easily accessible treatment option among the existing options. In conclusion, the risk of adverse cardiovascular events was found to be lower in patients with chronic coronary disease treated with low-dose colchicine.

Effects of colchicine on pericarditis

In the diagnosis and treatment guidelines of the European Society of Cardiology, colchicine has been supported and recommended as a first-choice treatment agent that can be added to traditional anti-inflammatory treatments to improve response to treatment, increase remission rates and reduce relapses in acute and recurrent (relapsing) pericarditis.⁵

Effects of colchicine in acute pericarditis (COPE trial)

In the COPE (Colchicine in Acute Pericarditis) trial, the safety and efficacy of adding colchicine as an adjunct to conventional treatment in the first attack of acute pericarditis were investigated.

In the prospective, randomized and open-label trial, 120 patients were divided into two groups: the conventional group (aspirin) and the group receiving colchicine with conventional treatment (aspirin + colchicine). Patients in the colchicine group were given 1-2 mg of colchicine on the first day, and then 0.5-1 mg of colchicine for 3 months. The primary endpoint was the rate of recurrent pericarditis. After 18 months, the rate of recurrent pericarditis was 10.7% in the colchicine group, while it was 32.3% in the conventional treatment group (P=0.004). In addition, symptomatic resistance in the first 72 hours was 11.7% in the colchicine group and 36.7% in the conventional group (p=0.003). Colchicine+conventional therapy provided clinically important and significant benefits compared to conventional therapy alone. As a result, colchicine as adjunctive therapy in people with acute pericarditis reduced the recurrence of pericarditis approximately 3-times compared to placebo.²⁹

Effects of colchicine in the prevention and treatment of recurrent pericarditis (CORE trial)

In the prospective, randomized, open-label CORE (COLchicine for REcurrent pericarditis) trial, colchicine was used in the treatment of the first episode of recurrent pericarditis in addition to conventional therapy. 84 patients who had the first attack of recurrent pericarditis were included in the trial. The patients were divided into two groups; one group received conventional treatment with aspirin and the other group received colchicine with conventional treatment. These patients were given 1.0-2.0 mg of colchicine on the first day and 0.5-1.0 mg/

day for the next 6 months. The primary endpoint was the pericarditis recurrence rate. The recurrence rate was significantly lower in the group treated with colchicine at a mean follow-up of 20 months (24% with colchicine, 50.6% with conventional therapy; $p=0.02$). In this trial, symptomatic resistance was found to be lower with colchicine within the first 72 hours (10% with colchicine, 31% with conventional treatment; $p=0.03$). Colchicine treatment provided a clinically important and significantly higher benefit than conventional treatment in both preventing recurrence and providing rapid symptomatic relief. In conclusion, the addition of low-dose colchicine to the treatment in patients who had a first recurrent episode of pericarditis reduced the next episode of pericarditis by approximately 50%.³⁰

Effects of colchicine in the prevention and treatment of recurrent pericarditis (CORP trial)

The efficacy and safety of colchicine for secondary prevention in recurrent pericarditis were investigated in a prospective, randomized, double-blind, placebo-controlled CORP (Colchicine for recurrent pericarditis) trial. 120 patients with their first episode of recurrent pericarditis were grouped into receiving placebo or colchicine in addition to conventional therapy. These patients were given 1.0-2.0 mg of colchicine on the first day and 0.5-1.0 mg/day for the next 6 months. The primary endpoint was pericarditis recurrence rate at 18 months. The recurrence rate at 18 months was 24% in the colchicine group versus 55% in the placebo group (absolute risk reduction 0.31); also, symptomatic resistance within the first 72 hours was significantly lower in the colchicine group (absolute risk reduction 0.30).^{14,31} Today, colchicine is a more preferred agent than corticosteroids as a supportive treatment for non-steroidal anti-inflammatories in the treatment of pericarditis. In conclusion, low-dose colchicine treatment in recurrent pericarditis reduced the recurrence of pericarditis by approximately 50% compared to placebo.³²

Effects of colchicine on stroke

Stroke is the second leading cause of death in the world, and cardiovascular diseases trigger neurological diseases such as ischemia accompanied by dementia. Despite the proven effects of anti-thrombotic, lipid-lowering, anti-hypertensive treatments, and lifestyle changes in the prevention of ischemic stroke, stroke is one of the causes of death triggered by coronary and vascular diseases, and the search for preventive treatment continues for stroke.^{33,34}

It is known that ischemic stroke is caused by atherosclerotic plaques. Therefore, in addition to anti-inflammatory treatments targeting atherosclerotic plaque inflammation, treatments that stabilize plaque and prevent thromboembolic events are also effective in ischemic stroke.³⁴ In a meta-analysis of 6630 patients, 3359 of whom received colchicine and 3271 of whom were observed as the placebo group, it was observed that colchicine reduced the risk of ischemic stroke in patients with cardiovascular risk.³⁵

In a meta-analysis trial in which 5553 patients at risk for cardiovascular (coronary artery) disease were followed up for 1-36 months, it was reported that 161 patients were protected from a stroke during the 23-month follow-up.³⁶ It has been shown that in patients who had a heart attack, colchicine reduced the frequency of stroke dramatically (77%); and protect against the risk of recurrent heart attack, angina, and stroke.³⁷

Cerebrovascular events were also evaluated in studies in which the benefit of colchicine was examined in cardiovascular diseases in a placebo-controlled manner. A 2020 review and meta-analysis looked at 4 randomized controlled trials on the topic (5553 patients in total).

In these studies, the development of stroke during the follow-up period was investigated. Colchicine-administered groups had significantly fewer strokes at follow-up compared to controls (HR=0.31). It was concluded that administration of low-dose colchicine to people with coronary artery disease would prevent stroke in at least one of 161 patients with a follow-up of up to 23 months.³⁶

In another meta-analysis, 5 studies were reviewed. Stroke/TIA was reported in 77 cases out of a total of 2170 patients. The incidence of stroke was significantly lower in the colchicine-treated patient groups than in the non-colchicine group (RR, 0.37; $P=0.0002$).³⁸ The ongoing CONVINCE (2,623 patients) trial focuses on the impact of colchicine in the secondary prevention of stroke.³⁹ As a result, colchicine treatment in coronary artery disease resulted in a significant decrease in cerebrovascular events (stroke) in the follow-up period compared to the control groups.

Colchicine and angioplasty

Restenosis of the coronary arteries after PCI is a serious problem. Neointimal hyperplasia and local inflammation are key components in restenosis.⁴⁰ The benefit of colchicine therapy was seen in diabetic patients with drug-eluting stent implants, and when patients were evaluated by ultrasound 6 months after PCI, the rate of *in-stent* restenosis and lumen loss decreased from 33% to 16% compared to those using placebo. Due to its antimitotic and anti-inflammatory properties, colchicine is theoretically an attractive candidate for the prevention of restenosis.¹⁰

Post-Operative Atrial Fibrillation (POAF)

POAF is a problem that occurs in 10-65% of all patients undergoing cardiac surgery and is associated with length of hospital stay, morbidity, and mortality. In the multicenter, double-blind, randomized COPPS (*Colchicine for the Prevention of the Post-pericardiotomy Syndrome*) trial by Imazio et al.^{41,42}, the frequency of POAF decreased by 45% in patients who were given colchicine for one month starting from the day 3 after surgery, and it shortened the length of hospital stay as it halved the average POAF attack duration.

In a randomized, double-blind, two-center trial, half of 170 patients on the day of ablation were started on colchicine (0.5 mg twice daily), half on placebo, and continued for 3 months. The patients were not given any antiarrhythmics. It has been reported that the frequency of POAF, CRP, and IL-6 levels were significantly decreased from day 4 in the colchicine group.⁴³

In a randomized trial with a total of 912 patients in which 457 patients were treated with colchicine and 455 with placebo,⁴⁴ in a randomized controlled trial with a total of 1257 patients,⁴⁵ and another randomized controlled trial with 1412 patients, preoperative colchicine treatment was found to be associated with a decrease in the incidence of POAF⁴⁴ and length of hospital stay.⁴⁶ Many studies suggest that colchicine can be used as adjunctive prophylaxis in POAF.

Effects of colchicine on AF relapse after ablation

A prospective, randomized, double-blind trial was conducted to examine the use of colchicine in patients with AF who underwent pulmonary vein isolation during AF ablation therapy. It was observed that patients with pulmonary vein isolation, who were treated with colchicine monotherapy for three months, were protected from AF recurrence compared to the placebo (16%) group (33.5%), and inflammatory mediators such as IL-6 and CRP were also significantly reduced. This trial highlights the continuous increase in CRP values in the first three months after ablation and the close relationship between

inflammation and early-stage AF recurrence. Considering that inflammation is the main factor in these cases, it can be expected that colchicine will turn into a promising preventive treatment strategy.⁴³

In addition to its anti-inflammatory effects, it should not be denied that other mechanisms are also effective in the reducing effects of colchicine on post-ablation AF and POAF. It is known that colchicine also has cytoskeleton-mediated electrophysiological effects. It has been shown that the mechano-mediated channels opened as a result of mechanical damage to rat atrial fibroblast cells are completely blocked by colchicine. It is known that mechanically induced channels in these cells are dependent on the polymerization of actin and tubulin. In another study, it was emphasized that L-type calcium channels, which are regulated by muscarinic and β -adrenergic agonists and responsible for Ca^{2+} flow, are affected by colchicine, and it is important to control abnormal Ca^{2+} flow in AF.⁴³

These studies also show that it is possible to benefit from the protective effect of colchicine from AF after cardiac surgery or catheter ablation treatment, with appropriate initial dosage and duration. Based on these data, the researchers concluded that colchicine is a safe and effective treatment modality for preventing AF recurrence after catheter ablation.⁴³

Conclusion

Colchicine is an effective and safe option as a first-choice treatment agent that can be added to conventional anti-inflammatory treatments in patients with recurrent cardiovascular events despite optimal medical therapy and in the secondary prevention of atherosclerotic cardiovascular diseases where other risk factors cannot be adequately controlled.

Acknowledgments

None.

Conflicts of interest

Fatmanur Otmar Ozcan, Kubra Saygisever-Faikoglu and Gokhan Faikoglu, are medical advisors of Recordati.

References

- Hartung EF. History of the use of colchicum and related medicaments in gout; with suggestions for further research. *Ann Rheum Dis*. 1954;13(3):190–200.
- Khanna D, PP Khanna, JD Fitzgerald, et al. American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447–1461.
- Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med*. 1972;287(25):1302.
- Mat C, S Yurdakul, S Uysal, et al. A double-blind trial of depot corticosteroids in Behcet's syndrome. *Rheumatology*. 2006;45(3):348–352.
- Adler Y, P Charron, M Imazio, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surg. *Eur Heart J*. 2015;36:2921–2964.
- Calkins H, G Hindricks, R Cappato, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Hear Rhythm*. 2017;14(10):e275–e444.
- Deftereos S, G Giannopoulos, C Angelidis, et al. Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. *Circulation*. 2015;132(15):1395–1403.
- Nidorf SM, JW Eikelboom, PL Thompson. Colchicine for secondary prevention of cardiovascular disease. *Curr Atheroscler Rep*. 2014;16(3):391.
- Gül A. Kolçisin: Yüzyıllar Boyu Damıtılan Bilgelik Akılçılık Kullanımı Dair Notlar. *Turkiye Klin Rheumatol-Spec Top*. 2015;8(3):28–31.
- Bhattacharyya B, D Panda, S Gupta, et al. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. *Med Res Rev*. 2008;28:155–183.
- Thompson PL, S Mark Nidorf. Colchicine: An affordable anti-inflammatory agent for atherosclerosis. *Curr Opin Lipidol*. 2018;29(6):467–473.
- Billy Lin, Pillinger M, Binita S, et al. Use of colchicine in atherosclerotic heart disease. *Curr Res Integr Med*. 2018;3(S1):2-4.
- Nidorf M, PL Thompson. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol*. 2007;99(6):805–807.
- Vaidya K, C Arnott, GJ Martínez, et al. Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome: A CT Coronary Angiography Study. *JACC Cardiovasc Imaging*. 2018;11(2 Pt 2):305–316.
- Hemkens LG, H Ewald, VL Gloy, et al. Colchicine for prevention of cardiovascular events. *Cochrane Database Syst Rev*. 2016;2016(1):CD011047.
- Deftereos S, G Giannopoulos, K Raisakis, et al. Colchicine Treatment for the Prevention of Bare-Metal Stent Restenosis in Diabetic Patients. *J Am Coll Cardiol*. 2013;61(16):1679–1685.
- Klingenber R, TF Luscher. Inflammation in Coronary Artery Disease and Acute Myocardial Infarction - is the Stage Set for Novel Therapies? *Curr Pharm Des*. 2012;18(28):4358–4369.
- Drakopoulou M, K Toutouzas, A Michelongona, et al. Vulnerable Plaque and Inflammation: Potential Clinical Strategies. *Curr Pharm Des*. 2011;17(37):4190–4209.
- Naruko T, M Ueda, K Haze, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. *Circulation*. 2002;106(23):2894–2900.
- Nidorf SM, JW Eikelboom, CA Budgen, et al. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61(4):404–410.
- Crittenden DB, RA Lehmann, L Schneck, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. *J Rheumatol*. 2012;39(7):1458–1464.
- Vergallo R, F Crea. Atherosclerotic Plaque Healing. *N Engl J Med*. 2020;383(9):846–857.
- Hemkens LG, H Ewald, VL Gloy, et al. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. *Heart*. 2016;102(8):590–596.
- Tardif JC, S Kouz, DD Waters, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*. 2019;381(26):2497–2505.
- Bouabdallaoui N, JC Tardif, DD Waters, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *Eur Heart J*. 2020;41(42):4092–4099.
- Nidorf SM, ATL Fiolet, A Mosterd, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. 2020;383(19):1838–1847.
- Population Health Research Institute. *Colchicine and Spironolactone in Patients with MI / SYNERGY Stent Registry*. Hamilton, Ontario, Canada; 2018.
- Kelly P, C Weimar, R Lemmens, et al. Colchicine for prevention of vascular inflammation in Non-CardioEmbolic stroke (CONVINCE) - study protocol for a randomised controlled trial. *Eur Stroke J*. 2021;6(2):222–228.

29. Imazio M, M Bobbio, E Cecchi, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COLchicine for acute PEricarditis (COPE) trial. *Circulation*. 2005;112(13):2012–2016.
30. Imazio M, M Bobbio, E Cecchi, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COLchicine for REcurrent pericarditis) trial. *Arch Intern Med*. 2005;165(17):1987–1991.
31. Imazio M, A Brucato, R Cemin, et al. Colchicine for recurrent pericarditis (CORP): randomized trial. *Ann Intern Med*. 2011;155(7):409–414.
32. Deftereos S, G Giannopoulos, N Papoutsidakis, et al. Colchicine and the heart: pushing the envelope. *J Am Coll Cardiol*. 2013;62(20):1817–1825.
33. World Health Organization. Cardiovascular diseases (CVDs); 2017.
34. Ridker PM. From CRP to IL-6 to IL-1: Moving Upstream To Identify Novel Targets for Atheroprotection. *Circ Res*. 2016;118(1):145–156.
35. Masson W, M Lobo, G Molinero, et al. Role of Colchicine in Stroke Prevention: An Updated Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2020;29(5):104756.
36. Katsanos AH, L Palaiodimou, C Price, et al. Colchicine for stroke prevention in patients with coronary artery disease: a systematic review and meta-analysis. *Eur J Neurol*. 2020;27(6):1035–1038.
37. Sanford E. *How Colchicine Reduces Stroke in Heart Attack Patients*. Life Extension; 2020.
38. Khandkar C, K Vaidya, S Patel. Colchicine for Stroke Prevention: A Systematic Review and Meta-analysis. *Clin Ther*. 2019;41(3):582–590. e3.
39. Kelly P, C Weimar, R Lemmens, et al. Colchicine for prevention of vascular inflammation in Non-CardioEmolic stroke (CONVINCE) - study protocol for a randomised controlled trial. *Eur Stroke J*. 2021;6(2):222–228.
40. Libby P, D Schwartz, E Brogi, et al. A cascade model for restenosis. A special case of atherosclerosis progression. *Circulation*. 1992;86(6 Suppl):47–52.
41. Imazio M, R Trinchero, A Brucato, et al. Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J*. 2010;31(22):2749–2754.
42. Imazio M, R Belli, A Brucato, et al. Rationale and design of the COLchicine for Prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation (COPPS-2) trial: A randomized, placebo-controlled, multicenter study on the use of colchicine for the primary prevention of the postpericardiotomy syndrome, postoperative effusions, and postoperative atrial fibrillation. *Am Heart J*. 2013;166(1):13–19.
43. Deftereos S, G Giannopoulos, C Kossyvakis, et al. Colchicine for Prevention of Early Atrial Fibrillation Recurrence After Pulmonary Vein Isolation: A Randomized Controlled Study. *J Am Coll Cardiol*. 2012;60(18):1790–1796.
44. Lee JZ, N Singh, CL Howe, et al. Colchicine for Prevention of Post-Operative Atrial Fibrillation: A Meta-Analysis. *JACC Clin Electrophysiol*. 2016;2(1):78–85.
45. Salih M, A Smer, R Charnigo, et al. Colchicine for prevention of post-cardiac procedure atrial fibrillation: Meta-analysis of randomized controlled trials. *Int J Cardiol*. 2017;243:258–262.
46. Lennerz C, M Barman, M Tantawy, et al. Colchicine for primary prevention of atrial fibrillation after open-heart surgery: Systematic review and meta-analysis. *Int J Cardiol*. 2017;249:127–137.