International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 04 Issue 07 July 2024

Page No: 1316-1322

DOI: https://doi.org/10.47191/ijmscrs/v4-i07-07, Impact Factor: 7.949

Use of Colchicine in the Reduction of Cardiovascular Atherosclerotic Events

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ABSTRACT

Introduction: Atherosclerosis begins when the injured artery wall creates chemical signals that cause certain types of leukocytes (monocytes and T cells) to adhere to the artery wall. These cells move towards the artery wall. There, they are transformed into foam cells that collect cholesterol and other fatty materials and trigger the growth of smooth muscle cells in the artery wall. Colchicine or colchicine is a highly poisonous alkaloid, originally extracted from the plant Colchicum autumnale. It has been used in the treatment of various diseases, but on an increasingly smaller scale due to its high toxicity.
Aim: The aim of this review is to provide a balanced, critical and comprehensive assessment of the evidence currently available regarding the use of colchicine in the context of atherosclerotic heart disease. Material and Methods: The research was carried out by means of an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences Descriptors (DeCS/BIREME) were used: r use of Colchicine in the reduction of atherosclerotic cardiovascular events.
Results and Discussion: Although there was variation between individual studies, meta-analyses also showed that colchicine reduced the risk of myocardial infarction, stroke or cardiovascular death by between 20 and 30%. The applicability of the results may vary according to subsets of patients. For example, the benefits of colchicine may be even greater in patients with diabetes mellitus. However, as most studies excluded patients with heart failure and chronic kidney disease, the effects of colchicine in these populations are still unknown.
Final considerations: if the use of colchicine in the treatment of ischemic heart disease is to be fully viable, a great effort must be made to personalize its use in terms of timing, duration of treatment and dose, reassessing the net clinical benefit of this strategy over time, taking into account the underlying severity of CV disease, the patient's comorbidities and the use of concomitant medications.

KEYWORDS: Colchicine, reduction of atherosclerotic cardiovascular events, heart failure.

ARTICLE DETAILS

Published On:
09 July 2024

Available on:
https://ijmscr.org/

INTRODUCTION

Atherosclerosis is a clinical condition in which irregular deposits of fatty material (atheromas or atherosclerotic plaques) develop on the walls of medium and large arteries, leading to reduced or blocked blood flow (ABREU et.al, 2020).

According to Alayli et.al (2023), cardiovascular disease, mainly coronary artery disease (atherosclerosis affecting the arteries supplying blood to the heart) and stroke (atherosclerosis affecting the arteries leading to the brain), caused almost 18 million deaths worldwide in 2023, making atherosclerosis the leading cause of death worldwide.

Atherosclerosis can affect the medium and large arteries of the brain, heart, kidneys, other vital organs and legs. It is the most important and common type of atherosclerosis (ARBEX et.al, 2010).

According to Bargiela (2013), the development of atherosclerosis is complicated, but the primary event seems to be related to subtle and repeated damage to the inner lining of the arteries (endothelium) through various mechanisms. These mechanisms include physical stresses resulting from turbulent blood flow (such as that which occurs where arteries branch off, especially in people who have hypertension), inflammatory stresses involving the immune system (such as when people smoke cigarettes), chemical abnormalities in the bloodstream (such as high cholesterol or high blood sugar levels as occurs in diabetes mellitus), infections by some bacteria or viruses (such as Helicobacter pylori or cytomegalovirus) can also increase inflammation in the inner lining of the artery (endothelium) and lead to atherosclerosis.

Atherosclerosis begins when the damaged artery wall creates chemical signals that cause certain types of leukocytes (monocytes and T-cells) to adhere to the artery wall. These cells move towards the artery wall. There, they are transformed into foam cells that collect cholesterol and other fatty materials and trigger the growth of smooth muscle cells in the artery wall (CARVALHO, 2015).

Over time, these fat-laden foam cells accumulate. They form irregular deposits (atheromas, also called plaques) with a fibrous covering on the lining of the artery wall. Over time, calcium builds up in the plaques. Plaques can spread to all medium and large arteries, but they usually start where the arteries branch off (CHAVES, 1995).

According to Da Rocha (2020), the wall of an artery is made up of several layers. The lining or inner layer (endothelium) is usually regular and uninterrupted.

Atherosclerosis begins when the lining is injured or develops some disease. Then, certain leukocytes called monocytes and T-cells are activated and leave the bloodstream, cross the lining of the artery and reach its wall. Inside the lining, they are transformed into foam cells, which are cells that collect fatty materials, mainly cholesterol.

According to De Almeida Braga (2023), over time, smooth muscle cells move from the intermediate layer to the lining of the artery wall and multiply in this region. Connective and elastic tissue materials also accumulate in the region, as can cell debris, cholesterol crystals and calcium. This accumulation of fat-laden cells, smooth muscle cells and other materials forms an irregular deposit called an atheroma or atherosclerotic plaque. As they grow, some plaques thicken the artery walls and invade the artery channel. These plaques can narrow or block an artery, slowing or stopping blood flow. Other plaques don't severely obstruct the artery, but can rupture, causing a blood clot to form and suddenly block the artery.

Plaques can grow inside the opening (lumen) of the artery, causing a gradual narrowing. When atherosclerosis narrows an artery, the tissues supplied by the artery may not receive enough blood and oxygen. Plaques can also grow on the artery wall, where they do not block the flow of blood (CUPERTINO et.al, 2024).

According to Ertürk (2023), both types of plaque can rupture, exposing material in the bloodstream. This material triggers the formation of blood clots. These blood clots can suddenly block all blood flow through an artery, which is the main cause of a heart attack or stroke.

Sometimes these blood clots break off, travel through the bloodstream and block an artery in other parts of the body. Similarly, pieces of plaque can detach, travel through the bloodstream and block an artery elsewhere.

When atherosclerosis becomes severe enough to cause complications, the complications themselves must be treated, and the use of Colchicine may be indicated.

Colchicine or colchicine is a highly poisonous alkaloid, originally extracted from the plant Colchicum autumnale. It has been used in the treatment of various ailments, but on an increasingly smaller scale due to its high toxicity (ERTÜRK, 2023).

The main aim of this review is to provide a balanced, critical and comprehensive assessment of the evidence currently available regarding the use of colchicine in the context of atherosclerotic heart disease.

MATERIAL AND METHODS

The methodology used was a literature review. A literature review is a meticulous and comprehensive analysis of current publications in a particular area of knowledge. This type of research aims to put the investigator in direct contact with the existing literature on a subject.

The research was carried out by means of an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences Descriptors (DeCS/BIREME) were used: r use of Colchicine in the reduction of atherosclerotic cardiovascular events.

The inclusion criteria were: original article, published in Portuguese and English, freely accessible, in full, on the subject, in electronic format and published in recent years, totaling 22 articles.

RESULTS AND DISCUSSION

Indications for Colchicine

According to Ferreira et.al (2018), Colchicine is intended for the treatment of acute gout flares and the prevention of acute flares in patients with chronic gouty arthritis.

Colchicotherapy may be indicated in Familial Mediterranean Fever and in cases of scleroderma, polyarthritis associated with sarcoidosis and psoriasis (FIGUEIREDO, 2021).

Colchicine is effective in the clinical treatment of Peyronie's disease in cases with a duration of less than a year, acting to reduce the inflammatory process that leads to the fibrous plaque. Its use is not well established in cases with a long evolution time, when the fibrosis plaque is already fully formed (FIGUEIREDO, 2021).

For Massonet.al (2021), it is contraindicated in patients with hypersensitivity to Colchicine and in patients with severe gastrointestinal, liver, kidney or heart disease or during pregnancy.

According to Ferreira et.al (2018), Colchicine should be administered at the first sign of an acute gout attack. The dose should be reduced if muscle weakness, nausea, vomiting or diarrhea occur.

Colchicine is widely used in the treatment of Peyronie's disease. Peyronie's disease is caused by repeated penile injury, usually during sexual intercourse or physical activity. Penises vary in shape and size, and having a curved erection is not necessarily a cause for concern. In Peyronie's disease, the curvature is significant and can be accompanied by pain or interfere with sexual function (MANCUSO et.al, 2011).

Adverse Reactions

Colchicine's adverse events are presented below in descending order of frequency, although some are not well defined. Very common (>10%) Gastrointestinal, Diarrhea, vomiting, nausea, colic, Common (>1% and < 10%); Central nervous system Fatigue, headache; Endocrine and metabolic, Gout; Respiratory, Pharyngolaryngeal pain; Uncommon (>0.1% and <1%) Alopecia, spinal cord depression, dermatitis, disseminated intravascular coagulation, hepatotoxicity, hypersensitivity reactions, increased creatine phosphokinase (CPK), lactose intolerance, myalgia, myasthenia, oligospermia (reversible with cessation of treatment), purpura, rhabdomyolysis, toxic neuromuscular disease, neutropenia, leukopenia, azoospermia (MANCUSO et. al, 2011).

Drug interaction: the effects of taking Colchicine with other drugs

According to Masson et.al (2021), rapidly cytolytic neoplastic drugs, bumetamide, diazoxide, thiazide diuretics, furosemide, pyrazinamide or triamterene can increase the plasma concentration of uric acid and decrease the effectiveness of prophylactic gout treatment.

Colchicine can increase the depressant effects on the bone marrow of drugs that produce blood dyscrasias or of radiotherapy (MASSON et.al, 2021).

Figueiredo (2021) describes that simultaneous use with phenylbutazone can increase the risk of leukopenia or thrombocytopenia, as well as gastrointestinal ulcers. Colchicine should be used with caution in patients using P-gp inhibitor drugs (ciclosporin, ranolazine) or moderate inhibitor drugs (amprenavir, fosamprenavir, diltiazem, erythromycin, fluconazole, verapamil) or strong inhibitors (atazanavir, clarithromycin, indinavir, nelfinavir, saquinavir, ritonavir, ketoconazole, itraconazole, naphazodone) of CYP3A4; significant increase in plasma

Colchicine plasma concentrations and fatal toxicity have been reported (ERTÜRK, 2023).

The dose of Colchicine should be adjusted when it is used concomitantly with protease inhibitors. Colchicine may increase the risk of rhabdomyolysis from HMG-CoA reductase enzyme inhibitors (statins) and fibric acid derivatives (fibrates). Vitamin B12 absorption may be altered by Colchicine and additional doses of this vitamin may be necessary (DEFTEREOS et.al, 2013).

According to Ertürk (2023), Colchicine interferes with urinary determinations of 17-hydroxycorticosteroids measured by the Reddy, Jenkins and Thorn method and can cause false-positive results in urine tests for erythrocytes and hemoglobin.

According to De Oliveira Santos (2021), the use of Colchicine should be given special attention, especially in attack treatment. Care should be taken in cases of renal or hepatobiliary insufficiency and a complete blood count should be carried out periodically to detect bone marrow depression. It should be used with drugs that reduce intestinal transit or with antidiarrheals if diarrhea or progressive colopathy occurs.

As a precaution, patients' possible adverse reactions should be assessed (DEFTEREOS et.al, 2013).

Pregnancy

Colchicine interrupts cell division in animals and plants and there have been reports of decreased spermatogenesis in humans. Colchicine crosses the placental barrier and may be teratogenic in humans, as observed in animal studies. Patients should be advised not to become pregnant during treatment and the doctor should assess the risk/benefit of using the drug (DE OLIVEIRA SANTOS,
2021).

The doctor should assess the risk/benefit of using Colchicine, as it is excreted in breast milk (DE OLIVEIRA SANTOS, 2021).

Geriatric use

According to Cupertino et.al (2024), elderly patients may be more sensitive to the cumulative toxicity of Colchicine and dose adjustments may be necessary.

Colchicine clearance may decrease in patients with hepatic insufficiency and in patients with renal insufficiency, who should be carefully monitored for adverse events. Dose adjustments may be considered depending on the degree of hepatic or renal impairment and may be affected by the concomitant use of drugs metabolized by CYP3A4 or P-gp inhibitor drugs (CARVALHO, 2015).

Alayli et.al (2005), cites that in patients with moderate renal insufficiency (estimated glomerular filtration rate of 30-59ml/min) Colchicine can be administered 1x/day at a dose of 0.5 to 0.6mg. In patients with severe renal insufficiency (estimated glomerular filtration rate of 15-29ml/min), Colchicine can be administered at a dose of 0.5-0.6mg every 2 or 3 days. Colchicine is contraindicated in patients with an estimated glomerular filtration rate < 15ml/min.

Action of the substance Colchicine

Arbex et.al (2010), a randomized, double-blind, multicentre, placebo-controlled study compared self-administration of Colchicine at a low dose (total of 1.8mg over 1 hour) and at a high dose (total of 4.8mg over 6 hours) with placebo, with the primary endpoint being a ≥ 50% reduction in pain over 24 hours without the use of rescue medication. In the intention-to-treat analysis, which included 184 patients, 28 out of 74 patients (37.8%) responded to the low dose, 17 out of 52 patients (32.7%) responded to the high dose and 9 out of 58 patients (15.5%) responded to placebo (P = 0.005 and P = 0.034, respectively, versus placebo). Rescue medication had to be used by 31.1%, 34.6% and 50% of patients in the low-dose Colchicine, high-dose Colchicine and placebo groups, respectively. The group of patients receiving low-dose Colchicine had an adverse event profile similar to the placebo group, while high-dose Colchicine was associated with a significantly higher frequency of diarrhea and vomiting.

Three double-blind, randomized, placebo-controlled, crossover studies established the efficacy of Colchicine in patients with Familial Mediterranean Fever; in 43 patients, the number of attacks of fever and serositis decreased from 178 with placebo to 29 with Colchicine. In addition, there was a significant reduction in the severity of the attacks (FERREIRA et.al, 2018).

Hijazi et.al (2017), studied 60 patients with Peyronie's disease during the acute phase (mean duration: 5.7 ± 4.3 months) who were treated with Colchicine. After a mean follow-up of 10.7 ± 4.7 months, penile deformity improved in 30%, remained unchanged in 48.3% and worsened in 21.7% of patients. Pain resolved in 95% of patients. The best results were obtained in patients without a risk factor for vascular disease, treated within the first 6 months of the disease, with a degree of penile curvature < 30 degrees, without erectile dysfunction in the anamnesis and with a positive response to the combination of injection and stimulation test.

A study carried out by Ahern et.al (2023), with 43 patients with acute gout crisis. All the patients had their diagnosis confirmed by aspiration of the synovial fluid and its evaluation by polarized light electron microscopy. The patients were randomized into 2 groups: Colchicine (n=22) or placebo (n=21). The initial dose of Colchicine was 1mg, followed by 0.5mg every 2 hours until complete response without toxicity. Non-hormonal anti-inflammatory drugs or analgesics were not allowed in the 48 hours before and during the study. Patients were assessed every 6 hours for 48 hours. Pain was assessed using the Visual Analog Scale. Of the patients treated with Colchicine, 2/3 of them showed improvement after 48 hours, but only 1/3 of the placebo group showed a similar response.

The Colchicine group responded earlier and significant differences in the placebo group occurred after 18-30 hours. All patients in the Colchicine group had diarrhea, which occurred before the pain improved in most patients, after an average time of 24 hours (with an average dose of 6.7mg). This study defined the natural history of acute gout and showed that although diarrhea occurred in most patients, Colchicine hastened their recovery.

Pharmacokinetics

Colchicine's binding to plasma proteins is low (~39%). Cmax is 2.2 nanograms per mL after oral administration of 2mg and Tmax is reached in 0.5 to 2 hours. Colchicine's metabolism is hepatic via the CYP3A4 pathway, it undergoes enterohepatic recirculation and has biliary and urinary excretion (40 to 65% as an unmodified drug). Renal excretion may be increased in patients with liver disease.

The elimination half-life ranges from 27 to 31 hours. Due to the high degree of tissue uptake, Colchicine elimination can continue for 10 days or more after discontinuation of the product (ABREU et.al, 2020).

The onset of action after the first oral dose is 12 hours. Relief of pain and inflammation in acute gouty arthritis occurs within 24 to 48 hours after the first oral dose. Relief of edema can occur in 72 hours or more. Drinking alcoholic beverages or alcoholic patients may have an increased risk of gastrointestinal toxicity from Colchicine. Alcohol increases plasma concentrations of uric acid, which can reduce the effectiveness of the drug's prophylactic treatment (ARBEX et.al, 2010).

Effects of using colchicine to improve myocardial alterations correlated with prevention and complications of acute myocardial infarction

Inflammation is the main pathophysiological process involved in the formation, progression, instability and healing of atherosclerotic plaques during the evolution of coronary artery disease (CAD). The use of colchicine, a drug used for decades in non-ischemic cardiovascular (CV) diseases and/or systemic inflammatory conditions, has stimulated new perspectives on its potential application in

CAD patients (TADIF et.al, 2019).

According to Nidorf et.al (2020), previous preclinical studies have revealed anti-inflammatory and immunomodulatory effects of colchicine exerted through its main mechanism of inhibition of microtubule polymerization, however, other beneficial pleiotropic effects on the CV system have been observed, such as inhibition of platelet aggregation and suppression of endothelial proliferation. In randomized which inform our clinical practice, low doses of colchicine were associated with a significant reduction in cardiovascular events in patients with stable CAD and chronic coronary syndrome (CCS), while in patients with recent acute coronary syndrome (ACS), early initiation of colchicine treatment significantly reduced major adverse CV events (MACE). On the other hand, the safety profile of colchicine and its potential causal relationship with the observed increase in non-CV deaths merits further investigation. For these reasons, the postulates of precision medicine and the personalized approach to the patient regarding the benefits and harms of colchicine treatment should always be employed due to the potential toxicity of colchicine, as well as the currently unresolved harm signal regarding non-CV mortality.

FIGURE 1 shows the actions of colchicine in the treatment of atherosclerotic diseases.

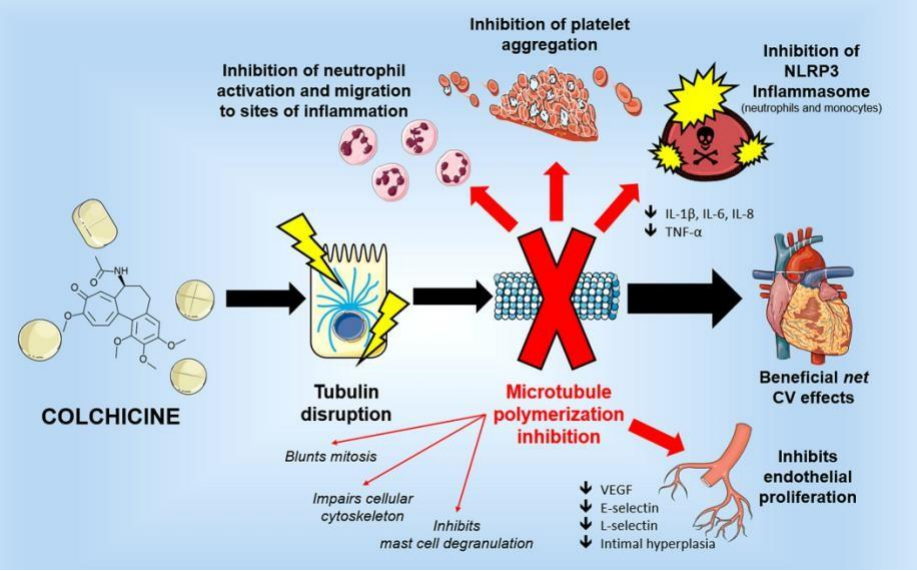

Figure 1. Colchicine's actions in the treatment of atherosclerotic diseases. Source: (DEFTEREOS et.al, 2013).

Currently, colchicine is widely used to treat acute outbreaks of gout and familial Mediterranean fever (FMF). It has also been used in other inflammatory conditions, such as pericarditis. Given its ease of access, low cost and favorable safety profile, colchicine has emerged as a potential oral treatment targeting the inflammatory component of atherosclerosis (OPSTAL et.al, 2021).

The Tardif et.al (2019) study, focused on Acute Coronary Syndrome (ACS), involved the randomization of 4,745 patients after acute myocardial infarction, and showed that colchicine significantly reduced the risk of adverse cardiovascular events by 23%, driven mainly by a decrease in the incidence of stroke and hospitalization for unstable angina.

In the Nidorf et.al (2020) study, there was a significant 40% reduction in a combination of adverse events after 24 months of colchicine treatment.

Another important study was by Massonet.al (2021), which focused on chronic coronary syndrome (CCS). It involved 532 patients and found that colchicine reduced the risk of the primary outcome by 67%. The subsequent study, which involved ten times as many patients and a more robust study design, confirmed these results by showing a 31% reduction in the primary endpoint.

Although there was variation between individual studies, meta-analyses have also shown that colchicine reduced the risk of myocardial infarction, stroke or cardiovascular death by between 20 and 30% (ABREU et.al, 2020).

The applicability of the results may vary according to subsets of patients. For example, the benefits of colchicine may be even greater in patients with diabetes mellitus. However, as most studies have excluded patients with heart failure and chronic kidney disease, the effects of colchicine in these populations are still unknown (ABREU et.al, 2020).

Despite the beneficial effects, there are concerns about the non-cardiovascular mortality associated with colchicine use. The COPS study indicated a higher rate of death from all causes in the colchicine group, due to an increase in non-cardiovascular deaths, especially infections and sepsis. Meta-analyses showed a non-significant lower incidence of cardiovascular mortality, offset by a non-significant higher incidence of non-cardiovascular deaths (FIGUEIREDO, 2021).

Prescription

As you can see from the summary of the studies, the dose used in the studies was 0.5mg 1x/day (SCC) or 0.5mg twice a day (SCA) (DE OLIVEIRA SANTOS, 2021).

With regard to prescription, colchicine can be considered in various contexts for patients with coronary artery disease. If, after optimizing clinical treatment, where traditional risk factors have been specifically addressed, and the patient still
residual inflammatory risk, colchicine can be considered (DE OLIVEIRA SANTOS, 2021).

Final considerations

Considering the growing body of evidence obtained from randomized clinical trial data, the use of colchicine has demonstrated an effective reduction in ischemic events in patients with acute and chronic coronary syndromes, providing a favorable cost/benefit ratio.

The disadvantages of its use are its narrow therapeutic index, potential long-term toxicity and notable drug interactions.

In addition, its net clinical benefit has yet to be unequivocally proven due to the signal of harm with regard to non-CV death.

These challenges will ultimately have to be tested in studies that take into account long-term efficacy and safety parameters.

For the use of colchicine in the treatment of ischemic heart disease to be fully viable, a great effort must be made to personalize its use in terms of timing, duration of treatment and dose, reassessing the net clinical benefit of this strategy over time, taking into account the underlying severity of CV disease, the patient's comorbidities and the use of concomitant medications.

Therefore, there is still no specific biomarker or combination of tools capable of predicting response to colchicine treatment, but it could add information not available in clinical evaluation and help in the decision-making process regarding the use of this drug in clinical practice

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