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ДВОЙНА АНТИАГРЕГАНТНА ТЕРАПИЯ С КОЛХИЦИН СЛЕД ПКИ ПРИ ОСТЪР КОРОНАРЕН СИНДРОМ. ЛИТЕРАТУРЕН ОБЗОР

С. Ямболов, Р. Григоров

Първа катедра по вътрешни болести, Медицински университет – Варна
Втора клиника по кардиология – инвазивна, УМБАЛ „Св. Марина“ – Варна

DUAL ANTI-PLATELET THERAPY WITH COLCHICINE AFTER PCI FOR ACUTE CORONARY SYNDROME: A LITERATURE REVIEW

S. Yambolov, R. Grigorov

First Department of Internal Diseases, Medical university – Varna
Second Cardiology Clinic – Interventional, UMHAT “Sveta Marina” – Varna

Резюме. Колхицинът, един от най-старите медикаменти, който все още се използва, е сравнително евтин и добре поносим препарат с доказана роля при редица възпалителни заболявания като подагра, болест на Бехчет и перикардит. През последните години различни клинични изпитвания проучват и тестват колхицин в лечението на сърдечно-съдовите заболявания и демонстрират положителни резултати. **Целта** на този литературен обзор е да оцени потенциалното приложение на колхицин на мястото на аспирин в двойната антиагрегантна терапия след перкутанна коронарна интервенция при пациенти с остър коронарен синдром.

Ключови думи: колхицин, аспирин, перкутанна коронарна интервенция, остър коронарен синдром

Адрес за кореспонденция: Д-р Стефан Ямболов, Втора клиника по кардиология, УМБАЛ „Св. Марина“, Варна, бул. “Христо Смирненски” 1, 9010, e-mail: stefan.yambolov@gmail.com

Abstract. Colchicine, one of the oldest medications still in use, is a relatively inexpensive and well-tolerated agent with a documented role in a range of inflammatory diseases, such as gout, Behchet’s disease and pericarditis. In recent years, different clinical trials also tested colchicine in the management of cardiovascular conditions and demonstrated favorable results. **The aim** of this literature review is to evaluate the prospective use of colchicine instead of aspirin as double-antiplatelet therapy (DAPT) after percutaneous coronary interventions in patients with acute coronary syndrome.

Key words: colchicine, aspirin, percutaneous coronary intervention, acute coronary syndrome

Address for correspondence: Stefan Yambolov, MD, Second Cardiology Clinic; UMHAT “Sveta Marina”, 1 "Hristo Smirnenski" Bvld., BG – 9010 Varna, e-mail: stefan.yambolov@gmail.com

Introduction

Acute Coronary Syndrome (ACS) remains a leading cause of morbidity and mortality, despite significant improvements in therapy and life expectancy in recent decades [1, 2, 3]. ACS is an umbrella term for conditions featuring recent changes in clinical symptoms or signs, with or without changes on 12-lead electrocardiogram and presence or absence of acute elevations in cardiac troponin concentrations [4]. Patients presenting with suspected ACS may eventually receive a diagnosis of acute myocardial infarction or unstable angina. The diagnosis of myocardial infarction (MI) is associated with cTn release and is made based on the fourth universal definition of MI. Therapeutic strategies in these patients include antithrombotic, antianginal, and cholesterol-lowering agents, but the cornerstone of treating high-risk patients with ACS is revascularization of the culprit lesion revascularization [2] and control of modifiable risk factors. However, even with optimal control of modifiable risk factors and the use of tailored pharmacological therapy, many patients will experience recurrent ischemic events [3].

One of the main contributing factors to cardiovascular disorders is inflammation. Increasing evidence implicates inflammation as the essential process for the pathogenesis of atherosclerotic plaque and its changing dynamics [5]. Processes such as atherosclerotic plaque formation, progression, destabilization, and rupture are influenced by active proinflammatory cytokines interleukin (IL)-1β and IL-18, both are generated in active forms by inflammasomes, which are cytosolic multiprotein oligomers of the immune system responsible for the activation of inflammatory responses [6]. In the coronary arteries, the inflammation is not limited to the main culprit lesion and consistent inflammatory cell activation may occur remotely, which may contribute to recurrent plaque rupture and cardiovascular events, even if the patient receives optimal medical therapy [7].

Statins are the most widely utilized drugs for treating lipid disorders [8] and they possess anti-inflammatory properties in addition to their lipid-lowering effects [5]. Statins are currently regarded as an essential part of the optimal medical therapy for the management of patients with ACS [7, 9] and they have a direct positive effect on cell types and pathways that are both lipid-independent and mediated by lipid modification [9]. Their suppression of inflammatory response contributes to their generally positive action in atherosclerosis, representing an important part of the vascular and atheroprotective effect of this drug class [9].

Other agents tested in recent trials include corticosteroids, which have demonstrated a 26% decrease in mortality but also a risk of cardiac rupture secondary to impaired wall healing [10], and nonsteroidal anti-inflammatory drugs (NSAID), which showed an increased risk of cardiovascular events, particularly at high doses or in patients with previous ischemic heart disease [11].

Antiplatelet agents significantly improve the outcomes of patients with ACS. Dual antiplatelet therapy (DAPT) is the standard of care after percutaneous coronary intervention (PCI) with drug-eluting stents because of its efficacy in preventing stent thrombosis [13]. DAPT includes Aspirin, an NSAID, in combination with a $P2Y_{12}$ antagonist. In addition to their antithrombotic efficacy, they may also exert powerful anti-inflammatory effects [12]. However, the improved antithrombotic efficacy comes at the expense of increased bleeding risk, a feared complication associated with significant morbidity and mortality, which should prompt the reevaluation of the antiplatelet strategy for those patients [14].

Currently, no recommendations exist regarding aspirin-free therapeutic strategies in patients with ACS [15] but the results of recent clinical trials can help guide future therapeutic choices for these patients. The TWILIGHT-HBR study revealed that aspirin discontinuation after three months of DAPT followed by ticagrelor monotherapy significantly reduced bleeding without increasing ischemic events [16], while the ASET trial showed no stent thrombosis in selected low-risk patients who received prasugrel monotherapy following successful everolimus-eluting stent implantation [17]. Three additional clinical trials (STOPDAPT-3, NEOMINDSET, and OPTICA) that are still ongoing are also exploring novel strategies of monotherapy to provide antithrombotic protection for patients with ACS.

Non-statin lipid-lowering agents like monoclonal antibodies (mAbs) added to statin treatment have also been the focus of studies in ACS [18]. While mAbs like inclacumab and pexelizumab were tested without differences in mortality and morbidity [19], another gained significant attention in recent years. Canakinumab is a human anti-IL-1β monoclonal antibody with a mode of action based on the neutralization of 1β signaling [20]. This agent showed a significantly lower incidence of recurrent cardiovascular events in patients with previous myocardial infarction and C-reactive protein (CRP) levels ≥ 2 mg/L [21]. Nevertheless, canakinumab is not cost-effective [5] and it may cause an increased risk of fatal infections [21].

Colchicine, on the other hand, is an inexpensive and tolerable anti-inflammatory agent used for decades to prevent acute inflammatory flares in familial Mediterranean fever and gout5. Using a mechanism similar to canakinumab, colchicine attenuates NLRP3 inflammasome activation [22] and experimental evidence suggests that colchicine also inhibits phagocytosis, neutrophil recruitment, and function [23]. Recent studies have yielded promising results on the role of colchicine in the management of ACS: three clinical trials (COLCOT, COPS, and LoDoCo) have shown reductions in ischemic cardiovascular events in patients with ACS receiving colchicine 0.5 mg/d (0.5 mg twice a day in COPS) [24, 25, 26] and two additional trials (CLEAR SINERGY [OASIS 9] and COLCARDIO-ACS) currently underway might also demonstrate a benefit for colchicine in the treatment of this high-risk group of patients.

In this article, we will review the existing literature on the possible role of colchicine as a replacement for aspirin in DAPT after PCI for acute coronary syndrome and its prospects for the treatment of these patients.

Methods

A MEDLINE search was conducted to identify relevant clinical trials from 2014 to 2023 using the following keywords: “colchicine”, “acute coronary syndrome” and “percutaneous coronary intervention”. An additional search on ClinicalTrials.gov was also conducted using the following keywords: “condition/disease: acute coronary syndromes”, “other terms: percutaneous coronary

intervention" and "intervention/treatment: colchicine" including only completed trials. A supplementary MEDLINE search was conducted with the same keywords but including the following types of studies: "meta-analysis", "review" and "systematic review" to identify additional trials from different sources.

Table 1. Results of the MEDLINE and ClinicalTrials.gov databases search

Authors	Title	Participants	Criteria	Results
Lee et al. (2023) [27]	$P2Y_{12}$ Inhibitor Monotherapy Combined with Colchicine Following PCI in ACS Patients: The MACT Pilot Study	200 patients received low-dose colchicine (0.6 mg daily) plus ticagrelor or prasugrel as maintenance therapy. Aspirin was discontinued. Three-month follow-up.	**Inclusion:** Patients with non–ST-segment elevation ACS or ST-segment elevation MI who underwent PCI with drug-eluting stents **Exclusion:** Anticoagulation therapy Cardiogenic Shock Prior intracranial hemorrhage Participation in another study	In ACS patients undergoing PCI, it is feasible to discontinue aspirin therapy and administer low-dose colchicine the day after PCI in addition to ticagrelor or prasugrel.
Shah et al. (2020) [28]	Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: COLCHICINE-PCI Randomized Trial	400 patients underwent PCI: 206 received 1.8 mg of colchicine. 194 patients received a matching placebo at the same time points	**Inclusion:** Adults > 18 years with suspected ischemic heart disease or ACS. **Exclusion:** Use of oral steroids or NSAID other than aspirin within the longer of 72 hours or 3 x the agent's half-life High-intensity statin treatment started within 24 hours of the procedure	Colchicine did not lower the risk of PCI-related myocardial injury, PCI-related MI, or MACE at 30 days but did significantly attenuate the increase in IL-6 and hs-CRP concentrations 22-24 hrs post-PCI.
Shah et al. (2023) [29]	Major Adverse Cardiovascular Events After Colchicine Administration Before Percutaneous Coronary Intervention: Follow-Up of the Colchicine-PCI Trial			On a mean follow-up of 3.3 years, the incidence of major adverse cardiovascular events did not differ between colchicine and placebo groups.
Cole et al. (2021) [30]	Colchicine to Prevent Periprocedural Myocardial Injury in Percutaneous Coronary Intervention: The COPE-PCI Pilot Trial	36 colchicine (1 mg followed by 0.5 mg one hour later) and 39 placebo Patients were all taking DAPT before PCI.	**Inclusion:** De-novo lesion amenable to PCI, and hs-Troponin-I and CK (creatinine kinase) peaked and stabilized. **Exclusion:** Active inflammation/infection Use of anti-inflammatory medications	Colchicine given 6 to 24 hours pre-PCI reduces periprocedural myocardial injury. Colchicine was more protective in patients with NSTEMI vs. patients with SA, although caution should be exercised due to the small sample size No adverse effects from colchicine.

Results and Discussion

Overall, the MEDLINE search of clinical trials produced 4 results (see Table 1). From them, one trial administered colchicine in combination with a $P2Y_{12}$ inhibitor, the remaining three studies used colchicine versus placebo in different schemes. A complementary MEDLINE search for meta-analyses, reviews, and systematic reviews produced only studies with perioperative use of colchicine and placebo in PCI; many of them were focused on evaluating the efficacy and safety profile of colchicine in ACS patients. As for the ClinicalTrials.Gov search, only two completed studies were retrieved and both also appeared in the MEDLINE results.

The study conducted by Lee et al. (2023) [27] showed that, after 3 months, only 1 patient showed high platelet reactivity and 1% of the patients had stent thrombosis. Additionally, 1 month later hs-CRP and platelet reactivity had both diminished, pointing to reduced inflammation. Unsurprisingly, the results confirm the safety of aspirin-free therapy with low-dose colchicine the day after PCI in combination with ticagrelor or prasugrel $P2Y_{12}$ inhibitors.

The study by Shah et al. (2020) [28] was the first to evaluate the administration of colchicine versus placebo in patients undergoing PCI and the effects on markers of inflammation and myocardial injury. While colchicine did not reduce PCI-related complications or MACE at 30 days compared to placebo, it exerted significant anti-inflammatory properties, that is, decrease of neutrophil-platelet aggregates, increase in IL-6, and decrease of hsCRP concentration. Nonetheless, the lack of reduction of PCI-related myocardial injury may be attributed to the short time of administration of colchicine as adequate dose regimens are yet to be established. That is also the primary limitation of the study.

On follow up in 2023, Shah et al. [29] concluded that the incidence of major adverse cardiovascular events between colchicine and placebo groups was the same.

In 2021 Cole et al. [30] found that pre-procedural colchicine significantly reduces both major and minor periprocedural myocardial injury, which could be related to direct trauma through balloon and stent injury or distal embolization. This effect seemed more prominent in patients with NSTEMI (non-ST-elevation myocardial infarction) compared to those with stable angina. Colchicine inhibits the NLRP3 iflammasome, which is one of the cornerstones of the upregulation of inflammatory activity in patients with ACS. The limitation of this study was its small sample size.

These results are timely, given the recent approval of LoDoCo (colchicine 0.5 mg) in the United States as the first anti-inflammatory drug to reduce the risk of stroke, myocardial infarction, coronary revascularization and cardiovascular death in adults with established atherosclerotic disease or multiple cardiovascular risk factors [31]. Given the risk of significant bleeding associated with aspirin, especially when used for prolonged time, the use of colchicine could potentially change the treatment of inflammation as a driver of atherosclerosis, as no specific agent targeting inflammation in cardiovascular diseases had been known before [32]. Interestingly, although their study evaluated colchicine vs. placebo, not as part of DAPT, the findings of the Colchicine PCI trial follow-up by Shah et al. (2023) [29] revealed no differences between colchicine and placebo groups on the incidence of major adverse cardiovascular events after 3.3 years of follow-up.

Conclusion

The current scarcity of clinical trials of colchicine as part of an aspirin-free DAPT post-PCI in ACS patients confirmed in this review should prompt the design of larger randomized clinical trials to evaluate the long-term results of the colchicine DAPT and to extend the clinical application of these findings. One such application would be to provide a non inferior DAPT with colchicine who have a significantly increased bleeding risk, have had a major bleeding event or are allergic to aspirin.

No conflict of interest was declared

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