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Colchicine and COVID-19: A Look Backward and a Look Ahead

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ABSTRACT

Colchicine, a tricyclic alkaloid derived from *Colchicum autumnale*, is well known for its anti-inflammatory properties, and has been used to treat conditions such as gout, familial Mediterranean fever, and pericarditis. Colchicine's inhibition of the NLRP-3 inflammasome and reduction of key pro-inflammatory cytokines has been considered potentially beneficial in managing COVID-19. While early anecdotal reports and small-scale studies suggest potential benefits, including reduced hospital stay and oxygen requirements, larger randomized controlled trials (RCT) have largely failed to demonstrate significant improvement in mortality, the need for mechanical ventilation, or ICU admissions. Meta-analyses of RCT data corroborate these findings, showing no substantial benefit of colchicine in treating COVID-19. In non-hospitalized patients, the data also suggests limited efficacy, with some studies indicating potential benefit in specific subgroups, though these findings have not been consistently replicated. Colchicine for the treatment of cardiac injury in individuals infected with COVID-19 has also been an area of interest; despite early work suggesting benefit, subsequent RCTs have not shown clear benefit in this subgroup of patients. Overall, despite its promising mechanism of action, the evidence does not support the use of colchicine as standard treatment for COVID-19, either in hospitalized or community-based settings, or with evidence of cardiac injury. This review highlights the need for further research to better understand the potential role of colchicine – looking back as well as a look ahead – in the management of COVID-19.

Background

Among the repurposed medications used for the treatment of COVID-19, colchicine emerged as a promising agent based on its low cost, oral administration, mechanism of action, and prior track record as an effective treatment for numerous inflammatory and cardiac conditions.[1-4] While the use of colchicine for COVID-19 treatment was a logical extension of its previous application, other researchers hypothesized its potential efficacy in mitigating COVID-medicated cardiovascular complications. This hypothesis was largely based on extensive literature demonstrating colchicine's clinical benefit in treating pericarditis, and post-myocardial infarction. In this report, we aim to provide a comprehensive exploration of the use of colchicine in the treatment of COVID-19, examining its potential benefits and limitations in multiple settings, including in hospitalized patients, in the outpatient setting, and in patients with cardiac injury.[5] We also review efforts to enhance the efficacy of colchicine by combining it with other commonly available oral agents. By outlining the mechanism of action of colchicine, we highlight why it has garnered such attention as a potential therapeutic target against COVID-19. Furthermore, understanding the inflammatory cascade that drives the COVID-19 pathobiology allows us to recognize why colchicine, with its unique anti-inflammatory properties, is such an appealing therapeutic option. Finally, we explore potential explanations for why colchicine may not have been effective in COVID-19 and review emerging data that suggest possible directions for future research.

Inhibition of the Inflammatory Cascade

Several mechanisms have been proposed to explain colchicine's effectiveness. During a COVID-19-triggered inflammatory response, various components of the innate immune system, such as interleukins (IL-1, IL-6, IL-8, IL-10), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ), become activated.[6] Among these, IL-6 is particularly critical in inducing the production of C-reactive protein (CRP), an early biomarker of the cytokine storm associated with severe COVID-19 complications and mortality.[7] The cytokine storm that ensues is a major contributor to the severe complications and increased mortality seen in COVID-19.[8] This hyperinflammatory response occurs when the body's immune system becomes excessively activated, leading to the uncontrolled release of pro-inflammatory cytokines. Their overproduction triggers widespread inflammation that leads to severely damaged tissues and organs. Elevated levels of IL-6 and CRP are strongly associated with poorer clinical outcomes. Furthermore, SARS-CoV-2 preferentially activates the NLRP3 (NOD-like receptor (NLR) subfamily pyrin domain containing inflammasome, with increased expression of NLRP3 in lung tissue linked to fatal outcomes.[9-10] The activation of the inflammasome occurs via the viral protein ORF3a, by increasing the levels of caspase-1 and pro-IL-1B.[11] Targeting these inflammatory pathways have been thought to be crucial in mitigating the damage during active infection.

Anti-Inflammatory Mechanism

By disrupting microtubule filaments, colchicine also inhibits key inflammatory pathways (including the NLRP3 inflammasome) leading to reduced cytokine release and neutrophil activity.[12-13] By binding A/B tubulin and inhibiting microtubule extension, colchicine limits the movement of adhesion molecules on the cell surfaces.[14] This effect reduces the expression of L- and E-selectins, which are critical for neutrophil rolling and adhesion on endothelium.[15] Microtubule breakdown also hampers neutrophil movement through blood vessels and negatively affects neutrophil signaling and phagocytic response. The mechanism for colchicine's benefit in severely ill patients likely is related to its inhibitory effects on the inflammasome, which then attenuates the cytokine storm that can lead to its most morbid consequences.

Viral Replication

Colchicine disrupts the microtubular network, which may inhibit the entry of SARS-CoV-2 into the cells or the assembly of new viral particles. The inhibition

of microtubule polymerization which is crucial for the life cycle of infecting viruses, interferes with the viral life cell cycle by affecting viral components and replication machinery within the cell.[16] Similar disruptions have been observed in other viral infections, such as dengue, Zika, RSV, and mouse hepatitis, where inhibition of microtubule polymerization can interfere with viral replication.[17-19] Additionally, microtubules play a significant role in the formation of double-membrane vesicles in infected cells, facilitate interactions between the spike protein and cytoskeletal proteins, and are involved in the transport of the spike protein within the virus.[20] Colchicine targets key viral enzymes, including RNA-dependent RNA polymerase (RdRp) and the main protease (Mpro), making it a promising candidate for antiviral therapy against COVID-19.[21]

Hospitalized Patients

Given its mechanism of action targeting the inflammasome and viral replication, coupled with a relatively low incidence of serious side effects, colchicine generated significant enthusiasm for use in hospitalized patients. Early studies showed promising results; Lopes et al found in a prospective randomized study of 72 moderate-to-severely ill COVID-19 patients that administration of colchicine reduced length of hospital stay (median 7 days versus 9 days, p = 0.003) and length of supplemental oxygen requirement (9% versus 42% at day 7 (p = 0.001).[22] Brunetti et al also report decreased length of hospital stay in a propensity-matched cohort study and more likely to be discharged (OR = 5.0; 95% CI 1.25-20.1; p = 0.023).[23] Furthermore, other studies reported clinical improvements when colchicine is used in combination with other medications. For instance, Gaitan et al observed a reduction in mortality and the need for mechanical ventilation in a randomized trial of 633 COVID-19 patients treated with a combination of colchicine, rosuvastatin, and emtricitabine/tenofovir (10.7% versus 17.4%; HR = 0.53; CI = 0.29-0.96).[24] Similarly, Sunil Naik et al found the combination of colchicine and aspirin was effective in reducing inflammatory markers and improving lung findings on computed tomography (mean reduction in CT severity score 3.65 in control group versus 4.82 in treatment group, p = 0.018).[25] Subsequently, however, larger randomized controlled trials such as the RECOVERY trial, which randomized 11,162 hospitalized patients to colchicine vs. standard of care, did not show a difference in the primary endpoint of 28-day mortality (risk ratio = 1.02, 95% CI: 0.94-1.11, p = 0.63).[26]

Several large meta-analyses initially suggested that colchicine may offer benefits in mortality and other clinical outcomes. A 2023 pooled meta-analysis by Danjuma et al, which included over 199,000 COVID-19 patients, found that colchicine use was associated with a 35% reduction in mortality compared to standard care alone (OR = 0.68; CI = 0.58-0.78; p < 0.01, I2=94%).[27] Similarly, a 2021 meta-analysis and systematic review by Nawangsih et al of over 5,500 hospitalized COVID-19 patients reported a lower mortality in patients treated with colchicine (OR = 0.47; CI = 0.31-0.72, p < 0.01, I2 = 30.9).[28] Additional meta-analyses of cohort and observational studies by Hariyanto et al (2021), Salah et al (2021), and Singh et al (2022) also suggested a mortality benefit, with odds ratios of 0.43, 0.62, and 0.35, respectively.[29-31] However, these studies have limitations, particularly the lack of stratification for randomized controlled trial (RCT) data. Notably, several meta-analyses that initially suggested a mortality benefit from colchicine in COVID-19 patients found that this benefit disappeared when only RCT data were analyzed separately.[32-34]

Outpatient Trials

The evidence supporting colchicine use in non-hospitalized COVID-19 patients is comparable to that observed in hospitalized patients. Anecdotal case series, such as the study by Della-Torre et al, have suggested potential benefits. In this study, nine symptomatic COVID-19 patients in the community experienced symptomatic improvement after receiving colchicine. Interestingly, this early study used higher doses of colchicine, up to 1 mg daily.[35] Some studies, such as a meta-analysis by Elshiwy et al that included over 16,000 patients from both

cohort and clinical trial data, suggest that colchicine may offer clinical benefits for outpatients, including a reduced need for oxygen therapy (RR 0.35; CI = 0.15-0.79, P < 0.01). However, the study reported no significant difference in mortality or need for mechanical ventilation.[36] The COLCORONA trial, a phase 3 randomized controlled trial that enrolled over 4,000 patients with both suspected and PCR-confirmed COVID-19, overall demonstrated no significant benefit in reducing hospitalization or mortality (OR=0.79; CI= 0.61-1.03, p = 0.08). However, in the subgroup of PCR-positive patients, the colchicine group showed a significant reduction in the composite outcome of death or hospital admission compared to placebo, suggesting potential benefit in specific patient subgroups (OR = 0.75; CI = 0.57-0.99, p = 0.042).[37] These findings have not been consistently replicated in other large-scale studies. For instance, the ACT outpatient trial, which involved nearly 4,000 patients with PCR-confirmed COVID-19, found no difference in hospitalization rates or mortality between patients treated with colchicine and those receiving standard care (HR = 1.02; CI = 0.72-1.43, p = 0.93).[38-39] Similarly, the PRINCIPLE trial, which enrolled over 2,000 community patients with COVID-19 (although only 150 patients received colchicine), indicated that colchicine did not reduce healthcare utilization or time to recovery.[40] Additionally, several smaller randomized trials have also reported no benefits in terms of mortality or oxygen usage.[41-42]

Colchicine in Patient with Cardiac Injury

Our group conducted one of the first studies on colchicine use in patients presenting with cardiac injury.[43] Early studies indicated that cardiac injury in the context of COVID-19 was prevalent, occurring in 16.1-62.3% of cases.[44-51] These studies also demonstrated that patients with COVID-19 who presented with elevated biomarkers and underlying cardiovascular disease experienced up to a 30% increase in mortality.[52-53] The GRECCO-19 trial, an open-label randomized controlled study, compared colchicine to standard care. Although the primary biochemical endpoint, high-sensitivity troponin concentration, showed no significant difference between groups, there was a notable improvement in the clinical endpoint of event-free survival time: 18.6 days in the control group versus 20.7 days in the colchicine group (log-rank P = 0.03).[54] Building on these data, our COLHEART-19 trial—a multi-center, open-label randomized controlled trial—investigated the use of colchicine in hospitalized COVID-19 patients with cardiac injury, which was defined as elevated troponin levels, newly elevated B-type natriuretic peptide, new arrhythmogenic or ischemic changes on ECG, new pericardial effusion on echocardiography, or newly reduced left ventricular ejection fraction. In our 93-patient trial, we did not observe a significant difference in the composite endpoint of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support at 90 days.[55] Although limited studies have explored colchicine in patients with cardiac injury, the existing data align with findings from other large RCTs, which similarly found no benefit of colchicine in this patient population.

Rethinking Colchicine's Role in COVID-19 Treatment

The negative results from large RCTs, such as the RECOVERY and COLCORONA trials, have tempered enthusiasm for colchicine as a therapeutic option in COVID-19, despite earlier promising findings from observational studies and smaller randomized trials. Nonetheless, interest in this widely available oral agent persists due to its theoretical mechanism of action, including inhibition of the NLRP3 inflammasome, reduction of cytokine release, and disruption of viral replication machinery. Several explanations may account for the conflicting results observed across studies.

Metabolic syndrome, characterized by obesity, dyslipidemia, hyperglycemia, and hypertension, leads to a chronic inflammatory state known as "metaflammation".[56] The activation of the NLRP3

inflammasome plays a pivotal role in metaflammation, which is closely linked to the progression of diseases and subsequent organ dysfunction. This process exacerbates adverse cardiovascular, renal and hepatic outcomes.[57-58] Obesity, a significant risk factor for severe COVID-19, has been associated with heightened NLRP3 inflammasome activity.[59-62] Consequently, it is hypothesized that colchicine may be particularly effective in treating COVID-19, and possibly other viral infections, in patients with obesity and diabetes who exhibit elevated levels of metaflammation.[63]

Supporting this hypothesis, Schattner et al observed a trend towards benefit from colchicine in diabetic patients in the COLCORONA trial (OR = 0.37, CI = 0.37–1.01).[64] Mondesheki et al also presented a case series presenting three high-risk morbidly obese patients with severe COVID-19, of which two did not require hospitalization with high doses of colchicine.[65] Future randomized trials aimed at improving outcomes in COVID-19 or other viral illnesses might benefit from targeting obese or diabetic patient populations with higher metaflammation and NLRP3 activation, as outlined above.

Early trials established the safety profile of colchicine, but concerns arose with escalating doses due to a potential worsening safety profile. However, by 2020, emerging evidence suggested that underdosing of colchicine might contribute to its perceived lack of efficacy in COVID-19 patients. Initial case reports demonstrated a fivefold reduction in mortality with colchicine doses up to 4.5 mg per day in a small cohort.[66] Tiholov et al later published a case-control study comparing increased doses of colchicine combined with bromhexine to standard of care (SOC) alone. In this study, colchicine dosing included either a 2- or 4-mg loading dose, resulting in an overall reduction in mortality (5.7% vs. 19.53%), with more significant improvement observed with the 4-mg loading dose.[67] Although these findings are compelling, they are derived from non-randomized or observational studies. Nevertheless, it is reasonable to consider that different pathologic conditions may require varying doses of colchicine. Typically, higher doses of colchicine are not required to achieve its cardioprotective effects, such as inhibition of platelet aggregation, or the pro-thrombotic activation of oxidized LDL and leukocyte-platelet aggregation, which contribute to conditions such as pericarditis and post-cardiotomy syndromes.[68-70] As previously discussed, higher doses of colchicine may be necessary to effectively inhibit the NLRP3 inflammasome in leukocytes, which plays a critical role in triggering the cytokine storm observed in COVID-19.[71-72] Further research is warranted to assess the therapeutic range of colchicine that could provide clinical benefit in patients with specific comorbidities infected with SRS-CoV-2 virus.

Conclusion

Despite its promising anti-inflammatory and antiviral mechanisms, colchicine has not demonstrated significant clinical benefits in the treatment of COVID-19 in large-scale randomized controlled trials. While early studies and smaller trials indicated potential efficacy, particularly in reducing inflammatory makers and improving clinical outcomes, subsequent rigorous trials have not supported these findings across broader populations, including those with cardiac injury. The disparity between early promise and later results suggests that while colchicine may hold potential for specific subgroups – such as those with metabolic syndrome or obesity – its role as a standard treatment for COVID-19 remains unproven. Looking ahead, future research should focus on refining patient selection and dosing strategies to understand where, if at all, colchicine may provide therapeutic benefit in managing COVID-19.

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None

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