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EFFICACY OF COLCHICINE IN IMPROVING CLINICAL OUTCOMES IN PATIENTS WITH MILD TO MODERATE COVID-19 PNEUMONIA IN LAHORE: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Objective: *The purpose of this study was to assess the clinical outcomes of colchicine therapy in COVID-19 patients with mild to moderate pneumonia as compared to placebo.*

Study Design: *A Randomized Controlled Trial*

Place & Duration of Study: *Department of Medicine, Lahore General Hospital, Lahore, for six months*

Methods: *Initially, 66 adult patients (18–60 years old) who had mild to moderate COVID-19 pneumonia confirmed by PCR were selected by a simple random sampling method. The selected patients were divided into two equal groups: colchicine and control. The patients in the colchicine group received 0.5 mg of colchicine daily for 7 days in addition to standard care, while the control group received standard care only. The main outcomes were trends of oxygen requirement, inflammatory markers, and length of hospital stay, and clinical recovery status was defined as a major secondary outcome. The statistical analysis was done using SPSS 27.0, with $p < 0.05$ being considered as the threshold for statistical significance.*

Results: *Patients receiving colchicine required significantly less oxygen and had lower CRP, ferritin, and D-dimer levels compared to the control group ($p < 0.001$ for all). Median hospital stay was remarkably shorter in the colchicine group (5.6 vs 14.2 days, $p < 0.001$). All colchicine-treated patients experienced complete clinical recovery, whereas only 51.5% of patients in the control group did.*

Conclusion: *Colchicine, in addition to standard therapy, significantly improved clinical outcomes and also reduced inflammatory burden, decreased oxygen requirements, and shortened duration of hospital stay in patients suffering from mild to moderate COVID-19 pneumonia.*

INTRODUCTION

Colchicine, which is an anti-inflammatory drug that has been used for a long time to treat gout and autoinflammatory diseases, has now been tested for COVID-19 pneumonia treatment, since it can prevent the strong inflammatory reactions that cause the disease to worsen and lead to a severe case(1,2). COVID-19 pneumonia, especially the mild to moderate cases, is a major public health threat not

only worldwide but also in Pakistan. Lahore, which is the second-largest city in the country, had more than 170,000 confirmed COVID-19 cases reported by the end of September 2020, which represented around 19% of the total COVID-19 cases in Pakistan, thus highlighting the local disease burden (3). On the other hand, the results of international research on markets' ability to influence positively varied from one study to another; some randomized control trials (RCTs) reported no marked decrease in patients' mortality and clinical deterioration, asking for intubation or moving to ICU admission, treated with colchicine as opposed to standard care (4,5).

Information on local clinical outcomes is still very limited; however, the very high incidence of COVID-19 pneumonia in Punjab province brings to light the need for an urgent evaluation of therapeutics that can lessen the clinical severity and improve the patient outcomes, particularly in resource-poor areas (6,7). The anti-inflammatory property of colchicine, which is a cytokine release and neutrophil activity blocker, is said to have a theoretical advantage in the prevention of the progression of the patient with mild or moderate pneumonia to the state of respiratory failure(8). While some international studies have indicated the reduced death rate or shorter hospitalization time due to the use of colchicine in COVID-19 patients, the findings are still inconsistent across the different patient groups involved in the research and the designs of the trials(9).

The idea for the investigation of colchicine's efficacy in mild to moderate COVID-19 pneumonia in Lahore is based on the need for finding affordable, easily accessible interventions to slow down the transition to severe disease and release the burden on healthcare resources. The mixed international evidence notwithstanding, this randomized controlled trial is going to strictly determine colchicine's effect on clinical outcomes in a local patient population, thus helping to possibly draw treatment guidelines that fit the specific epidemiological and healthcare needs of Lahore and similar areas. In addition to this, more information is necessary about the management of patients at the early stage of the disease since meta-analyses have been calling for RCTs that target early treatment initiation to clarify the advantages of colchicine in this population.

Methodology:

This randomized controlled trial (RCT) was done at the Department of Medicine, Lahore General Hospital, Lahore, following the ethical clearance from the Postgraduate Medical Institute/Ameer-ud-Din Medical College's Institutional Review Board (IRB). The RCT aimed at assessing the effectiveness of colchicine in enhancing the clinical outcomes of patients with mild to moderate COVID-19 pneumonia. The research conformed to the CONSORT guidelines for randomized trials.

A total of 66 patients (33 in each group) formed the sample that was selected by a simple random sampling method. The sample size was determined considering the reported discharge rates of 91% and 58% in the colchicine and standard-care groups, respectively, with 80% power and 5% significance level. The total period of the study was six months.

Inclusion Criteria: Adults aged 18–60 years with confirmed laboratory COVID-19 infection (PCR positive) and pneumonia, having mild to moderate symptoms according to the operational criteria, were accepted to participate. Mandatory for enrollment were the oxygen supply of >5 L/min, normal calcium and potassium, and a QT interval <450 ms in ECG. The participants who signed the written consent were included.

Exclusion Criteria:

The patients were not allowed to enroll in case they had an allergy to colchicine, eGFR <45 mL/min/1.73 m^2, advanced liver disease, pregnancy or lactation, or were being treated with CYP3A4 or P-glycoprotein inhibitors. In addition, the participants having severe comorbidities that could impact the outcome evaluation or that were thought not to survive the study period were also excluded.

Single-blinded study participants were randomly assigned to one of two study groups through a computer-generated sequence after their first assessment was completed. The group that participated in the experiment was given 0.5 mg of colchicine every day for a week, plus standard treatment. The other group just received standard care consisting of antibiotics, corticosteroids,

prophylactic anticoagulation, and oxygen therapy, if needed. Demographic data, comorbidities, vital signs, inflammatory markers, and radiological findings were documented at enrollment.

Patients were monitored every day until they were discharged from the hospital. Length of hospital stay, disease progression, and inflammatory markers trend were the primary outcomes measured. Secondary outcomes included time until symptoms disappeared and treatment-related adverse effects. The Eight-Category Ordinal Scale was used to record clinical status, whereby a score of 1 or 2 represented clinical recovery.

Data were analyzed with SPSS version 27.0. The Shapiro-Wilk test was utilized to test the normality of continuous variables. According to the findings, the disease duration variable was normally distributed ($W = 0.986$, $p = 0.657$). In contrast, age ($W = 0.936$, $p = 0.002$), oxygen requirement ($W = 0.928$, $p = 0.001$), CRP levels ($W = 0.899$, $p < 0.001$), ferritin levels ($W = 0.927$, $p = 0.001$), D-dimer levels ($W = 0.883$, $p < 0.001$), and hospital stay ($W = 0.877$, $p < 0.001$) were all non-normally distributed. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as median and interquartile range(IQR). Mann-Whitney U test and chi-square tests were employed to compare group outcomes. A p-value of less than 0.05 was regarded as statistically significant.

Results:

The median age of participants was identical in both groups, with a median age of 48 years in each group. The duration of the disease was also similar; the colchicine group had a median of 6.1 days while the control group had a median of 5.9 days. Nonetheless, the patients assigned to receive colchicine needed significantly less oxygen, having a median of 5.1 L/min as opposed to 7.8 L/min for the control group. Likewise, the inflammatory markers were significantly lower in the group receiving colchicine: CRP had a median of 3.7 mg/dL as compared to 9.7 mg/dL, ferritin 739.7 ng/mL against 1184.5 ng/mL, and D-dimer levels were 0.67 mg/L versus 1.86 mg/L in the control group. The length of hospitalization was also shorter for those receiving colchicine, having a median stay of 5.6 days versus 14.2 days for controls.

Table I: Comparison of clinical and laboratory parameters between the Colchicine(n=33) and Control groups (n=33)

Variable	Colchicine Group(n=33)	Control Group(n=33)
Age (years)	48.0 (15)	48.0 (15)
Disease Duration (days)	6.1 (1.4)	5.9 (1.4)
O_2 Requirement (L/min)	5.1 (2.8)	7.8 (2.8)
CRP (mg/dL)	3.7 (6.1)	9.7 (6.1)
Ferritin (ng/mL)	739.7 (449.4)	1184.5 (449.4)
D-Dimer (mg/L)	0.67 (1.22)	1.86 (1.22)
Hospital Stay (days)	5.6 (8.7)	14.2 (8.7)

Females prevailed by number in both groups in respect of gender distribution, with 23 individuals in the colchicine group and 19 in the control group, while the number of males was 10 and 14, respectively. With respect to clinical recovery, recovery occurred in the entire group, i.e., 33 patients in the colchicine group, while 17 patients in the control group had recovered. On the other hand, the control group counted 16 patients who had not recovered, while the colchicine group had zero non-recovered patients.

Table II: Gender distribution and clinical recovery outcomes in the Colchicine(n=33) and Control groups (n=33)

Variable	Category	Colchicine (n)	Control (n)	Total (n)
Gender	Female	23	19	42
	Male	10	14	24
Clinical Recovery	Recovered	33	17	50
	Not Recovered	0	16	16

The results of the median test revealed that there was no significant difference between the two groups in age or duration of disease. However, all key clinical and laboratory parameters—oxygen requirement, CRP, ferritin, D-dimer levels, and hospital stay—were significantly ($p < 0.001$ for all) lower in the colchicine group as compared to the control group. Thus, these results imply that the patients treated with colchicine experienced less inflammation, lower dependence on oxygen, and significantly shorter periods of hospitalization, which is in line with a much better clinical course.

Table III: Comparison of median clinical and laboratory parameters between Colchicine(n=33) and Control groups (n=33)

Variable	Median (Colchicine)	Median (Control)	p-value
O_2 Requirement (L/min)	5.1	7.8	<0.001
CRP (mg/dL)	3.7	9.7	<0.001
Ferritin (ng/mL)	739.7	1184.5	<0.001
D-Dimer (mg/L)	0.67	1.86	<0.001
Hospital Stay (days)	5.6	14.2	<0.001

The treatment group and clinical recovery had a very important relationship ($p < 0.001$). Every patient in the colchicine group healed completely, while a considerable share of the other group did not recover at all.

Table IV: Clinical recovery outcomes in the Colchicine(n=33) and Control groups (n=33)

Clinical Recovery	Colchicine (n)	Control (n)	Total (n)	p-value
Not Recovered	0	16	16	
Recovered	33	17	50	
Total	33	33	66	**<0.001**

Discussion:

The colchicine's capacity to cure the clinical deteriorations in people suffering from mild to moderate COVID-19 pneumonia in Lahore was proven by the present randomized controlled trial. The median age and duration of illness were similar in both the colchicine and control groups; thus, these variables did not create any confounding effects. On the other hand, the patients taking colchicine needed much less oxygen support (median 5.1 vs 7.8 L/min), and their levels of inflammatory markers were much lower, including CRP (3.7 vs 9.7 mg/dL), ferritin (739.7 vs 1184.5 ng/mL), and D-dimer (0.67 vs 1.86 mg/L). These impacts resulted in a markedly shorter hospital stay (5.6 vs 14.2 days) and total clinical recovery in all colchicine-treated patients as opposed to just 17 recovered in the control group, and none of the colchicine patients were left unrecovered. All these variances were significant from a statistical standpoint ($p < 0.001$), signaling a strong clinical advantage of colchicine treatment.

The results of this research are in agreement with numerous recent studies that have reported the anti-

inflammatory and clinical advantages of colchicine in the treatment of COVID-19(10,11). In particular, a randomized trial conducted by Rahman et al. (2022) revealed that colchicine resulted in a 56% decrease in the need for ventilation or death at day 14, although at day 28 clinical deterioration and mortality reduction mainly reached statistical significance, hence supporting a delayed protective effect similar to our findings related to clinical recovery and hospital stay reduction(12). The colchicine group showed a significant decrease in their median inflammatory markers as well.

Moreover, a meta-analysis that combined five randomized controlled trials with more than 16,000 patients also came to the same conclusion that colchicine significantly reduced COVID-19 severity and CRP levels, and there was a trend towards less need for mechanical ventilation, although it did not reach statistical significance(13). D-dimer levels remained unchanged, and this finding was in contrast to our statistically significant reductions, perhaps indicating differences in patient severity or dosing protocols. This difference suggests that the study's intervention and patient cohort may have yielded a more drastic impact on coagulation markers than expected(14).

The positive influence of colchicine on the length of hospital stay and oxygen requirement is in agreement with the results of the Lopes et al. (2021) study, which also stated that colchicine treatment for moderate to severe COVID-19 patients led to a reduction in the duration of hospital stays and supplemental oxygen. Their findings confirm the role of colchicine in the response to hyperinflammation that causes lung damage and prolonged oxygen dependency(15,16). In the same way(17), Kow et al. (2022) also noted shorter stays in the hospital connected with the use of colchicine, thus confirming our findings(18).

On the other hand, some research, including the RECOVERY trial and some hospital-based trials, did report that colchicine did not affect clinical outcomes or mortality in hospitalized COVID-19 patients, and this could be due to the variation in the severity of diseases, the timing of drug administration, and the background treatments like corticosteroids and antivirals used which are different among the studies(19). These contradictions stress the importance of accurate patient choice and drug administration timing to make the most out of colchicine's effect, with our trial indicating its advantage in mild to moderate pneumonia rather than in advanced or critical illness stages.

The process through which colchicine proves to be beneficial seems to be associated with its anti-inflammatory properties, particularly through inhibition of the NLRP3 inflammasome, which leads to a decrease in IL-1β and other pro-inflammatory cytokines responsible for the COVID-19 cytokine storm(20,21). The notable decrease in CRP, ferritin, and D-dimer in our study and other studies is a biomarker indication of inflammation and coagulation being lessened, and thus oxygenation being better and quicker clinical recovery(22,23).

Among the few, this randomized controlled trial assessed colchicine in COVID-19 pneumonia from a low-resource setting. Reliable findings due to rigorous randomization, daily monitoring, and inclusion of multiple objective inflammatory markers. Full follow-up of all participants helped to keep attrition bias to a minimum.

Limitations

The sample size was rather small, which reduced the capacity for generalization. The study was single-blinded, which could result in performance bias. Long-term outcomes and post-discharge complications were not evaluated. Furthermore, the trial did not consider severe COVID-19 cases, as it was restricted to mild to moderate disease, thus limiting its applicability.

Conclusion:

This randomized control trial reveals that colchicine provides a significant improvement in clinical outcomes for mild to moderate COVID-19 pneumonia patients by lowering oxygen consumption, decreasing the levels of inflammatory markers, and shortening the duration of hospital stay, with total clinical recovery in all treated patients. These findings are in line with the global evidence that has been building up and pointing to the same conclusion—colchicine is effective in controlling hyperinflammation and speeding up recovery in COVID-19. Even though there are some

differences in the literature coming from larger trials in the case of severe COVID-19, colchicine remains a promising and affordable adjunct therapy, which has a greater relevance in underserved areas. More large-scale, multicenter, double-blind trials are needed to validate these results and to ensure proper patient selection and treatment protocols.

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