**The efficacy of colchicine as an adjuvant treatment in non-hospitalized COVID-19 patients: A randomized placebo-controlled trial**

**Running title: Effect of colchicine on the treatment of non-hospitalized COVID-19 patients**

**Materials and Methods**

*Trial design*

A double-blind, two-arm randomized, placebo-controlled trial was performed to evaluate the efficiency of colchicine in the treatment of non-hospitalized COVID-19 patients. This study protocol was approved by the Ethical Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1399.096) and the Iranian registry of clinical trials (IRCT20200408046990N2). The eligible subjects interested in participating were enrolled in our study and randomly allocated (1:1) to either the placebo or colchicine group based on block randomization. The randomization sequence was prepared using the online randomization software (www.sealedenvelope.com) with a block size equal to six.

*Trial population*

Between 21 April and 23 July 2021, the non-hospitalized adult COVID-19 patients aged 18 to 85 years who were referred to Ghaem hospital clinics of Mashhad University of Medical Sciences were considered in the present study. The COVID-19 patients were confirmed by reverse transcription-polymerase chain reaction testing. The non-hospitalized subjects who had clinical symptoms including fever and cough, as well as lymphopenia and positive C-reactive protein (CRP) due to SARS-COV-2 infection and also given consent, were included in this study. The exclusion criteria contained hypersensitivity to colchicine, pregnancy or lactation, hepatic failure, kidney failure (glomerular filtration rate < 30 ml/min), heart failure with ejection fraction (EF) under 40%, known diabetes mellitus, history of neuromuscular disease or chronic diarrhea or malabsorption, active gastrointestinal disorders such as active peptic ulcers, under treatment with colchicine for other diseases, usage of protease inhibitors, concomitant use of classes of Cytochrome P450 3A4 (CYP3A4) enzyme inhibitors or P-glycoprotein (PGP) inhibitors, or concomitant usage of statins except rosuvastatin.

*Trial procedure*

The enrolled subjects were randomly allocated to the case or control groups to receive a daily dosage of the colchicine or placebo tablets besides other medical treatments according to the COVID-19 protocols. The individuals in the case group received a single dose of 1 mg oral colchicine tablet (Modava Company, Iran) per day for 14 days. In the control groups, one mg of lactose placebo tablet was administered to the volunteers once daily for 14 days. The side and adverse effects of colchicine treatment were recorded in this study. All participants were assessed during the follow-up time with a daily check of clinical manifestations such as fever and cough, as well as laboratory hematologic and biochemical tests to evaluate the lymphopenia and CRP every week.

*Outcomes*

The duration of clinical features including fever and cough were determined in patients of case and control groups within the follow-up time. Based on para-clinical findings, the duration of lymphopenia and positive CRP inflammatory marker was compared in the placebo and colchicine groups. The frequency of subjects who had the fever, cough, lymphopenia, or positive CRP was evaluated at baseline, 7 days, and 14 days of intervention. Secondary outcomes were the rates of recovery and mortality in participants and the total adverse effect of intervention at the endpoint of follow-up.

*Statistical analysis*

Data were gathered and analyzed by SPSS software version 22. The qualitative variables were expressed as the frequency (%) and compared using Chi-square or Fisher’s exact test between the placebo and case groups. The Kolmogorov-Smirnov test was used to determine the normal distribution of quantitative variables. Accordingly, the normal and non-normal distribution variables were described as the mean ± standard deviation (SD), and median (percentile 25-75), respectively. The independent sample T-test or Mann-Whitney test was accomplished to compare quantitative variables between the two groups. The Cochrane's Q test was performed to compare the frequency of participants in terms of fever, cough, lymphopenia, or positive CRP within the group at baseline, 7 days, and 14 days of treatment. A *p*-value less than 0.05 was considered significant.

**Results**

In the present investigation, the therapeutic effect of colchicine on clinical and para-clinical findings was evaluated in non-hospitalized COVID-19 patients within 14 days. 418 individuals were assessed for eligibility, and 84 participants were enrolled in our study. Subjects were randomly divided into the control and case groups to receive the placebo or colchicine for two weeks, respectively. Two patients were excluded from each group through the follow-up time, and finally, 40 subjects were analyzed in every group.

the mean age of the placebo and case groups was 58.58±19.15, and 53.80±21.09, respectively, with no significant between-group difference (*P*=0.292). 60% of individuals were male in the control group versus 52.5% of the colchicine group, and no significant difference was found between the mentioned groups (*P*=0.652). Additionally, there were no significant between-group differences as regards COVID-19 severity (*P*=1.000). All participants had a fever, cough, lymphopenia, and positive CRP at the baseline of our study. None of them required oxygen therapy during the COVID-19 infection.

The mean duration of the clinical features including fever, and cough was 6.62±3.42, and 6.95±3.64 days in the case group relative to 7.07±3.98, and 7.08±3.63 days in the control group, respectively (Table 2). The mean duration of lymphopenia and positive CRP in the placebo and case groups was 10.15±3.53, and 9.10±3.25 days, as well as 9.27±3.32, and 8.40±2.83, respectively. No significant differences were observed in terms of the duration of mentioned symptoms due to COVID-19, lymphopenia, and CRP inflammatory marker between the two groups .

the comparison of clinical and para-clinical findings in the two groups during 14 days of intervention. At post-treatment, 12.5% and 2.5% of subjects had a fever in the case and control groups versus 7.5% and 5% of cough signs, respectively (Fig. 2A, and 2B). The frequency of individuals with fever and cough symptoms was 10% and 2.5% reduced in the case group relative to the control group after two weeks, respectively. However, no significant between-group differences were observed in mentioned signs at 7 days, and the end point of treatment.

According to the laboratory evaluation, 45% of the placebo group had lymphopenia versus 30% of the case group at 7 days of follow-up (Fig. 2C). Although the lymphopenia was 15% decreased in the case group compared to the control group, there was no statistically significant difference between the two groups (*P*=0.248). Furthermore, none of them had lymphopenia after 14 days of intervention. The frequency of patients with positive CRP was 32.5% and 20% in the placebo and case groups after 7 days versus 10% and 7.5% at the end point of the study, respectively . No significant difference was found concerning CRP inflammatory marker between the two groups at the 7 days (*P*=0.310) and 14 days (*P*=1.000) of follow-up. Significant within-group differences were observed in the case or control group as regards the frequency of participants who had a fever (*P*<0.001), cough (*P*<0.001), lymphopenia (*P*<0.001), and positive CRP (*P*<0.001) at the intervals of follow-up (Table 3).

At the endpoint of the study, the recovery rate of individuals with fever and cough signs was 97.5%, and 95% in the case group versus 87.5%, and 92.5% in the control group, respectively. 100% of lymphopenia patients were recovered in both groups. Moreover, the rate of recovery in the case and control groups with positive CRP was 92.5% and 90%, respectively. None of the participants expired or had adverse events of intervention during a time frame of two weeks.