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Randomised Controlled Trial

Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection

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ABSTRACT

Background: COVID19 complications cause inflammatory storm. Colchicine is a potent anti-inflammatory medication that has been proposed as a possible treatment option for COVID-19.

Objective: to assess effectiveness and safety of add on use of colchicine to the standard treatment in moderate and severe COVID-19.

Patients and methods: In this randomized controlled open label clinical trial, 160 patients hospitalized equally divided between moderate and severe COVID19 categories were randomized to 4 study groups in a 1:1:1:1 allocation (n = 40 for each group) according to type of treatment. Patients were randomly assigned to receive the standard treatment for 14 days (control group) or colchicine add on to the standard treatment 1 mg daily orally for 7 days then 0.5 mg daily for another 7 days. Survival rate, time to cure in days, and side effects were assessed.

Results: Colchicine add on treatment was associated with a significantly shorter time to cure (referring to start of first symptom) by an average of 5 days in severe disease and 2 days in moderate disease (log-rank P=<0.001). In addition, the Colchicine add on significantly increased the risk of cure per unit of time by 2.69 times compared to controls after adjusting for disease severity, age, and time since the start of the disease to start of treatment. A severe COVID19 disease, a longer time for starting treatment, and the older age notably reduced the risk of cure (HR = 0.72, p = 0.07; HR = 0.74, p < 0.001; and HR = 0.59, p = 0.015 respectively). Possible side effects reported due to colchicine were 8/40 (20%) of severe COVID19 patients and 3/40 (7.5%) of moderate COVID19, non of which warranted stopping treatment by the data monitoring board. Generally, the side effects were 8/11 (72.73%) gastrointestinal disturbances. No immediate or late allergic reactions were observed.

Conclusions: Colchicine add on treatment reduced significantly time to recovery in severe COVID19 (by five days) and in moderate cases (by two days) but did not lower the death rate. Side effects were mild, well tolerated and confined to gastrointestinal adverse events.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The outbreak of COVID19 has become a global pandemic disease with significant healthcare and economic burdens, impact on human quality of life, and significant increase in mortality[2, 3].

Early data showed that COVID19 results in cytokine storm syndrome by activating the inflammasome which triggers the inflammatory cascade leading to acute lung injury[4, 5]. Within this pathophysiologic framework, a potentially successful treatment should possess a potent anti-inflammatory action with a known favorable safety and tolerability profile. In addition, ideally requires a clinically available, orally administered and cheap medication.

Colchicine is a potent anti-inflammatory medication that has been proposed as a possible treatment option for COVID19. It exerts its anti-inflammatory effects via inhibition of neutrophil chemotaxis, adhesion, and mobilization; suppression of superoxide production; and reduction

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of tumor necrosis factor (TNF)-a generation and activity(6). Additionally, it is proposed that colchicine may have some antiviral properties through inhibition of microtubule polymerization and regulation of production of antioxidative factor[6–8] Early reports suggested possible benefits for colchicine in patients with COVID19[9]. Further, a recent meta-analysis showed mortality benefit associated with the use of colchicine in patients with COVID19[10].

The current study was designed to assess the clinical benefit and safety of the adjuvant use of colchicine with the standard therapy in COVID19 comapred to standard therapy only gorup (control group).

1.1. Patients and methods

1.1.1. Study design

This pilot randomized controlled open label trial was conducted at Alkarkh hospital in Baghdad city from April 2021-to August 2021. The study was performed according to the Declaration of Helsinki and its amendments, and the Guidelines for Good Clinical Practices issued by the Committee of Propriety Medicinal Product of the European Union. Ethical approval was obtained from The Arab Board of Health Specializations in Iraq, Ministry of Health with a number of 20210407 on 7/04/2021. The study was also registered in pubmed.gov (Registration number NCT05151614). An informed written consent were secured from all study participants. A data monitoring board was assembled from two internists, a clinical pharmacist and a statistician to monitor the safety of study participants. The work has been reported in line with the CONSORT Criteria [11]

1.1.2. Participants

Eligible patients included in the study were adults aged 18 years and above with a moderate to severe COVID19 diagnosed according to the WHO classification criteria [12]. COVID-19 patients with comorbid conditions were included in this study.

To qualify for recruitment in the study the treatment for symptomatic patients should not be postponed for more than three days after being labeled as a moderate cases, and no more than two days after being classified as severe cases.

Exclusion criteria included: Patients with hypersensitivity to colchicine, chronic diseases (renal failure with eGFR<30 ml/min; chronic liver disease with hepatic failure and AST/ALT >3 times normal), decompensated heart failure, long QT syndrome with QTc >450 msec, uncontrolled arrhythmia; inflammatory bowel disease, chronic diarrhea or malabsorption, pre-existent progressive neuromuscular disease, and metastatic cancer. Pregnant and breast-feeding women, those who were receiving immunosuppressive chemotherapy, regular use of digoxin, amiodarone, verapamil or protease inhibitors, and colchicine were other exclusion criteria.

1.1.3. Randomization and sample size calculation

This study is a randomized controlled trial with 2 arms study trial 1:1 allocation. The sample size was calculated and we needed a total of 160 patients (80 Colchicine add on group and 80 controls) to get mean effect size of 30% with an α error of 0.05 and Beta error not exceeding 0.15.

1.1.4. Binding

This study was open label non blinded study.

1.1.5. Recruitment of study participants

Patients were recruited from inpatients and outpatients according to the WHO classification criteria of severity of the disease [12]. Study participants were divided into two groups:

Colchicine group: Colchicine + standard therapy of COVID-19.

Control group: Standard therapy of COVID-19.

1.1.6. Arms and interventions

For the colchicine add-on group, colchicine 0.5 mg tablet 1x2 for 1 week followed by 0.5 mg tablet 1x1 for another week + the standard therapy (total duration of colchicine 14 days). For the Control group, the patients in this group received only standard care which included all or some of the following, according to the clinical condition of each patient:

- Acetaminophen 500 mg on need
- Vitamin C 1000 mg twice/day
- Zinc 75–125 mg/day
- Vitamin D3 5000IU/day
- Azithromycin 250 mg/day for 5 days
- Oxygen therapy/C-Pap if needed
- Dexamethasone 6 mg/day or methylprednisolone 40 mg twice per day, if needed
- Mechanical ventilation, if needed

1.1.7. Outcome Measurements

The first outcome measure was to assess the percentage of cure/death of patients and evauated by normalization of clinical evaluation, laboratory investigations, and imaging. [Time Frame: up to 14 days]. The second outcome was to evaluate time to recovery (stay days in hospital). [Time Frame: up to 14 days]. The third outcome was to investigate the proportion and nature of possible side effects seen during the trial.

1.1.8. Statistical analysis

Statistical analyses were done using IBMSPSS (IBM Statistical Package for Social Sciences) version 28 computer software. Frequency distribution for selected variables was done and differences between the four study groups in selected explanatory variables were tested for statistical significance by Chi-square test of homogeneity. The log-rank test was used to assess the statistical significance of the difference between the two survival curves. The Kaplan Meier survival analysis was used to calculate the mean and median survival time for cure after treatment in addition to calculating the cumulative rates. The Cox-regression model was used to calculate the Adjusted Hazard Ratio for the risk of cure after treatment per unit time for a set of predictors. We assumed the level of statistical significance at $P < 0.05$. All analyzed tests were bilateral.

2. Results

2.1. Participant flow

A total of 220 patients infected with COVID19 were screened for eligibility to be included in the study. Of those 60 patients were excluded: 51of them were mild cases of COVID-19, 3 patients were pregnant, 2 had chronic kidney disease, 2 congestive heart failure, 1 alcoholic liver cirrhosis, and 1 lymphoma. The remaining 160 patients were classified into moderate and severe disease categories with an equal number of individuals in each group. A simple computer generated random number method was used to randomly allocated each group of disease severity to intervention (Colchicine add on) and control group (standards of care therapy) in equal 1:1 ratio. The colchicine add on group were 40 patients with severe COVID19 and 40 patients with moderate COVID19 severity. The control group also were 40 of severe COVID19 and 40 moderately severe COVID19 severity. All of the patients in both groups completed the study as in Fig. 1.

2.2. Baseline characteristics of the study groups

The median [Interquartile range] age of participants was 49 [37–60.5] years, with 85 (53.1%) males. As shown in Table 1, there were no important or statistically significant difference in age, gender, and smoking habit between the 4 study groups. The absence of difference is an indication of good randomization procedure, which would cancel the possible confounding effect of these variables. In addition,

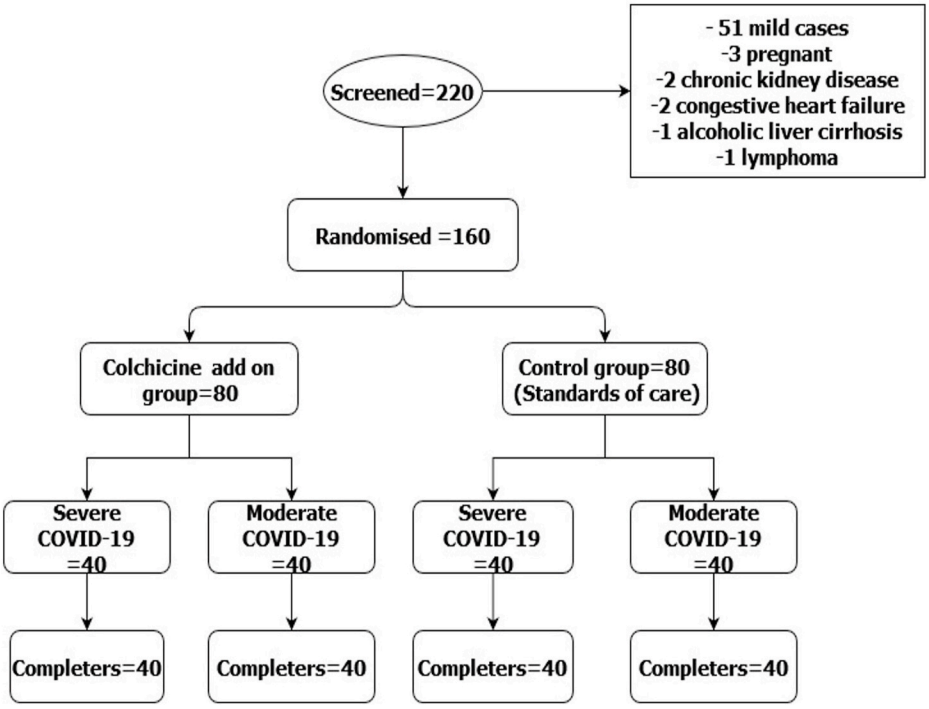

Fig. 1. Study flow chart.

Table 1
Baseline characteristics of the study groups.

	Study groups								
	Intervention (Colchicine add on) + Severe disease		Intervention (Colchicine add on) + moderate disease		Control + Severe disease		Control + moderate disease		
	N	%	N	%	N	%	N	%	P
Age group (years)									0.07[NS]
18–39	8	20.0	15	37.5	14	35.0	17	42.5	
40–59	14	35.0	18	45.0	18	45.0	12	30.0	
60+	18	45.0	7	17.5	8	20.0	11	27.5	
Total	40	100.0	40	100.0	40	100.0	40	100.0	
Gender									0.13[NS]
Female	13	32.5	21	52.5	23	57.5	18	45.0	
Male	27	67.5	19	47.5	17	42.5	22	55.0	
Total	40	100.0	40	100.0	40	100.0	40	100.0	
Smoking habit									0.12[NS]
Non-smoker	25	62.5	28	70.0	23	57.5	20	50.0	
Current smoker	10	25.0	6	15.0	13	32.5	18	45.0	
Ex-smoker	5	12.5	6	15.0	4	10.0	2	5.0	
Total	40	100.0	40	100.0	40	100.0	40	100.0	
Comorbidities									
Hypertension	18	45.0	11	27.5	21	52.5	16	40.0	0.14[NS]
Diabetes Mellitus	11	27.5	7	17.5	10	25.0	5	12.5	0.32[NS]
Ischemic Heart Disease	4	10.0	1	2.5	4	10.0	4	10.0	0.52[NS]
Asthma	0	0.0	2	5.0	0	0.0	0	0.0	0.11[NS]
Cancer	2	5.0	1	2.5	1	2.5	0	0.0	0.56[NS]
Stroke	2	5.0	1	2.5	0	0.0	0	0.0	0.29[NS]
Others	2	5.0	2	5.0	2	5.0	1	2.5	0.93[NS]
Any co-morbidity	23	57.5	21	52.5	23	57.5	19	47.5	0.78[NS]
Obesity	16	40.0	17	42.5	12	30.0	11	27.5	0.41[NS]
Death as an outcome	1	2.5	0	0.0	2	5.0	1	2.5	0.56[NS]
Possible side effects of medication	8	20	3	7.5	1	2.5	0	0.0	0.003

there was no difference in the relative frequency of selected comorbidities measured between study groups. These comorbidities include: Hypertension, Diabetes Mellitus, Ischemic Heart Disease, Asthma, Cancer, obesity and Stroke. The mortality rate in the 4 treatment groups ranged between zero to 5%, with no important or statistically significant differences in the risk of death between groups. The reported side effects were significantly higher in the intervention group (20.5% and 7.5% among severe and moderately severe group of COVID19 respectively) compared to both control groups.

2.3. Difference in time of starting treatment among the study group since first symptom

As shown in Table 2, the possible confounding effect of lead time survival bias on the possibility of cure was evaluated. There was no statistically significant difference in median survival time (time elapsing from the first symptom till starting treatment) between the intervention and control groups after stratifying for the disease severity. i.e. both the intervention and control standard treatment were initiated at a comparable time in each study strata (moderately severe and severe COVID19 disease).

2.4. Outcome measurement

1) Time to cure since first symptom

The colchicine add on group had a significantly shorter time to cure (time being counted since the first day of COVID19 illness signified by symptoms) by an average of 2 days compared to control group (standard treatment) among the moderately severe disease strata. This treatment effect was more accentuated among the severe disease strata. The treatment being associated with 5 days shorter time to cure than the standard treatment, Table 3 and Fig. 2.

2) Time to cure since the start of treatment

The colchicine add-on treatment group had a significantly shorter time to cure since the first day of starting treatment by an average of 3 days compared to control group among the moderately severe disease strata. This treatment effect was more accentuated among the severe disease strata. The colchicine add on treatment was associated with 4 days shorter time to cure on average than the control standard treatment, Table 4 and Fig. 3.

3) Multivariate modelling

The cox-regression model was used to assess the net effect of colchicine add on treatment compared to the standard control treatment after adjusting for disease severity and duration of the disease before starting treatment in addition to age and gender.The backward stepwise method was used to retain the explanatory variables that have a significant effect on the risk of cure. Being treated with the intervention treatment (colchicine add on) increased the risk of cure by 2.69 times compared to control (standard treatment) after adjusting for disease severity, age, and time since the start of the disease to start of treatment. A severe disease category reduced the risk of cure (HR = 0.72) compared to moderate disease category. A longer time for starting treatment reduced the risk of cure (HR = 0.74). In addition, an older age group reduce the risk of cure compared to younger age. The model was statistically significant as shown in Table 5.

Table 2
Kaplan Meier survival analysis showing the cumulative incidence of starting treatment with time (days) since first symptom (start of the disease).

	Moderate disease		Severe disease	
Time	Control (standard treatment)	Intervention (Colchicine)	Control (standard treatment)	Intervention (Colchicine)
Median survival time	7.0	7.0	9.0	10.0
95% confidence interval	(6.2–7.8)	(6.4–7.6)	(8.1–9.9)	(9.4–10.6)

Log Rank (Mantel-Cox) = 0.05[NS].

Table 3
Kaplan Meier survival analysis showing the cumulative incidence of cure with time (days) since first symptom (start of COVID19).

	Moderate disease		Severe disease	
Time	Control (standard treatment)	Intervention (Colchicine)	Control (standard treatment)	Intervention (Colchicine)
Median survival time	14.0	12.0	19.0	14.0
95% confidence interval	(13–15)	(10.2–13.8)	(15.9–22.1)	(12.5–15.5)

Log Rank (Mantel-Cox) < 0.001.

4) Safety of colchicine as add on treatment

The adverse effects possibly related to Colchicine therapy were monitored. Up to 8/40 (20.5%) of severe COVID19 patients and 3/40 of moderate COVID19 patients (7.8%) showed side effects possibly related to Colchicine.

3. Discussion

This study was designed to assess the effectiveness and safety of colchicine as add-on to the standard therapy in COVID19 management compared to the standard treatment (control) group. The findings of the present study suggest an obvious and statistically significant clinical benefit in shortening time required to cure referring to the time of first symptom or the time of starting treatment.

COVID19 pandemic highlighted the necessity for investing more efforts to discover antiviral agents. To date, viruses are still largely not under control by medicines.

Recently, WHO consolidarity Trial Consortium reported that repurposed antiviral drugs for COVID-19 like remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay [13].

The burden of recovery from viral infection is mostly the immune system responsibility. Nevertheless, not all viral infections are easily self-limiting. Some infections impose life-threatening sequel. SARS-CoV-2 is a good example of community-debilitating and life-threatening viral infections. oreover, mortality and morbidity of COVID19 is mainly attributed to immune-pathogenic response of the host body namely, cytokine storm [14]. Cytokine storm is found as the main driving cause for acute respiratory distress syndrome (ARDS) and fatality among COVID19 patients. Cytokine storm is uncontrolled upregulation of innate immunity cytokines leading to exhaustion phase of cell-mediated immunity and uncontrolled systemic and pulmonary inflammation which might lead to ARDS and death. Hence, immunomodulating and/or immunosuppressing agents might be of benefit. In a clinical trial conducted in 2020 in UK, Dexamethasone was found effective in lowering morbidity and mortality in severe and critical cases of COVID-19. In this instance, the mechanism of action of steroids is ameliorating the uncontrolled release of pro-inflammatory cytokines during the cytokine storm phase of disease, the step necessary to

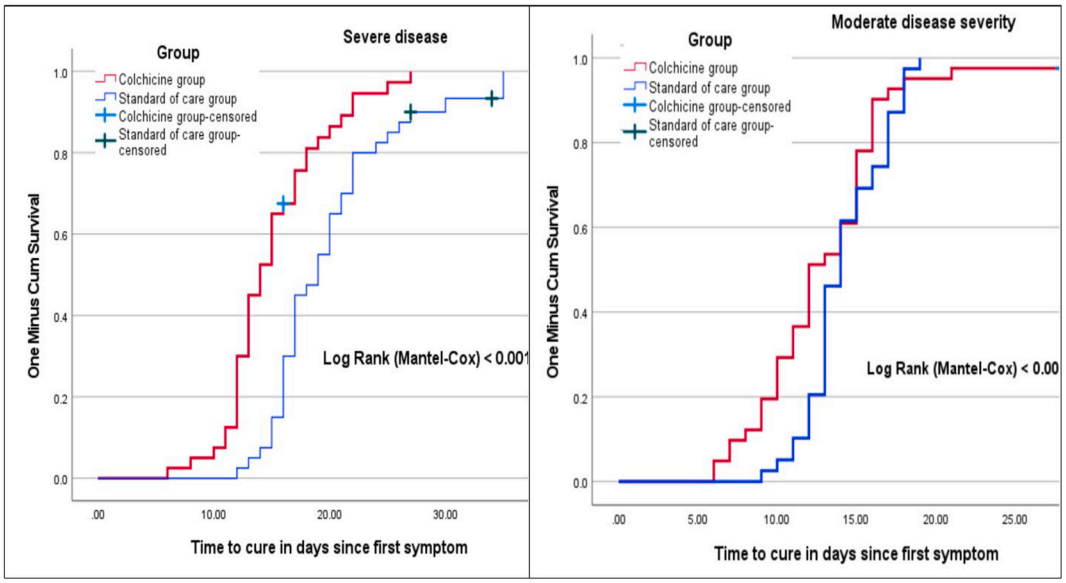

Fig. 2. Survival curves comparing the cumulative incidence rate of cure between the intervention(colchicine addon) and control groups with time (days) since the first day of symptoms (start of COVID 19) stratified by disease severity (A severe Vs moderate disease.

Table 4
Kaplan Meier survival analysis showing the cumulative incidence of cure with time (days) since the start of treatment.

	Moderate severity of disease		Severe disease	
Time	Control (standard treatment)	Intervention (Colchicine)	Control (standard treatment)	Intervention (Colchicine)
Median survival time	7.0	4.0	9.0	5.0
95% confidence interval	(6.3–7.7)	(3.4–4.6)	(7.8–10.2)	(3.7–6.3)

Log Rank (Mantel-Cox) < 0.001.

enhance chances of survival and recovery [15].

Like steroids, immunomodulating agents seem to be another way of controlling the unwanted cytokine storm and preventing ARDS. One of the prominent immunomodulating agents is the intervention under consideration in this clinical trial. Colchicine has several potential mechanisms of action, including mechanisms that reduce the chemotaxis of neutrophils, inhibit inflammasome signaling, and decrease the production of cytokines such as interleukin-1 beta[16].

The current study showed that colchicine effectively reduced the time needed to recovery by an average of four days in severe cases and three days in moderate cases referring to the time of starting treatment. However, the death rate was not significantly affected by the type of treatment used in this study. The sample size was too small for enough death outcome to allow a valid calculation of difference in survival for this outcome. The acceleration in recovery especially in severe patients treated with colchicine is an indicator for the effectiveness of colchicine as anti-inflammatory, immunomodulatory and as cardiovascular protective agent as all these factors constitute the pillars for complicated

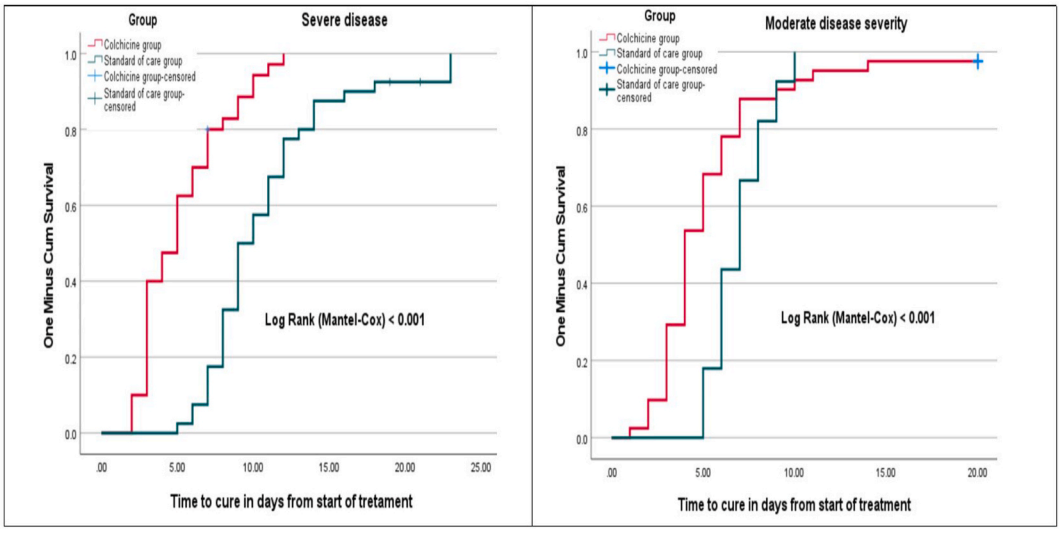

Fig. 3. Survival curves comparing the cumulative incidence rate of cure between the intervention and control groups with time (days) since the first day of starting treatment by disease severity (A severe Vs less severe disease).

Table 5
Cox regression model with the risk of cure with time (days) since starting treatment as the outcome and selected explanatory variables.

Backward Stepwise (Conditional LR) method	Adjusted HR	P
Intervention (Colchicine) compared to Control (standard treatment)	2.69	<0.001
Severe COVID19 disease compared to moderately severe category	0.72	0.07 [NS]
Time interval (days) since first symptom to start of treatment	0.74	<0.001
Age group (years)		0.05 [NS]
adults (40–59 years old) compared to very young adults (18–39 years old)	0.80	0.25 [NS]
Old age (60+ years) compared to very young adults (18–39 years old)	0.59	0.015

ARDS in COVID19 cases. Moreover, the lower effectiveness in reducing time to recovery in moderate patients can endorse the theory that colchicine activity is mainly anti-inflammatory and immunomodulatory rather than an antiviral activity.

However, the findings of the current study is not in harmony with RECOVERY study published in 2021 which showed that adults hospitalized with COVID19, colchicine was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death[17]. Although the death outcome is the same, our study revealed an obvious and statistically significant reduction in time to recovery in severe cases. The discrepancy in findings might be due to differences in the standard of care given to patients, their age or health status and associated comorbidities between studies. Another study revealed that in hospitalized COVID19 patients, colchicine treatment neither improved the clinical status, nor the inflammatory response, over the standard treatment. However, a preventive effect for further clinical deterioration might be possible[18].

Other studies reported beneficial effects for Colchicine in COVID19. One study conducted in Brazil and published in 2021 found that colchicine reduced the length of both, supplemental oxygen therapy and hospitalization and the drug was safe and well tolerated. However, it was not possible to comment on the effect of colchicine on reducing mortality in COVID19 because of the low frequency of death as an outcome[19]. Moreover, COLCORONA study found that the colchicine treatment is effective in preventing the cytokine storm phenomenon and reducing the complications associated with COVID19[20].

The differences in outcomes of the earlier mentioned studies is not well understood. However, it might come from different protocols of COVID19 therapies, timing of colchicine treatment, immunity status against the virus, disease severity of patients, and the differences in viral strains.

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports. Some studies have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, the findings of these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, and differences in the clinical and demographic characteristics of participants and permitted use of various cotreatments (e.g., remdesivir, corticosteroids) in the treatment arms [21–23].

Another observation in the current study was possible side effects of colchicine add on group were significantly more frequent than the side effects in the standard treatment only. These untoward complaints were mainly gastrointestinal upset and/or diarrhea but no immediate or late allergic reactions were observed. Similar findings were reported in other studies which reported significantly higher incidence of gastrointestinal adverse events[9, 20]. However, in PRINCIPLE trial (a randomized, open-label, platform trial that evaluated colchicine in symptomatic non-hospitalized patients with COVID-19, the occurrence of adverse events was similar in the colchicine and usual care arms [24].

The current study has some limitations. Its an open label study with a fairly small sample size and executed in a single center (a large central teaching hospital). A larger multicenter for longer period and blinded study may address these limitations. However, this study reported important clinical findings which is shortening of hospital stay specially for severe COVID-19.

4. Conclusions

Colchicine in the current study reduced time to recovery by an average of 5 days less in severe and 2 days in moderate COVID19 cases. The association between this add on treatment and mortality was not established. Side effects were mild and confined to gastrointestinal upset and diarrhea. Hence, there seems a potential role for using Colchicine as an add on to treat severe COVID19 patients.

Funding

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Trial registry number

Ethical approval was obtained from The Arab Board of Health Specializations in Iraq, Ministry of Health with a number of 20210407 on 7/04/2021.

Research registry UN 7658

Link https://www.researchregistry.com/browse-the-registry#home/

Authors contribution

All authors(contributed in concept or design of the study. Mohammed Fauzi Maulood contributed in data collection, Faiq I. Gorial, Ahmed S. Abdulamir' and Ahmed Sameer Alnuaimi contributed in data analysis or interpretation, writing the paper, and approval of the final version of the paper. Manal K. abdulrrazaq and Fadil Agla Bonyan contributed in writing the paper and approval of final version.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

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Authors contribution

All authors(contributed in concept or design of the study.

Mohammed Fauzi Maulood contributed in data collection.

Faiq I. Gorial, Ahmed S. Abdulamir [1,] and Ahmed Sameer Alnuaimi contributed in data analysis or interpretation, writing the paper, and approval of the final version of the paper.

Manal K. abdulrrazaq and Fadil Agla Bonyan contributed in writing the paper and approval of final version.

Please state any conflicts of interest

No Conflicts of interests.

Registration of research studies

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Researchregistry7658.

Link

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Guarantor

Faiq I. Gorial.

Consent

All patients signed written informed consent for participation in the study.

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The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Declaration of competing interest

None.

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