



REVIEW ARTICLE

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Exploring position of colchicine in management of COVID 19 – A systematic review

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ARTICLE INFO ABSTRACT



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Introduction: One of the goals of managing COVID 19 patients is controlling inflammatory responses, which are majorly responsible for morbidity and mortality associated with SARS CoV 2 infection. A novel approach to address inflammation could be Colchicine. It invariably decreases pulmonary complexities, showing antimetabolic action, causing metaphase arrest by inhibiting microtubule and spindle formation, and is effective in reducing granulocyte migration, ultimately reducing inflammation.

Method: For this systemic review, literature was searched using PubMed, Embase, Cochrane Central, medRxiv, and researchsquare.com. The keywords used were – COVID 19, colchicine, SARS-CoV-2, and clinical outcome. Studies published between January 2020 and October 2021 were evaluated and screened to identify those that had reported the effect of colchicine in SARS CoV 2 infected patients and to assess clinical outcomes including mortality, intensive care unit (ICU) admissions, or mechanical ventilation.

Results and Discussion: In this systematic review among 8 quantitative clinical researchers, it was observed that colchicine administration was related to improved clinical outcomes in COVID 19 patients, without statistical significance.

Conclusion: The mortality risk of COVID-19 patients can be reduced by colchicine. Need more prospective clinical researches which could help to evaluate the efficacy of colchicine to treat COVID-19 patients in different stages of the disease, including post-hospitalization and long-term care follow-up.

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Introduction

The morbidity and mortality due to SARS-CoV-2 infection is related to inflammatory responses which causes aggressive lung disorders. There are three stages of SARS CoV 2 infection related natural history of disease including (Akhmerov & Marbán, 2020):

- Early infection phase (virus infiltrates host cells in the lung parenchyma)
- Pulmonary phase (viral mediated lung parenchymal insult and activation of host immune response)
- Inflammatory cascade sets in (triggered by pathogen-associated molecular patterns)

Neutrophil activation, stimulation of inflammasome followed by production of cytokines IL 1 and IL 6 have set in cytokine storm, which is majorly responsible for development of severe disease associated with COVID 19.

Inflammasome is further upregulated by IL-1 β , tumour necrosis factor (TNF) and NF- κ B (Mehta et al, 2020). One of the goals of managing COVID 19 patient is controlling inflammatory responses. Anti-inflammatory with limited immunosuppressive potential make colchicine placed in special position among therapeutics used for COVID 19 infection.

Colchicine – Mechanism of Action:

Colchicine binds to soluble non polymerised tubulin heterodimers to form a tight tubulin- colchicine complex and blocks neutrophil chemotaxis and degranulating lysosome. Colchicine interferes with at low doses microtubule formation and at high doses microtubule depolymerisation (Schlesinger, 2020). In Figure 1 mechanism of action of colchicine has been depicted.

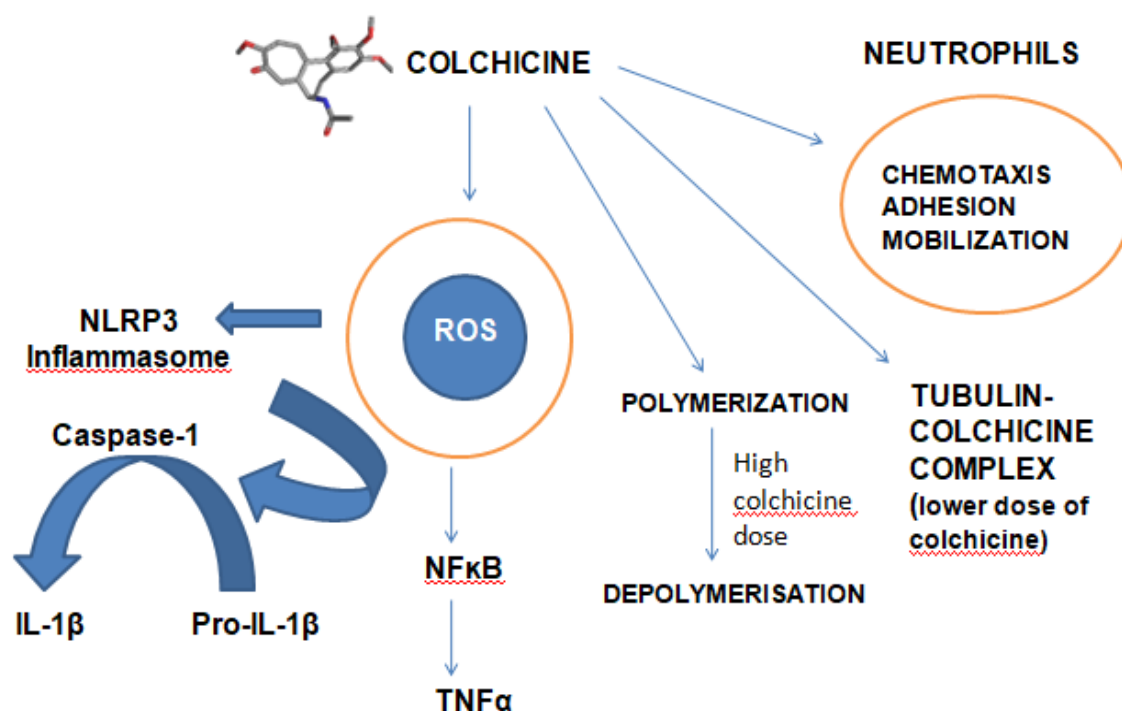


Figure 1: Action of colchicine on ROS, neutrophils; Formation of tubulin-colchicine complex Colchicine produces potent inhibition of P2X7 – induced pore formation, therefore, causing reduced levels of ROS and IL-1 β .

There is no expression of P glycoprotein (efflux protein) in neutrophil, which lead to more accumulation of colchicine in it. Inhibition on reactive oxygen species production exhibited by colchicine is also beneficial to combat against cytokine release syndrome. Figure 2 is depicting the role

of colchicine in different steps of SARS CoV 2 infection related natural history to improve outcome exerting anti-inflammatory with a little immunosuppressive property.

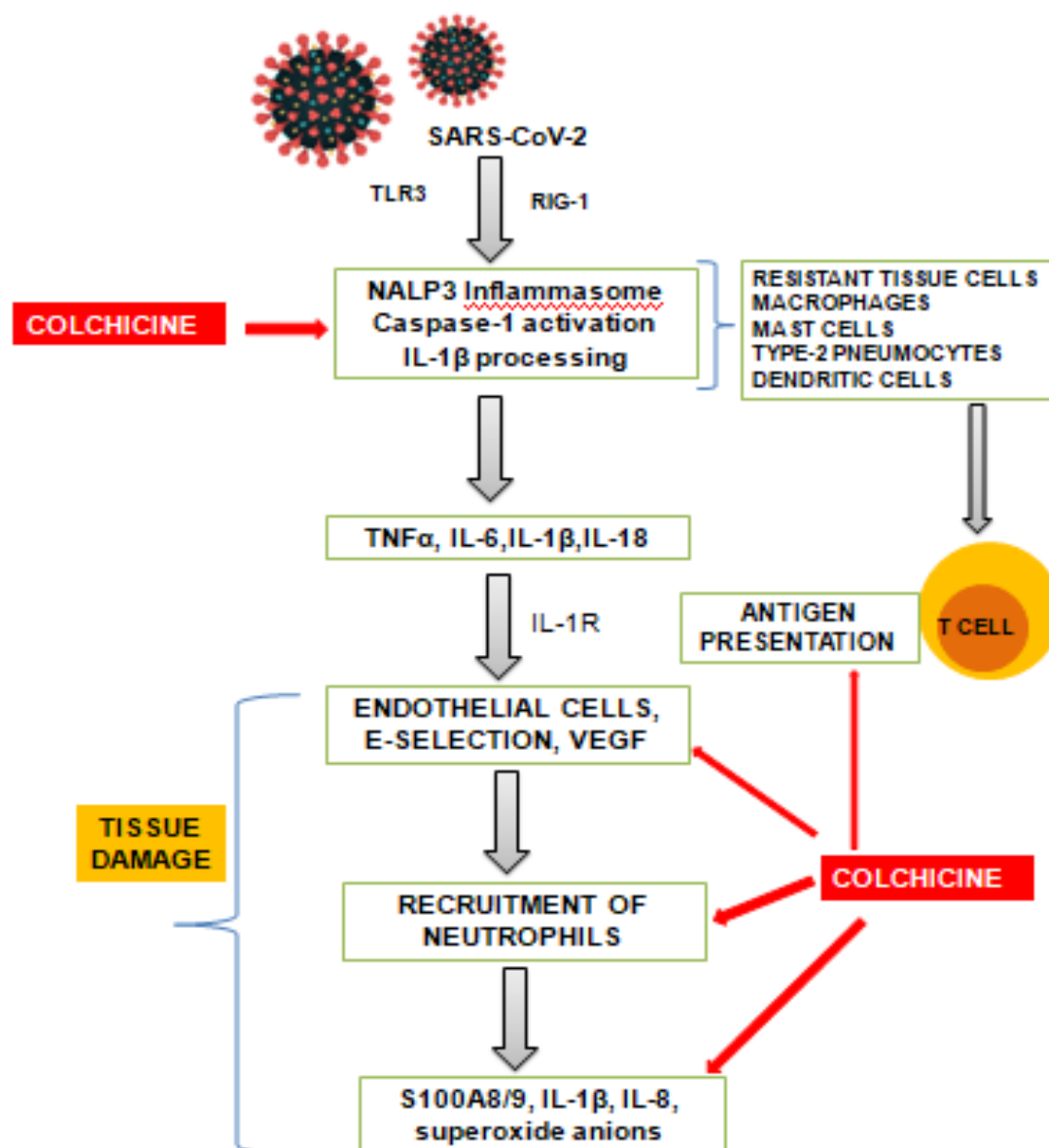


Figure 2: Colchicine: i. Reduces proinflammatory cytokines, lipopolysaccharide induced secretion of TNF α , IL1, IL6 (two generations), ii. NALP3 inflammasome block.

Methods

For this systematic review, research papers were searched using PubMed, Embase, the Cochrane Central Register of Controlled Trials, medRxiv, and researchsquare.com. The keywords used were – COVID 19, colchicine, SARS-CoV-2 and clinical outcome. Studies published between January 2020 and December 2021 were evaluated and screened to identify those that had reported the effect of colchicine in

SARS CoV 2 infected patients and assess clinical outcomes including mortality, intensive care unit (ICU) admissions, or mechanical ventilation.

Analysing Clinical Studies

We had found 8 clinical studies where adjusted relative risk ratios were mentioned. In **Table 1** we had mentioned study design, sample size, ICU stay at enrolment, measured outcomes and relative risks.

Table 1: Brief Summary of Different Clinical Studies with Colchicine Conducted in COVID 19 Patients (ICU – Intensive Care Unit, CI – Confidence Interval, RCT – Randomized Control Trial)

Clinical Study	Study design	Sample size	Measured outcomes	Relative risks (CI)
Brunetti <i>et al.</i> , 2020	Cohort Study	66	Mortality, Mechanical Ventilation, Clinical Deterioration	0.21 (0.06 – 0.71)
Deftereos <i>et al.</i> , 2019	RCT	105	Mortality, Mechanical Ventilation, ICU Admission	0.28 (0.04 – 1.88)
Lopes <i>et al.</i> , 2020	RCT	35	Mortality, ICU Admission, ICU length of stay	0.20 (0.01 – 4.31)
Mareev <i>et al.</i> , 2021	RCT	43	Mortality, length of stay, Symptomatic Hospital and Outpatient Clinical Scale for COVID-19 (SHOCS-COVID) score	0.21 (0.01 – 4.61)
Recovery (Randomised Evaluation of COVID-19 Therapy) Trial, 2021	RCT	11,162	28 day mortality	1.01 (0.93 – 1.10)
Rodriguez-Nava <i>et al.</i> , 2020	Retrospective Study	87	Mortality, Hospital discharge	0.41 (0.17 – 0.98)
Scarsi <i>et al.</i> , 2020	Retrospective Study	262	Mortality	0.15 (0.06 – 0.37)
Tardif <i>et al.</i> , 2021	RCT	4488	Mortality, Hospitalization, Mechanical Ventilation	0.56 (0.19 – 1.66)

Among the depicted clinical studies of colchicine for managing COVID 19 patients, only Rodriguez-Nava *et al.*, had included ICU patients and Tardif *et al* RCT had included non-hospitalized patients during enrolment. All other studies had included hospitalized non ICU patients during enrolment. Apart from Recovery trial all other studies were showing benefit in favour of colchicine Statistical significance with 3 of them. (Scarsi *et al*, 2020; Rodriguez-Nava *et al*, 2020; Brunetti *et al*, 2020).

In one systematic review and meta-analysis it was established that excluding RECOVERY trial considering the other clinical researches colchicine receiving patients had a lower risk of mortality with a hazard ratio (HR) of 0.25 (95 % CI: 0.09 – 0.66) and odds ratio (OR) of 0.22 (95 % CI: 0.09 – 0.57). In considering the risk of ICU admissions it was found that there was no statistical difference between patients receiving colchicine with COVID-19 and those who were not with an OR of 0.26 (95 % CI: 0.06 – 1.09) (Chiu *et al*, 2021).

Another meta-analysis had shown significantly reduced mortality in colchicine group (OR 0.35, 95 % CI: 0.25-0.48 and I². 0 %) compared with placebo (Elshafei *et al*, 2021). This systematic review and meta-analysis was conducted with published reports of observational studies, only few RCTs were included. One RCT conducted in Russia was excluded from final meta-analysis as OR was not calculated due to zero death in colchicine arm. Colchicine versus Ruxolitinib and Secukinumab in Open Prospective Randomized Trial (COLORIT 2021) was a quasi-randomized trial, conducted in moderate to severe COVID 19 in-patients. In control group 2 patients (9.09 %) died whereas in colchicine group no death was reported (Mareev *et al.*, 2021). Colchicine 0.5 mg twice daily for 10 days or until discharge on top of other drugs as recommended by standard of care was followed in most of the trial.

Discussion

Colchicine is indicated to treat acute gout flare and familial Mediterranean fever. Though mechanism is not completely understood, it is hypothesised that it inhibits intracellular assembly of inflammasome complex which activates interleukin-1 β present inside neutrophils and monocytes. Apart from that colchicine also inhibits of β -tubulin polymerization into microtubules followed by interference with cytoskeletal functions. This event leads to prevention of activation, degranulation, and migration of neutrophils. SARS CoV 2 infection related cytokine release syndrome, which plays a critical role in determining morbidity and mortality, is developed due to activation of NLRP3 inflammasome (Nieto-Torres *et al.*, 2015). This is why colchicine could be beneficial in preventing this activation.

Timing of initiating colchicine therapy was varying in different studies. In Tardiff *et al.*, 2021, colchicine was initiated pre-hospitalized, while in Brunetti *et al.*, 2020, Deftereos *et al.*, 2019, Lopes *et al.*, 2020 and Scarsi *et al.*, 2020, colchicine use was on hospitalized non-ICU patients and in Rodriguez-Nava *et al.*, 2020, it was initiated post ICU admission. It is therefore important to consider heterogeneity of the studies conducted, population included and parameters studied; we need well designed RCTs including high risk population to study efficacy and safety of colchicine.

COVID 19 infection and associated inflammatory state produce a prothrombotic state. There is rise in fibrin, fibrin degradation products, fibrinogen, and D-dimers (Samajdar *et al.*, 2020). Colchicine has an antithrombotic property. In a systematic review and meta-analysis, it was found that in patients suffering from atherosclerotic cardiovascular disease, colchicine reduced risk of stroke (Katsanos *et al.*, 2021). Colchicine was found to be beneficial in Behcet's diseases where inflammation playing the pivotal role to develop thrombus (Nonaka *et al.*, 2020). In this background colchicine therapy could be ameliorating COVID 19 outcome.

Conclusion

Though number of COVID 19 cases had gone down, but in India we are expecting the development of fourth wave as already it had landed in various part of world. Epidemiologists are confident that COVID 19 would be staying with us and could have potential to produce endemic in future in different parts of world. Colchicine, as a cheap anti-inflammatory without much immunosuppressive action can be expected to help us as a potential therapeutic option to prevent morbidity and mortality associated with COVID 19. Researchers need to consider focused study design to explore efficacy and safety of this molecule for final comment.

Conflict of Interest

The authors declare having no conflict of interest.

Abbreviations

SARS-COV 2 -Severe Acute respiratory Syndrome – Coronavirus

NF κ B: Nuclear factor κ B

ROS: Reactive oxygen species

IFN: interferon

TBCs: tubulin cofactors

VEGFs: Vascular Endothelial Growth Factors

TNF: Tumor necrosis factor

IL – Interleukin

NLRP3- NOD, LRR and Pyrin 3 containing protein

P2X7- Purinergic Ionotropic Receptor Antagonist

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