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Effect of colchicine and aspirin given together in patients with moderate COVID-19

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ABSTRACT

Background: The objective of the study was to evaluate the effect of Colchicine 0.5 mg and Aspirin 75 mg oral tablets given together on management of moderate COVID-19.
Methods: The study was carried out in 122 moderate COVID-19 patients between ages 40–80 years in hospital, instructed to take either 1 tablet of Colchicine 0.5 mg and Aspirin 75 mg each (treatment group), or 1 tablet of Aspirin 75 mg (Control group), twice a day along with standard of care.
Result: At the end of treatment, reduction was seen in the treatment group in score of 8-point ordinal scale, troponin, D-Dimer, Hs-CRP from baseline. There was a fall of 51.1% among control arm and 53.4% among treatment arm in 8-point ordinal score. The reduction in mean D-Dimer was 37% in control group and 38.1% in treatment group. The mean reduction in CT severity score in control group was 3.65 and in treatment group was 4.82, and the difference between the two groups was statistically significant (P value = 0.018)
Conclusion: It was evident from CT scan scores that the treatment group has shown significant improvement in the reduction of inflammation and other COVID-19 symptoms as compared to the control group. The fall in Ferritin, Hs-CRP and D-Dimer level after treatment were indicative of improvement in internal inflammatory response of body in COVID-19 disease. As increased troponin levels indicate some degree of heart damage, the fall in troponin levels indicated that test treatment improved heart health in COVID-19 patients.

1. Introduction

A viral disease caused by a novel coronavirus, SARS-CoV-2, originated in the Wuhan district of China in the beginning of December 2019. This became a pandemic of respiratory illness and came to be known as corona virus disease 2019 (COVID-19). The COVID-19 disease can be mild, self-limiting respiratory tract illness or can progress to moderate to severe disease characterized by pneumonia, multi organ failure, and death. In October 2020, remdesivir was approved by the FDA for use in adult and pediatric patients (≥12 years old; weighing ≥40 kg) for the treatment of COVID-19 requiring hospitalization [1]. However, though several trials are ongoing, no specific therapeutic agents were approved for the treatment of mild to moderate corona virus infections [2].

SARS-CoV-2 interacts with the immune system and the subsequent dysfunctional immune responses lead to disease progression [3]. Aggressive inflammatory response, mostly in form of pro-inflammatory cytokines and chemokines (including IL-6, IP- 10, MIP1α, MIP1β and MCP1) contribute to damaged airways and other organs [4]. Additionally, IL-1β, IL-6 and IL-8 have been postulated to cause hyper coagulation that leads to scattered fibrin clots [5]. Therefore, disease severity in COVID-19 is not just due to viral infection but also because of host's (patient's) inflammatory response to viremia. Additionally, SARS-CoV-2-mediated micro- and macro vascular thrombosis in multiple organs is an important indication of disease progression and occurs due to over activation of the coagulation cascade and platelet aggregation [6–8].

Preliminary results on anticoagulant therapy in moderate and severe COVID-19 patients with signs of coagulopathy appear to be associated with better outcomes; anticoagulation also shows improved outcomes in COVID-19 patients requiring mechanical ventilation. Hence, drugs/medications that have anti-inflammatory and anti-thrombotic effect are likely to help halt or slow or maybe reverse SARS-CoV-2- mediated disease progression [4].

With the advent of COVID-19 and understanding that thrombosis and coagulopathy with cardiac and pulmonary inflammation are few key clinical features of the COVID-19, there have been trials evaluating

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repurposing of available anticoagulants. In comparison to that there are far less trials conducted for anti-inflammatory agents and for a combination of anti-inflammatory and anticoagulant agents [9].The existing treatment options like LMWH (Low molecular weight heparin), enoxaparin have to be given in form of intravenous or sub-cutaneous injections which may cause more discomfort to the patients as compared to oral formulations, especially in patients with mild or moderate symptoms. The oral formulations like lopinavir/ritonavir have their own set of adverse effects ranging from diarrhea, nausea to metabolic derangements, including hyperlipidemia and glucose intolerance [10].

Colchicine, an anti-inflammatory agent, has been approved for treatment of inflammatory conditions. Colchicine also has anti-fibrotic activities and affects the endothelial function in multiple ways, thereby finding use in osteoarthritis, pericarditis and atherosclerosis [11]. Aspirin or acetylsalicylic acid (ASA) has been approved in inflammatory conditions and in prevention of thrombotic conditions.

Aspirin is also an analgesic and antipyretic [12].

Colchicine has been approved to treat gout and Familial Mediterranean fever (FMF). Colchicine is also being used off-label with a good efficacy and safety profile for the treatment of other inflammatory conditions such as pseudo-gout (acute calcium pyrophosphate arthritis), sarcoid and psoriatic arthritis, Behcet's disease, and pericarditis [13]. Low-dose colchicine (0.5 mg once daily) has proved to be effective in preventing major cardiovascular adverse events after a recent myocardial infarction [14]. Aspirin has been approved for relief of pain associated with headache, arthritis, backache and fever [15]. Extended release Aspirin has been approved for secondary prevention of stroke and acute cardiac events such as myocardial infarction in high-risk patients [16,17].

Since, colchicine had a strong anti-inflammatory action with an acceptable safety profile, several trials were initiated with the hypothesis that colchicine might be an effective and safe anti-inflammatory for the treatment of COVID-19. Similarly, aspirin is being tried in various clinical trials either alone or in combination with other drugs for the treatment of COVID-19.

The anti-inflammatory action of colchicine and aspirin and antithrombotic properties of Aspirin have shown positive effects in clinical trials in COVID-19 patients [18–20].

Colchicine and aspirin are cheap drugs and likely to provide an affordable treatment for moderate COVID-19 disease if proved to be efficacious and safe in this setting. In this study fixed doses of colchicine (0.5 mg) and aspirin (75 mg) will be given twice daily at the same time and if found efficacious and safe in moderate COVID-19 disease will become the rationale for developing fixed dose combination of colchicine (0.5 mg) and aspirin (75 mg).

2. Material and methods

2.1. Ethical principles and consent to participate

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). In addition, the study followed ethical principles in ICH-GCP Guidelines, ethical guidelines of Indian Council of Medical Research, New Delhi.

Trial subjects were given participant informed consent document in vernacular language containing trial related information. Informed consent was obtained from all the trial subjects before any trial procedure was conducted.

2.2. Clinical trial sites

The study was conducted at two sites, the Government General Hospital, Srikakulam in Southern India and SRV hospital, Chembur located in the city of Mumbai in Western part of India.

The study was approved by the "Institutional Ethics Committee Government Medical College and Government Hospital, Srikakulam" (ECR/492/Inst/AP/2013/RR-19) and "Institutional Ethics Committee Center for Research SRV Hospital, Mumbai, India" (ECR/1459/Inst/MH/2020).

2.3. Study participants

40–80 year old subjects with positive RT-PCR test result for Sars-CoV2 (No older than 2 days), diagnosed with COVID-19 with moderate symptoms within 4 days, with at least one of the risk factors for developing severe symptoms of COVID-19 (age more than 65 years, type 2 diabetes mellitus, obesity (BMI $\geq$30), moderate to severe asthma, smoking (current or former), cancer (active history), Chronic Obstructive Pulmonary Disease (COPD), chronic heart disease (CHF, CAD, cardiomyopathy, pulmonary hypertension) were included in the study. The moderate symptoms were characterized with presence of cough, weakness/fatigue, sore throat, fever $>38.5^0$C, clinical signs of pneumonia as per investigator and features of dyspnea/hypoxia including respiratory rate $\geq$24/min, resting SpO2$<$94% (range 90–94%) on room air. The study excluded patients with signs of dehydration, chronic diarrhea, severe acidity, peptic ulcer disease, history of GI bleed or other known contraindications for aspirin, sepsis. The study also excluded patients with known history of organ failure or conditions requiring ICU monitoring, deep vein thrombosis, pulmonary embolism, stroke, atrial fibrillation, mechanical heart valve, recent stent placement or any other cardiovascular event or any other condition for which the patient is taking systemic anticoagulation/antiplatelet therapy. Pregnant, lactating women and those who didn't want to take contraception during the study were excluded.

2.4. Study design

The study was designed as an open label, two arm, parallel, randomized study. The subjects were randomized in a 1:1 ratio to either treatment arm (colchicine 0.5 mg tablet + aspirin 75 mg tablet), or control arm (aspirin 75 mg tablet). Subjects were given the assigned treatments twice a day. The trial allowed Standard Of Care (SOC) as directed by government in both the arms in the trial. The study however, prohibited the use of anticoagulants and corticosteroids. If a subject was required to be given any of the prohibited therapy as part of SOC, that subject was excluded from the analysis.

The study was designed to be conducted for 15 days with 4 visits, visit 1 or screening visit at day −1 followed by three visits that the center considered as "study visits" on days 1, 7 and 15. If subject was discharged before day 15 (as per PI's discretion based on patient's health condition), then discharge day was to be considered as last day of study treatment and assessments scheduled for Day 15 were to be carried out on the discharge day.

2.5. Outcome measures

National Early Warning Score (NEWS), 8-point ordinal scale score, composite Major Adverse Event (MAE) score and inflammatory cardiac biomarkers like, Hs-CRP, D-dimer, Ferritin and Troponin were assessed on baseline (day 1), day 7 and End of Trial (EOT, discharge day) to assess the efficacy of treatment in managing inflammatory and thrombotic condition in moderate COVID-19. Change in the 8-point ordinal scale score was to be considered as primary outcome variable. The patients were scored based on their health status as follows: Score 1 meant patient: not hospitalized (discharged from hospital) and no limitations of activities written on discharge order. Score 2 meant patient: not hospitalized (discharged from hospital), with discharge order mentioning limitation of activities, home oxygen requirement, or both. Score 3 meant patient: hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons).

Score 4 meant patient: hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions). Score 5 meant patient: Hospitalized, requiring any supplemental oxygen. Score 6 meant patient: Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices. Score 7 meant patient: Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Score 8 meant patient's death.

Assessments of adverse events, ECG, CT scan and various laboratory parameters including CBC, ESR, liver function test, renal function test, prothrombin time, INR, routine urinalysis etc. were done at screening and EOT visit to assess safety of the treatment.

2.6. Subject Disposition

A total of 122 participants, found eligible based on all inclusion/exclusion criteria were included in trial. Out of these 17 subjects were given enoxaparin (anticoagulant) as part of SOC according to govt. guidelines. Since, anticoagulant therapy was prohibited in the trial, the 122 participants comprised of Intent to treat population with 58 subjects in aspirin 75 mg group and 64 subjects in colchicine 0.5 mg + aspirin 75 mg group. These 17 subjects were excluded to create per protocol population i.e. PP population (105 subjects from total 122 subjects). (Fig. 1).

3. Results and discussion

3.1. Effect on 8-point ordinal score

A reduction in 8-point ordinal score would mean improvement in health status of a patient. At baseline, mean 8 Point Ordinal score was found to be 3.95 in control arm and 4.06 in the treatment arm. At the end of treatment, there was a reduction of 51.1% in control arm and 53.4% in the treatment arm in 8-point ordinal score from baseline, indicating a better improvement in the treatment group. The improvement from baseline to end of treatment within group was statistically significant (Table 1).

In the statistical analysis within ITT population, similar results were observed. At baseline, mean 8 Point Ordinal score was found to be 3.97 in control arm and 4.06 in the treatment arm. At the end of treatment, there was a reduction of 50.9% in control arm and 53.4% in the treatment arm in 8-point ordinal score from baseline. The change was comparable in both the groups and the difference was not significant.

Along with mean score, proportion of cases with reduction in high 8-point ordinal score at baseline were compared between two groups. At baseline, **100%** of the cases in control arm had score "4" as compared to **95.2%** in treatment arm. The treatment arm had cases which had more severity as compared to the control arm. 2 of the subjects in the treatment arm, had 8-point ordinal score as 5 and 1 subject had the score as 6. At the end of treatment, **100.0%** of the cases in control arm and **98.4%** of the cases in treatment arm had "1 or 2" score which showed a significant decrease among both the groups from baseline (Table 2). The difference between the two arms was not statistically significant. Similar results were observed in ITT population as well where at the baseline all 58 cases in control arm had a score of 4 and by end of trial 100% of cases had a score of 1 or 2. Whereas in the treatment arm, 1 (1.6%) of the case had a score of 6 and 2 (3.6%) cases had a score of 5 at baseline, with rest of the 95.3% cases having a score of 4. The recovery in 98.4% proportion of cases could be explained by the death in the treatment arm, which was found to be unrelated to the study drug. Similar results were seen in composite MAE and NEW score.

3.2. Disease progression as per National Early Warning Score

When rate of progression to severe COVID-19 was assessed as per NEWS, 2.3% cases in the control group had progressed to severe COVID-19 during the course of study as compared to 4.8% cases in the treatment arm. By end of trial, all the cases but 1 death case in treatment group had improvement in health status and were discharged (Table 3). While it is true that in treatment arm 1 subject died for reasons unrelated to the treatment, two others worsened, the difference between the two arms was not statistically significant.

The analysis for ITT population revealed that by end of treatment there was disease progression in 1.7% of cases in control arm, and in 4.8% of cases in treatment arm.

3.3. Mean troponin level in blood

As increased troponin levels indicate some degree of heart damage, the fall in troponin levels was indicative of efficacy of aspirin and colchicine in improvement of heart health in COVID-19 patients.

At baseline, mean troponin was found to be 0.03 ng/mL in aspirin 75 mg as well as in colchicine 0.5 mg + aspirin 75 mg, and the difference was not statistically significant. At the end of treatment, mean troponin showed a significant fall of 33.3% in both the groups from baseline. If compared, the change was same in both the groups and the difference was not significant (Table 4). The same result was also found in the ITT population.

3.4. Mean D-dimer level

As per the trial data, the baseline mean value of D-Dimer was 756.60 ng/mLin aspirin 75 mg group and 686.38 ng/mL in colchicine 0.5 mg + aspirin 75 mg group but the difference was not statistically significant.

At the end of treatment, a significant fall from baseline in mean D-dimer in both the groups was seen. There was a reduction of 37.0% in aspirin 75 mg group and 38.1% in colchicine 0.5 mg + aspirin 75 mg group from baseline. When compared between the two groups, the reduction in D-dimer level was not significant (Table 4).

The statistical analysis of ITT population showed that at end of treatment, a significant fall from baseline in mean D-dimer in both the groups was seen. There was a reduction of 38.5% in aspirin 75 mg group and 39.2% in colchicine 0.5 mg + aspirin 75 mg group from baseline.

3.5. Effect on other inflammatory biomarkers (Hs-CRP and ferritin)

With respect to change in mean ferritin level from baseline to EOT, in PP population, at the end of treatment, an insignificant fall of 11.8% within aspirin 75 mg group and 4.1% in colchicine 0.5 mg + aspirin 75 mg group from baseline was seen. The difference between the two groups was not significant. Similar results were seen in ITT population at the end of treatment. There was an insignificant fall of 10.1% within aspirin 75 mg group and 4.6% in colchicine 0.5 mg + aspirin 75 mg group from baseline.

On comparing change in mean Hs-CRP level from baseline to EOT, in PP population, at the end of treatment a significant fall of 72.7% in aspirin 75 mg group and 69.9% in colchicine 0.5 mg + aspirin 75 mg group from baseline was seen. The difference between the two groups was not statistically significant. In the ITT population, at the end of treatment a significant fall of 72.6% in aspirin 75 mg group and 70.2% in colchicine 0.5 mg + aspirin 75 mg group from baseline was seen.

The fall in Ferritin, Hs-CRP and D-Dimer level after treatment were indicative of improvement in internal inflammatory response of body in COVID-19 disease.

3.6. Effect on hospital stay

The mean no. of days of hospital stay in colchicine aspirin arm (N = 42) was 6.57, and for aspirin arm (N = 56) it was 6.95 in PP Population (removing ICU admissions). In case of ITT population, the mean no. of days of hospital stay in colchicine aspirin arm was 6.95, and for aspirin arm it was 6.96. The difference between the two groups was not

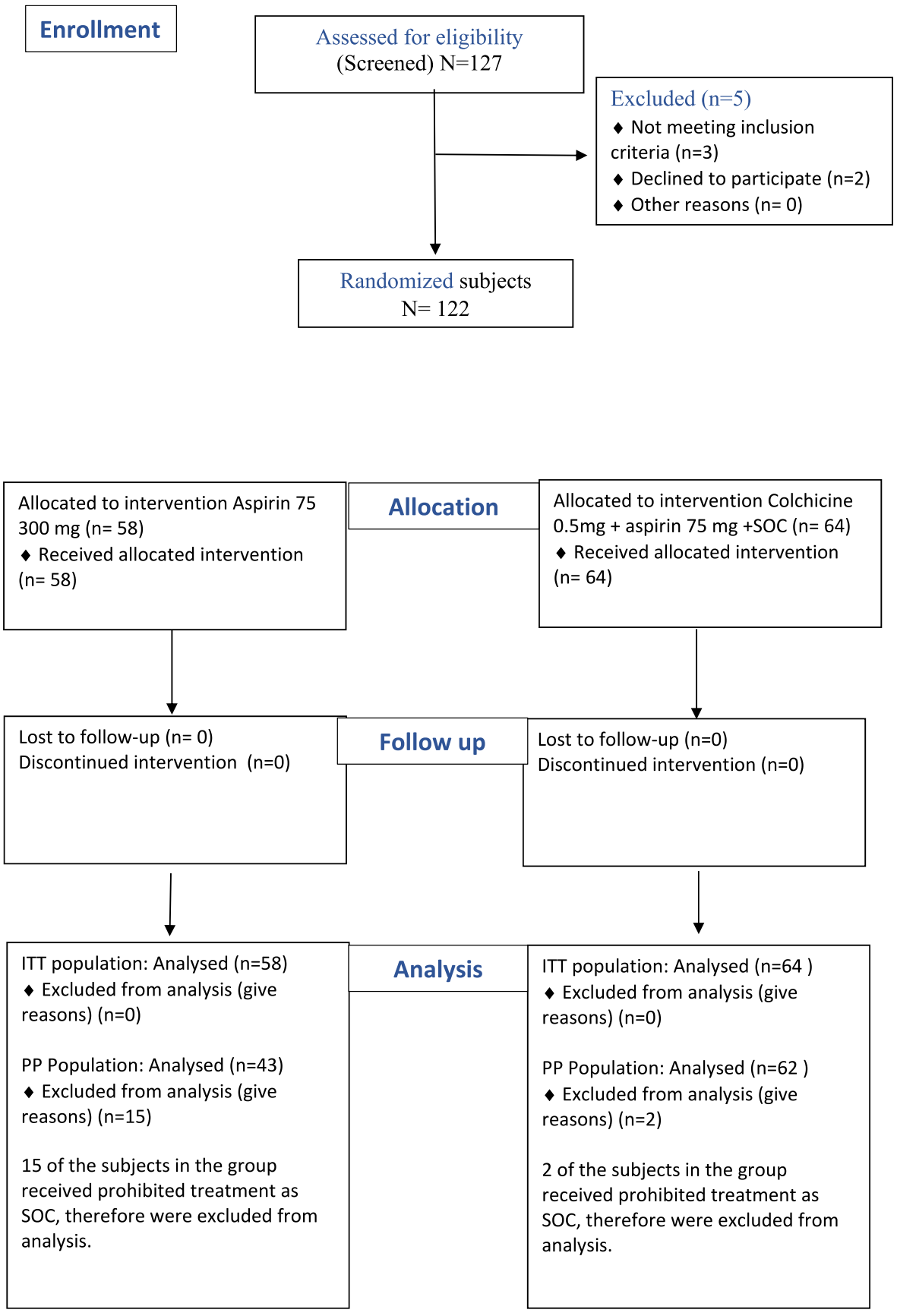

Fig. 1. Subject Disposition CONSORT Diagram.

Table 1
Comparison of changes in mean 8-point ordinal score between two groups.

Duration	Mean 8-Point Ordinal Score ($\overline{X} \pm SD$)		P value
	Aspirin 75 mg (N = 43)	Colchicine 0.5 mg + Aspirin 75 mg (N = 62)	
Baseline	3.95 ± 0.30	4.06 ± 0.31	0.541 (NS)
End of Treatment	1.93 ± 0.26	1.89 ± 0.89	
Mean diff (Baseline – End of Treatment) (p value)	*-2.02 ± 0.41 (0.001)	*-2.18 ± 0.74 (0.001)	0.207 (NS)

By Wilcoxon Sign Rank Test × Significant.
By Mann Whitney *U* Test NS = Not Significant.
$\overline{X} \pm SD$ = Mean + Standard Deviation.

Table 2
Comparison of changes in proportion of cases with 8-point ordinal score between two groups.

Scores	Proportion of cases with 8-Point Ordinal Score							
	Aspirin 75 mg (N = 43)				Colchicine 0.5 mg + Aspirin 75 mg (N = 62)			
	Baseline		End of Treatment		Baseline		End of Treatment	
	No	%	No	%	No	%	No	%
0	–	–	–	–	–	–	–	–
1	–	–	03	07.0	–	–	13	21.0
2	0	–	40	93.0	–	–	48	77.4
3	–	–	–	–	–	–	–	–
4	43	100	–	–	59	95.2	–	–
5	–	–	–	–	02	03.2	–	–
6	–	–	–	–	01	01.6	–	–
7	–	–	–	–	–	–	–	–
8	–	–	–	–	–	–	01	01.6
P Value			*0.001				*0.001	

By Chi Square Test Between groups P = 0.402, Not Significant, *Significant.

Table 3
Profile of rate of progression to severe as per NEW score between two groups.

Groups	Proportion of cases	
	No	%
Aspirin 75 mg (N = 43)	01	2.3
Colchicine 0.5 mg + Aspirin 75 mg (N = 62)	03	4.8

By Chi Square Test P = 0.508, Not Significant.

significant.

3.7. Exploratory analysis/effect on CT value

The study included the exploratory efficacy analysis of CT score with selective grouping to even out the groups (41 in each group – where we had selected all CT scan values over 7 and above in col-asp group). This grouping was done excluding the patients that were given enoxaparin. Further, the analysis was done to evaluate the superiority of colchicine 0.5 mg + aspirin 75 mg over aspirin 75 mg given individually. It was evident from CT scan scores that the treatment group has shown significant improvement in the reduction of inflammation and other COVID-19 symptoms as compared to the control group. It's important to note that the treatment group had few patients with more severity than the control group at baseline. Based on CT score analysis, inference could be drawn that the treatment group showed significant improvement in the reduction of inflammation and severity of symptoms. The difference in the reduction of CT severity score was found to be

Table 4
Comparison of changes in mean troponin and mean D-dimer between two groups.

Duration			P value
	Aspirin 75 mg	Colchicine 0.5 mg + Aspirin 75 mg	
MEAN TROPONIN ($\overline{X} \pm SD$)			
N	41	61	
Baseline	0.03 ± 0.01	0.03 ± 0.01	1.000 (NS)
End of Treatment	0.02 ± 0.01	0.02 ± 0.01	
Mean diff (Baseline – End of Treatment) (p value)	*-0.01 ± 0.01 (0.001)	*-0.01 ± 0.01 (0.001)	1.000 (NS)
Mean D-DIMER ($\overline{X} \pm SD$)			
N	42	60	
Baseline	756.60 ± 232.02	686.38 ± 149.49	0.087 (NS)
End of Treatment	477.00 ± 571.23	424.72 ± 159.50	
Mean diff (Baseline – End of Treatment) (p value)	*-279.60 ± 418.13 (0.001)	*-261.67 ± 237.15 (0.001)	0.802 (NS)

By Student 't' Test × Significant NS = Not Significant.

statistically significant (P < 0.05) which is a good indicator that this combination is working very well in the moderate to severe COVID-19 population (Table 5).

3.8. Safety analysis

All subjects who were randomized, received at least one dose of study drug and provided at least one post-baseline efficacy measurement were included in safety analysis.

During the course of the trial, death of 1 subject at SRV hospital happened. PI deemed the death as a complication of COVID-19 and ruled out the possibility of death being associated with the investigational product. Other adverse events reported were of mild severity and included cases of vertigo, mouth ulcers and rashes in both treatment as well as control arm. There were two cases of abdominal pain reported in treatment arm. All of these adverse events were resolved by end of study, and those reported in treatment arm were found to be not related with the investigational product.

3.9. Limitations in the trial

In both the groups for few subjects certain biomarkers were not available (d-dimer, Hs-CRP). We considered these protocol deviations different/unrelated from NEW score, hence these subjects were included for NEWS analysis, but not for d-dimer/Hs-CRP analysis. In NEWS analysis and pulse oximetry, 1 more subject was excluded (the death case) as subject had maximum NEW score which would have completely skewed the data analysis towards one arm.

4. Conclusion

The reduction in 8-point ordinal score, composite MAE score, NEWS score by the EOT indicates improvement in condition of study population.

The data shows that 100% of cases in aspirin arm showed meaningful

Table 5
Comparison of Reduction in CT scan score (PP Population).

Mean Reduction of CT report score from Screening to EOT		
Aspirin 75 mg (N = 41)	**Colchicine 0.5 mg + Aspirin 75 mg (N = 41)**	P value = 0.01854[a]
3.65	4.82	

[a] Significant.

reduction in 8 point- ordinal score but not in the colchicine aspirin arm. This can be explained by the death case in colchicine aspirin arm. The colchicine aspirin arm does not show 100% cases to have reduced 8-point ordinal score due to death of a subject during trial, which was found to be unrelated to the study drug. In addition to this, in colchicine aspirin arm there were more severe cases as indicated by 8-point ordinal score at baseline. The data also shows that the rate of progression in colchicine aspirin arm was higher during the trial, it is important to note that before the end of trial all the cases, except 1 death case (unrelated to trial product), had recovered and were discharged. The data also shows that colchicine aspirin arm treated more number of patients those were more severe in condition as compared to the aspirin arm.

The symptomatic severity led to exploration of diagnostic severity through CT scan of subjects. In the period when this trial was conducted the focus of government medical authorities shifted to hospital admission of COVID-19 patients, not only based on symptomatic severity but also through diagnostic severity. The hospital admissions were later based on CT severity score in many parts of the country. The focus on CT severity and availability of the same for trial led to the exploratory analysis of CT severity score. Reduction in CT severity score from baseline, which was found to be more in colchicine aspirin group as compared to aspirin 75 mg group, indicated efficacy of colchicine and aspirin given together in management of respiratory distress caused in COVID-19 disease in moderate COVID-19 patients with co-morbidities.

The reduction in mean D-dimer level in blood, was found to be more in colchicine + aspirin group than aspirin group which indicates the efficacy of colchicine and aspirin given together in reducing internal inflammation and improving health in moderate COVID-19 patients with co-morbidities.

There were several other parameters that showed improvement in subjects in this trial, although a statistically significant difference was not found in comparison between colchicine + aspirin group and aspirin group. No clinically significant change was seen in the safety laboratory parameters for active or control group.

The analysis of the study parameters showed the efficacy of colchicine 0.5 mg and aspirin 75 mg in symptomatic management of moderate COVID-19 and was found to be safe at the tested dose in this study.

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Authors' contributions

Dr. K. Sunil Naik contributed as principal investigator of the study. Mr. Niranjan Andhalkar contributed by managing overall clinical trial process. Mr. Sohal Pendse contributed in clinical trial operations overview, data review, analysis overview, Data interpretation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.The study has been funded by ROMEG therapeutics LLC n but there is no financial interest to disclose related to trial results and manuscript writing/reviewing/publishing.

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References

[1] Office of the Commissioner FDA, FDA approves first treatment for COVID-19. FDA, Published October 22, 2020, https://www.fda.gov/news- events/press-announcements/fda-approves-first-treatment-covid-19. (Accessed 10 November 2020).
[2] B. Cao, Y. Wang, D. Wen, et al., A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19, N. Engl. J. Med. 382 (19) (2020) 1787–1799, https://doi.org/10.1056/NEJMoa2001282.
[3] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (6) (2020) 363–374, https://doi.org/10.1038/s41577-020-0311-8.
[4] C. Godino, A. Scotti, N. Maugeri, et al., Antithrombotic therapy in patients with COVID-19? - rationale and evidence-, Int. J. Cardiol. (2020), https://doi.org/10.1016/j.ijcard.2020.09.064, 0(0).
[5] J. Bester, C. Matshailwe, E. Pretorius, Simultaneous presence of hypercoagulation and increased clot lysis time due to IL-1β, IL-6 and IL-8, Cytokine 110 (2018) 237–242, https://doi.org/10.1016/j.cyto.2018.01.007.
[6] Violi F. BianconiV, F. Fallarino, P. Pignatelli, Pirro M. SahebkarA, Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? Drugs 80 (14) (2020) 1383–1396, https://doi.org/10.1007/s40265-020-01365-1.
[7] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, J ThrombHaemost 18 (6) (2020) 1421–1424, https://doi.org/10.1111/jth.14830.
[8] D. Giannis, ZiogasIA, P. Gianni, Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past, J. Clin. Virol. 127 (2020), 104362, https://doi.org/10.1016/j.jcv.2020.104362.
[9] Krishna Sriram, A. Paul, Insel Inflammation and thrombosis in COVID-19 pathophysiology: proteinase-activated and purinergic receptors as drivers and candidate therapeutic targets, Physiol. Rev. 101 (2) (2021) 545–567.
[10] A. Chandwani, J. Shuter, Lopinavir/ritonavir in the treatment of HIV-1 infection: a review, Therapeut. Clin. Risk Manag. 4 (5) (2008) 1023–1033, https://doi.org/10.2147/tcrm.s3285.
[11] Y.Y. Leung, L.L. Yao Hui, V.B. Kraus, Colchicine-Update on mechanisms of action and therapeutic uses, Semin. Arthritis Rheum. 45 (3) (2015) 341–350, https://doi.org/10.1016/j.semarthrit.2015.06.013.
[12] H. Arif, S. Aggarwal, Salicylic acid (aspirin), in: StatPearls. StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK519032/. (Accessed 15 December 2020).
[13] N. Schlesinger, B.L. Firestein, L. Brunetti, Colchicine in COVID-19: an old drug, NewUse, CurrPharmacol Rep (2020) 1–9, https://doi.org/10.1007/s40495-020-00225-. Published online July 18.
[14] J.-C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, N. Engl. J. Med. 381 (26) (2019) 2497–2505, https://doi.org/10.1056/NEJMoa1912388.
[15] FDA, FDA: center for drug evaluation and Research; labelling of aspirin, Food and Drug Administration (2013). Published, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203697Orig1s000Lbl.pdf.
[16] R. Marotta, New aspirin formulation nabs FDA approval, Pharmacy Times. Published2015. (2020). https://www.pharmacytimes.com/news/fda-approves-novel- aspirin-formulation. (Accessed 15 December 2020).
[17] Healio, FDA approves ticagrelor-aspirin DAPT to reduce MI, stroke in CAD. Healio, Published, https://www.healio.com/news/cardiology/20200601/fda-approves-ticagreloraspirin-dapt-to-reduce-certain-events-in-cad, 2020. (Accessed 15 December 2020).
[18] S.G. Deftereos, G. Giannopoulos, VrachatisDA, et al., Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019, JAMA Netw. Open 3 (6) (2020), https://doi.org/10.1001/jamanetworkopen.2020.13136.
[19] M.I.F. Lopes, L.P. Bonjorno, M.C. Giannini, et al., Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial, medRxiv (2020), https://doi.org/10.1101/2020.08.06.20169573. Published online. (Accessed 12 August 2020), 08.06.20169573.
[20] J.H. Chow, A.K. Khanna, S. Kethireddy, et al., Aspirin Use Is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19, Anesthesia & Analgesia, 2020, https://doi.org/10.1213/ANE.0000000000005292. Publish Ahead of Print.