Efficacy and Tolerability of Curmune Formulation in the Management of COVID-19: A Randomised Comparative Clinical Study

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Abstract

Background: COVID-19 outbreak is a global threat, with lack of vaccines and antiviral medicine exaggerating the issue further. The Centers for Disease Control and Prevention recommend maintenance of personal hygiene as a modality to reduce chances of infection. Yet, another way is by improving the immunity. Viral infections are depended on body's natural defences. Authors of current paper have studied the formulation containing proprietary blend of natural ingredients viz. Curcumin, Vitamin C, and Zinc based on their individual reported activities against SARS-CoV-2's peptide.

Objective: To evaluate role of Curmune Tablets in the management of SARS-CoV-2 Infection (COVID-19) and its tolerability in comparison with standard treatment protocol designed by Ministry of Health and Family Welfare (MOHFW).

Study design: In a randomized study, 100 patients tested positive for COVID-19 were enrolled during the month of September to December 2020 from Vakratund Hospital, Nashik, Maharashtra, India. The enrolled patients were administered either Curmune Tablets twice daily or given standard treatment protocol designed by MOHFW for 10 days. The patients were evaluated for decrease in axillary temperature; SpO_2 and VAS score for cough and respiratory distress along with evaluating markers such as Interleukin-6, D-dimer, Ferritin and C Reactive Protein.

Results: In the Curmune group, within two to three days, temperature reduced considerably to afebrile level in all the subjects and remained afebrile till end of study. While in the standard treatment group, temperature reduced to afebrile stage in all the subjects by 4 days and thereafter remained afebrile till the end of study. The elevated levels of serum Interleukin-6, D-dimer, Ferritin and C-Reactive Protein at baseline dropped considerably within normal limits within 10 days in the Curmune group in comparison to standard treatment group.

Conclusion: Curmune has shown for the first time to be useful in management of COVID-19 positive patients along with improvement in the immunity, within 48 to 36 hours of starting treatment. Curmune Tablets were well tolerated without any side effects in any of the patients treated, throughout the study duration.

Registration: CTRI/2020/09/027938

Keywords: Curcumin, Vitamin C, Zinc, COVID-19, Immunity

Conflict of Interest: Dr. Yogesh Dound and Mr. Bhushan Dound are Directors of Particle Life Sciences Pvt. Ltd.

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Introduction

The 2019–20 coronavirus pandemic is an ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The outbreak was first identified in the city of Wuhan, Hubei, China in December 2019, and was recognized as a pandemic by the World Health Organization (WHO) on 11 March 2020.[2]

Till date, there is no specific antiviral medicine to prevent or treat COVID-2019. Various vaccine trials are under different stages of finalization. In India, based on the potential availability of vaccines in the initial phase, the Government of India has selected the priority groups who will be vaccinated on priority as they are at higher risk. The first group includes healthcare and frontline workers. In the second phase, persons over 60 years of age and persons between 45 to 59 years with co morbid conditions.[3] The health department officials claim that it could take 6-7 months to a year for the vaccine to be available for the public. However, till such a time those affected should receive care to relieve symptoms. A standard treatment protocol has been designed by MOHFW and is followed throughout India. Most patients recover due to supportive care. Possible vaccines and some specific drug treatments are under investigation. They are being tested through clinical trials. WHO is coordinating efforts to develop vaccines and medicines to prevent and treat COVID-19.

There are several ongoing clinical trials that include both western and traditional medicines. Since ancient times, herbs have been used as natural treatments for various illnesses, including viral infections. Thus, herbal medicines and natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions.[4] Traditional Indian Medicine or Ayurveda has been practiced in India almost for 3000 years.[5] Various traditional herbs from many geographical areas and environments have been considered as potential new drugs for treatment of viral infections, including those caused by SARS-CoV. Traditional Indian medicine has shown promising results in the management of various illnesses, including viral infections. The detailed analysis and study have shed light on the mechanism of action and hence providing a lead to develop as antiviral drug. [6-9]

Researchers from Particle Life Sciences have developed a formulation from proprietary blend of FSSAI approved ingredients viz. Curcumin, Vitamin C, and Zinc. The ingredients from this formulation have been reported to have potent activity against SARS-CoV-2's main peptide. Based on these reported evidences for the therapeutic potential, the authors proposed the clinical study for the management of COVID-19. The objective of the current study was to evaluate clinical efficacy and safety of Curmune Tablets in COVID-19 infected patients.

Materials and Methods

Study Design

This was a randomized comparative study to assess the role of Curmune Tablets in the management of COVID-19 positive patients in comparison with standard treatment protocol designed by MOHFW. This study was conducted at Vakratund Hospital, Nashik, Maharashtra, India. The Study Protocol was approved by Navsanjeevani Hospital Ethics Committee and registered with CTRI (CTRI/2020/09/027938). Written informed consent was obtained from all patients.

Study participants

Among the 130 patients screened, 100 patients including men and non-pregnant women who were at least 18 years of age met the eligibility criteria. Table 1 gives the demographic details of these subjects. These 100 patients were randomized to receive either Curmune Formulation (Active group) or standard treatment protocol designed by Ministry of Health and Family Welfare (MOHFW) (Standard group) for 10 days. Table 2 gives the details of study intervention in both the groups. The random sequence was generated based on computer generated randomization (https://www.randomizer.org/).

Inclusion Criteria

- Quarantine/non hospitalized or hospitalized and fulfils WHO case definition, including a positive RT-PCR confirmed COVID-19 illness
- Age more than 18 & less than 65 years of either sex
- Mild to Moderately COVID-19 disease (NEWS score less than or equal to 8)
- Patients with oxygen saturation (SpO_2) less than 95%
- Respiratory rate is more than 20/min
- Pulse rate more than 90/min
- Imaging evidence of lung infection in the form of Reticulonodular opacities, ground-glass opacities, and consolidation

Exclusion Criteria

- Pregnant women
- Breastfeeding women
- Requiring ICU admission at screening
- Patients above 65 years of age and below 18 Years
- History of MI, Epileptic episodes
- Any other co-morbidity (uncontrolled diabetes, severe hypertension from subject history) which is at critical stage at screening
- Asymptomatic patients
- Patients unwilling for informed consent
- Patients with prolonged QTc interval on ECG
- In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.
- Participant with any immunosuppressive condition or haematological disease.
- Participation in any other A.S.U and H protocol.

The subjects had undergone a detailed history and complete physical examination along with the laboratory investigations. These include CBC, Lipid profile, Liver Profile, Pro inflammatory cytokine Interleukin-6 (IL-6), D-Dimer, Ferritin and C Reactive Protein (CRP). Once enrolled, these subjects received the care as per the standard practices prescribed by WHO and/or applicable regulatory guidelines for 10 days. During this period, the patients were randomized to receive either Curmune Tablets or standard treatment protocol designed by MOHFW. The subjects were examined daily for symptoms which include cough, fever with or without chills and difficulty in breathing. Each subject received the test formulation daily till the end point i.e., 10 days. All the laboratory investigations were repeated at end point. The investigations were carried out in NABL accredited laboratory.

Study Outcome

The primary outcome included clinical status as decided by the Principal Investigator based on the physical examination, laboratory investigations and signs such as axillary temperature, respiratory rate, pulse, blood pressure and symptoms which include cough, fever with or without chills and difficulty in breathing.

Patients were assessed once daily by trained nurses using cards that captured data on a six-category ordinal scale and safety from day 0 to 10. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-category ordinal scale (from 1 = discharged to 6 = death), or live discharge from the hospital, whichever came first. A special WHO committee arrived at this ordinal scale which measures illness severity over time.[10] This scale has been widely used in randomized clinical trials for the management of COVID-19. The clinical status was assessed based on the symptoms at baseline and at the end point along with parameters including Pro inflammatory cytokine IL-6, D-Dimer, Ferritin and CRP.

Statistical Analysis

Data was presented as descriptive statistics such as Mean (SD) and analysed by using students unpaired t test method using GraphPad software.

Study intervention

The formulation tablets, i.e., Curmune Tablets were supplied by Particle Life Sciences in packed as 30 tablets per bottle. The tablets were supplied in bottles to patients at the time of the enrolment. Patient consumed each tablet orally twice a day immediately after breakfast and after dinner for 10 days. The tablets compliance was judged by counting the number of tablets in the bottle left at the end of study. Patient was said to be compliant if he had consumed minimum 80% of the total dispensed tablets.

Table 1: Demographic details of the subjects participating in the study

	Active group		Standard group	
	Males	Females	Males	Females
N	24	26	28	22
Age (yrs.)	42.79 (11.2)	39.65 (12.8)	39.32 (11.5)	43.59 (14.1)

Values expressed in Mean (SD); SD- Standard Deviation

Table 2: Intervention details in both the treatment groups

Active group (Intervention)	N = 50	Curmune Formulation tablets	Twice daily for 10 days
Standard group (Comparator Agent)	N = 50	Standard Treatment protocol designed by MOHFW	HCQS 400 mg 1-0-1 (first day) HCQS 200 mg 1-0-1 after Day 1 Azithromycin 500 mg 1-0-0 Antiviral/Tamiflu 1-0-1 and Vitamin support

HCQS: Hydroxychloroquine

Results

All the 100 patients enrolled in the study completed their study. All the patients had complaints of cough, fever without chills and difficulty in breathing. The SpO_2 levels in these patients ranged from 80-85%. These patients received the care as per the standard practices prescribed by WHO and/or applicable regulatory guidelines for 10 days.

Out of 100 patients, 50 patients were randomized to receive Curmune Tablets (Active group) while 50 patients received standard treatment protocol designed by MOHFW (Standard group). In the Active group there were 24 males and 26 females, while in the Standard group there were 28 males and 22 females.

Table 3: Levels of serum IL-6, Ferritin and CRP levels and plasma D-Dimer levels in each group for males and females

Parameters	IL-6 (pg/ml)		D-Dimer (mg/L)		Ferritin (ug/L)		CRP (mg/L)	
	M	F	M	F	M	F	M	F
Active Group								
Day 0	1264.38 (153.0)	1279.07 (126.9)	2.34 (0.3)	2.28 (0.2)	551.85 (97.5)	529.40 (91.7)	31.74 (6.3)	30.17 (4.6)
Day 10	316.10 (38.2)#	319.77 (31.7)#	0.43 (0.1)#	0.41 (0.0)#	143.48 (25.4)#	137.64 (23.8)#	5.08 (1.0)#	4.83 (0.7)#
Standard Group								
Day 0	1355.45 (21.8)	1354.94 (20.2)	2.34 (0.2)	2.39 (0.3)	570.57 (77.3)	578.84 (88.8)	28.09 (4.5)	31.40 (5.3)
Day 10	874.69 (122.4)	862.53 (130.0)	1.42 (0.2)	1.37 (0.3)	361.45 (27.2)	370.21 (41.9)	18.57 (1.3)	18.32 (1.3)

Values expressed in Mean (SD); SD- Standard Deviation; M- Males, F-Females; #- Statistically significant (p <0.0001).

Axillary Temperature

In the Active group, the average temperature at baseline was 102.28 ± 0.4°F. By the end of 48 hours, the temperature reduced to 99.39 ± 0.3°F. The temperature reduced to 98.18 ± 0.2°F in all the patients by day 4. The temperature continued to remain afebrile till day 10 (Figure 1). In the Control group, the temperature at baseline was 102.31 ± 0.5°F. By the end of 48 hours, the temperature remained around 101.3 ± 0.7°F. The temperature reduced to 99.32 ± 0.3°F in all the patients by day 4. These patients continued to remain afebrile till day 10 from 5 days onwards (Figure 1).

SpO_2 levels

The average SpO_2 in the Active and Standard groups at baseline was 84.86 ± 0.6 and 83.44 ± 0.6, respectively. On 2nd day the average SpO_2 levels in the Active group increased to 88.42 ± 1.3, while in the Standard group the levels increased to 86.80 ± 1.4. By day 4 the levels increased to 94.52 ± 0.8 in the Active group and to 89.66 ± 0.5 in the Standard group. By the end of 10th day, the SpO_2 levels in both the groups the SpO_2 levels were around 97.68 ± 0.6 and 95.98 ± 0.1 in all the Active and Standard Groups respectively (Figure 2).

6 category ordinal scale

The patients in both the groups were in category 3 of the six-category ordinal scale of clinical status at baseline. Category 3 refers to the patients who are hospitalized with mild to moderate disease. The subjects in the Active group were in the category 0 of this scale by day 10. The subjects in the Standard group were in the category 1 of this scale by day 10. Category 0 refers to the patients who are not infected with no clinical or virological evidence of infection. Category 1 refers to the patients who are ambulatory with no limitation of activities. The Standard treatment group could not achieve category 0 on this scale by day 10.

Clinical Assessment

The serum IL-6, Ferritin and CRP levels and plasma D-Dimer levels were very high at baseline in both the groups as compared to their respective normal range for males as well as females. The IL-6 (pg/ml) levels reduced from 1272.02 ± 138.7 to 318.01 ± 34.7 in both males and females in the Active group within 10 days. In the Standard group, the levels reduced from 1355.22 ± 20.9 to 869.34 ± 124.6 by the end of day 10 (Figure 3). The CRP (mg/L) levels reduced from 30.92 ± 5.5 to 4.95 ± 0.9 and from 29.55 ± 5.1 to 18.46 ± 1.3 in the Active group and Standard group respectively (Figure 4). The Ferritin (ug/L) levels reduced from 540.18 ± 94.2 to 140.45 ± 24.5 in the Active group while they reduced from 574.20 ± 81.8 to 365.31 ± 34.4 in the Standard group

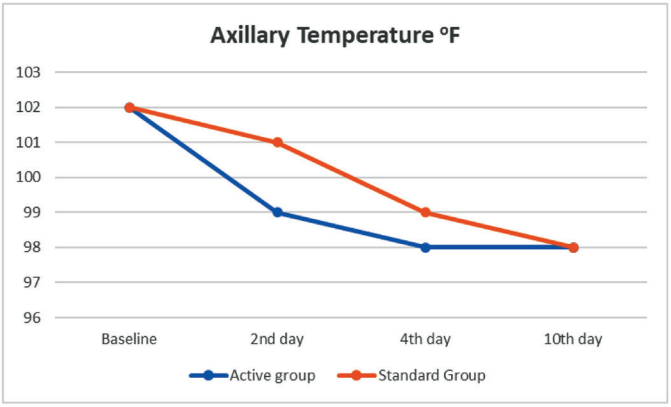

Figure 1: Axillary Temperature in both the groups from Baseline to 10th day

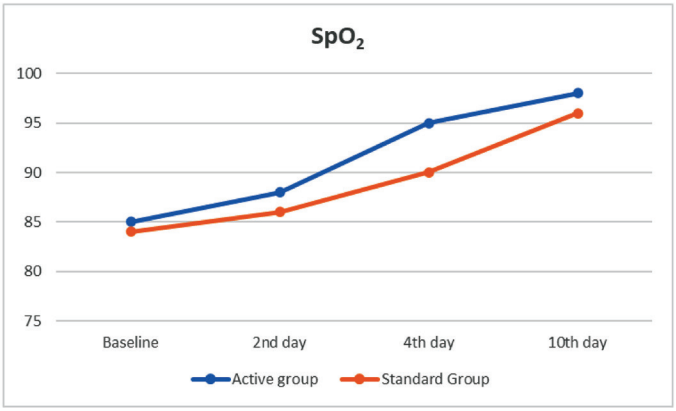

Figure 2: SpO_2 levels in both the groups from Baseline to 10th day

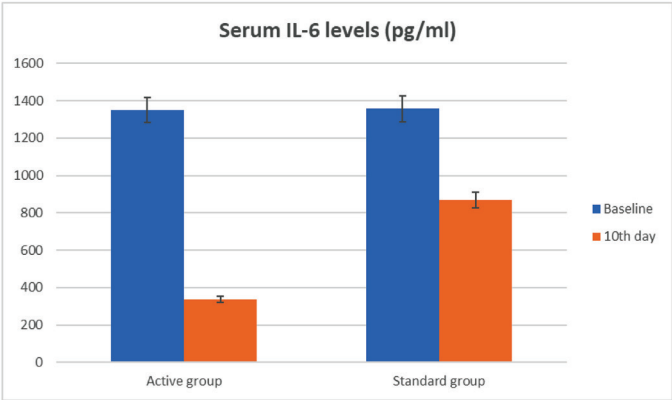

Figure 3: Serum IL-6 levels in both the groups from baseline to 10th day

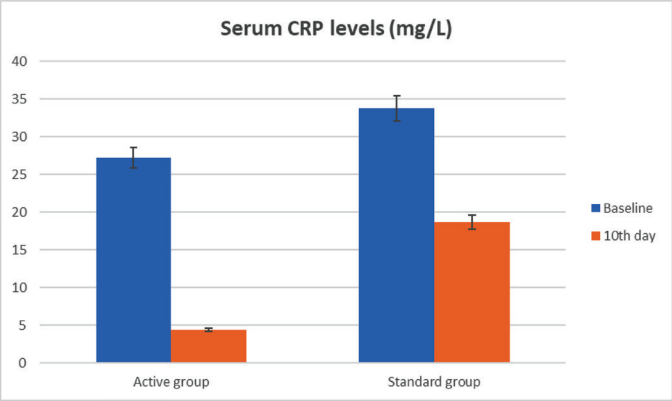

Figure 4: Serum CRP levels in both the groups from baseline to 10th day

(Figure 5). The plasma D-Dimer (mg/L) levels reduced from 2.31 ± 0.2 to 0.42 ± 0.1 in the Active group, while it reduced from 2.36 ± 0.3 to 1.40 ± 0.3 in the Standard group (Figure 6). Table 3 gives a summary of the levels of these parameters in each group for males and females. There was no change in rest of the biochemical as well as organ function tests within 10 days in both the groups.

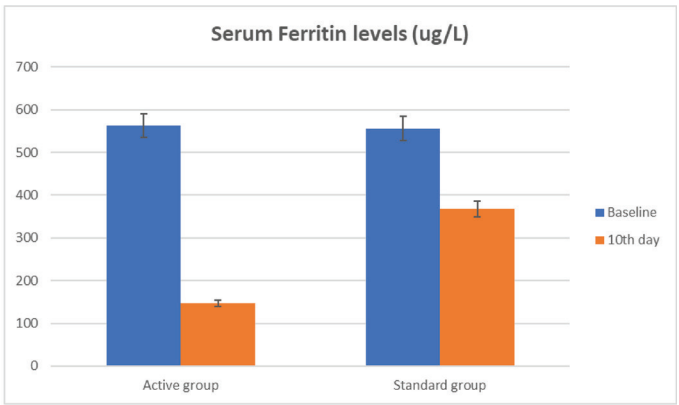

Figure 5: Serum Ferritin levels in both the groups from baseline to 10th day

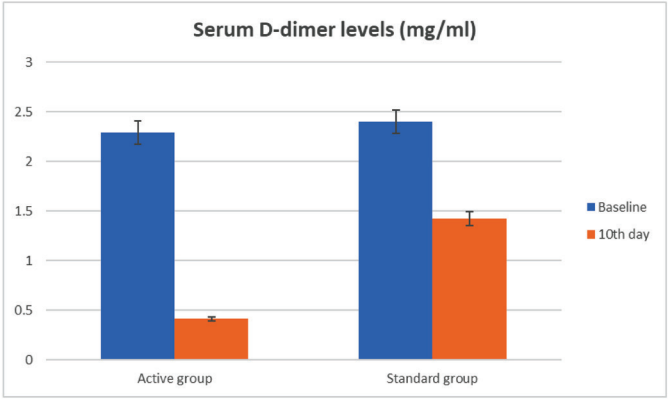

Figure 6: Serum D-dimer levels in both the groups from baseline to 10th day

Tolerability and Safety

Curmune Tablets were well tolerated without any major side effects in any of the patients treated, throughout the study duration. Few side effects of abdominal pain and constipation were reported in some subjects, which were said to be unrelated to the test substance as decided by the Principal Investigator. There was no decrease in body weight of the subjects in the Active group, while there was decrease in body weight of many subjects in the Control group. No serious adverse events were reported during the period of therapy. Among these patients there were some who were on oral medications for Type 2 diabetes mellitus. These patients continued with their regular medications along with Curmune Tablets. It was observed that there was no drug interaction of Curmune Tablets with any of these medications

Discussion

In the current study, the formulation containing the proprietary blend of Curcumin, Vitamin C, and Zinc was evaluated for the management of COVID-19 and also to improve the immunity.

Curcumin has exhibited various pharmacological activities attributed to its major metabolites like dimethoxycurcumin[11] and tetrahydrocurcumin.[12] Recently Demethoxycurcumin was shown to have the best potential to act as COVID-19 M^{pro} inhibitor.[13] Tetrahydrocurcumin, also has shown promising antiviral effect by inhibiting SARS-CoV's main peptide and COVID-19 M^{pro}.[14] In a recently conducted Relative Oral Bioavailability Study (Pharmacokinetic Study) in rats for Curcume, it was seen that the C_{max} and t_{max} of Curmune was 21.83 ng/ml and 0.25 hours respectively in comparison to Curcumin with C_{max} and t_{max} of 12.60 ng/ml and 0.5 hours respectively [Data Unpublished].

Vitamin C acts as an antioxidant, which destroys free radicals and supports the body's natural immune response. Vitamin C potentially protects against infection caused by SARS-CoVs by improving the immunity, function of phagocytes, transformation of T lymphocytes and production of interferon.[15,16] Vitamin C is also recommended for prevention of SARS-CoV-2 infections by the Chinese Center for Disease Control and Prevention and Chinese Nutrition Society.

Zinc is an essential metal involved in cell signalling, proliferation, differentiation, oxidative stress, the immune response, and numerous other important cellular processes.[17,18] Various clinical studies have linked Zinc supplementation with less severe and reduced duration of symptoms along with lower recurrent infections for viral infections.[19] Zinc is recommended by the National Institutes of Health (NIH) for inducing the immune system and preventing viral infections.

IL-6 acts as a pro-inflammatory cytokine as well as an anti-inflammatory myokine. Inflammation is closely related to severity of COVID-19 and IL-6 is one of the important therapeutic targets.[20] It has also been shown that the serum levels of IL-6 predict the outcome in patients with COVID-19.[21] In the current study the very high levels of IL-6 at baseline reduced by approximately 75% within 10 days.

Ferritin plays a role in the modulation of immune function. It is known to suppress several global measures of the immune response. Laboratory investigations in the patients with severe COVID-19 showed elevated inflammatory markers, including ferritin, and hence it has been associated with critical and life-threatening illness.[22] In the current study the high levels of Ferritin at baseline reduced approximately by 70-75% within 10 days.

CRP levels are associated with the levels of inflammation, and its concentration level is unaffected by factors such as age, sex, and physical condition.[23] CRP levels can activate the phagocytosis, thus clearing the pathogenic microorganisms which invade the body. It is an important index for the diagnosis and assessment of various infectious diseases.[24] The elevated levels of CRP are linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. Higher levels of CRP are considered as a predictive marker in determining which patients with mild COVID-19 symptoms will progress to a severe case. In the current study the high levels of CRP at baseline reduced approximately by 75-80% within 10 days.

D-dimer assays are routinely used as part of a diagnostics to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels.[25] D-dimer concentrations are found to be helpful to rapidly identify COVID-19 patients with high risk of pulmonary complications and venous thromboembolism, facilitating the early initiation of effective therapies.[26] In the current study the high levels of D-dimer at baseline reduced approximately by 80% within 10 days.

Thus, statistically significant decrease in the above clinical parameters along with axillary temperature, SpO_2 and asymptomatic status for COVID-19 within 10 days is quite suggestive of improvement in the status of viral infection and inflammation, thereby suggestive for the management of patients tested positive for COVID-19.

Conclusion

In the Curmune group, within 3 to 4 days, temperature reduced considerably to afebrile level in all the subjects and remained afebrile till end of study. The very high levels of Interleukin-6, Di-dimer, Ferritin and CRP at baseline dropped considerably within normal limits within 10 days in the Curmune group in comparison to standard treatment group. All the subjects in the Curmune group were asymptomatic within 10 days.

Curmune has shown for the first time to be useful in management of COVID-19 positive patients along with improvement in the immunity, within 48 hours of starting treatment. Curmune was well tolerated without any side effects in any of the patients treated. Hence, Curmune could be developed into a valid therapeutic option for the management of COVID-19.

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