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A double blind, randomized, placebo-controlled study to evaluate efficacy and safety of "ViraCide" in the management of Corona Virus Disease 2019 (COVID-19)

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Abstract

Introduction: The purpose of this study was to evaluate the safety and efficacy of ViraCide in the management of Corona Virus Disease 2019.

Methodology: The study was a randomized, multi center, parallel design, placebo controlled, double blind, clinical trial in patients diagnosed with corona virus disease 2019 with mild or no symptoms and with stable co-morbidities. 118 enrolled subjects were randomized in a 1:1 ratio to either placebo treatment or ViraCide (active treatment).

Result: The primary efficacy parameters of National Early Warning Score (NEWS) and 7 point ordinal showed a significantly greater improvement in the active group at the end of the study ($P < 0.05$). In case of NEWS, in the ViraCide group at visit 3, 74.6 % of the subjects had score of "0" which was higher than the placebo in which only 49.2% showed the reduction. In case of the 7 point ordinal scale, in the active group 76.3 % of the subjects had score of 1 which is significantly higher than that of placebo group which is only 47.5%. Time taken for clinical improvement with respect to negative RT PCR test also showed significant difference in the active v/s placebo group. The mean time taken by patients in the active group to test negative was 5.47 days which was significantly lower than placebo which was 6.97 days. The adverse events rate and severity were comparable in both the groups and no clinically significant adverse event was found in the active or placebo group.

Conclusion: The use of ViraCide in mild or asymptomatic COVID-19 patients showed time frame reduction with respect to RT-PCR test, as well as clinical improvement demonstrated by NEWS and 7-point ordinal scale and certain laboratory parameters. Further clinical trials are required to evaluate role of ViraCide in managing COVID-19 and establish its mode of action.

Introduction

In the beginning of December 2019, a novel coronavirus, designated SARS-CoV-2, originated in the Wuhan district of China, and subsequently caused an international outbreak of respiratory illness termed as corona virus disease 2019 (COVID- 19) [1]. Since then, the disease has wreaked havoc on the world population. While the mild state of the disease presents with symptoms like fever, dry cough, tiredness, progression to severe state is characterized by pneumonia, multi-organ failure and death. The COVID-19 pandemic places adults 50 years and older with medical comorbidity at greater risk for poor physical and mental health outcomes [2,3].

A nation-wide analysis of 1590 laboratory-confirmed hospitalized patients between December 11th, 2019 and January 31st, 2020, from 575 hospitals in China showed that patients with comorbidities were at higher risk of disease progression to severe than those without. Hypertension and diabetes were the most prevalent comorbidities (16.9% and 8.2% of study population, respectively); and about 8.2% of the study population had two or more comorbidities [3]. Of the reported COVID-19 related deaths in India, 71% had comorbidities; with hypertension and diabetes being the most common comorbidities [4].

Currently, no specific therapeutic agents have been approved for the treatment of corona virus infections [1]. Thus a double blind, randomized, placebo-controlled study was conducted in 2020 with 118 male or female asymptomatic or mild COVID-19 patients aged 50 years or more, with chronic, but stable medical conditions like diabetes mellitus, hypertension, or chronic heart disease. The objective of the study was to evaluate the efficacy and safety of "ViraCide" in the management of Corona Virus Disease 2019 (COVID-19).

ViraCide is the investigational product that was used in this study. It is a dietary supplement helpful in managing general well-being of the individuals, especially

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those with comorbidities. The product contains a proprietary formula of Arachidonic acid, Oregano, Sage, Sweet basil, Holy basil, Fennel, Garlic, Lemon balm, Peppermint, Rosemary, Echinacea Purpurea, Elderberry, Licorice root, Astragalus root, Ginger, Panax ginseng, Dandelion, Calendula, Cat's claw and Olive leaf.

It was proposed that these ingredients of ViraCide would be helpful in building immunity, and general well-being of older adults with comorbidities, thereby reducing the risk of progression to severe disease. Additionally ViraCide has antiviral, anti-inflammatory and antibacterial properties which can help manage asymptomatic and mildly symptomatic patients with COVID-19 disease. The efficacy and safety of the combined effect of the constituents of ViraCide supplement have not been studied in any disease. The study aimed to test the efficacy and safety of ViraCide in this patient population in preventing progression to severe disease.

Methods

Setting

The study was conducted at two sites, the Government General Hospital, Srikakulam in Southern India and Gunjkar multispecialty hospital, Chinchwad located in the city of Pune 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-16) and "Independent Ethics committee Royal Ethics committee, Pune, India" (ECIV45/Indt/MII/2013/RR-19).

Study design and participants

The study was designed for five visits in the duration of 28 days, out of which duration of treatment was planned as 14 days. The subjects were randomized in a 1:1 ratio to either ViraCide with SOC (Standard of Care) or placebo with SOC. Concomitant medications like medication for diabetes mellitus, hypertension, and statins were allowed in the study. The visits were planned as follows: Visit 1 (Screening, Day 0), Visit 2 (Baseline/Randomization Visit, Day 1), Visit 3 (Day 7), Visit 4 (Day 15 or Discharge day), and Visit 5 (End of Study, Day 28) which was planned to be the telephonic follow up visit to gather safety data related to adverse events (AE) reported. The window period of ±2 days was considered acceptable for each scheduled visit following the screening visit. In case if a subject was discharged before Day 15 on investigator's discretion as per patients health condition, then assessments scheduled for Day 15 were to be carried out on the discharge day.

The efficacy of ViraCide in patients diagnosed with COVID-19, was determined by assessing reduction in NEWS (National Early Warning Score) [5], 7 point ordinal scale [1], time taken for clinical improvement with respect to negative RT-PCR (Reverse transcription- Polymerase chain reaction) test. To evaluate the safety of ViraCide in COVID-19 patients, evaluation included several laboratory parameters, hematology, biochemistry and urinalysis at screening and end of study as well as adverse events during the study. The scale for NEWS and 7-point ordinal scale is shown in Table 1 and Table 2, respectively.

Table 1. *National Early Warning Score*

Physiological Parameters	Score						
	3	2	1	0	1	2	3
Respiration Rate (per minute)	≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1 (%)	≤91	92-93	94-95	≥96			
SpO_2 Scale 2(%)	≤83	84-85	86-87	88-92 ≥93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or Oxygen?		Oxygen		Air			
Systolic Blood Pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Pulse per minute	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1-36	36.1-38.0	38.1-39.0	≥39.1	

Table 2. *7- Point Ordinal Scale*

Score	Assessment criteria	Management
1	Not hospitalized with resumption of normal activities	Manage in isolation ward and manage as SOC
2	Not hospitalized, but unable to resume normal activities	Manage in isolation ward as SOC but monitor strictly
3	Hospitalized, not requiring supplemental oxygen	In hospital
4	Hospitalized, requiring supplemental oxygen	In hospital/ICU
5	Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both	In ICU
6	Hospitalized, requiring ECMO, invasive mechanical ventilation, or both	In ICU
7	Death	-

The study screened 124 patients diagnosed with corona virus disease 2019 with positive RT- PCR for Sars-Co-V2, who were either asymptomatic or had mild symptoms with onset of symptoms within (not more than) 4 days and had chronic, but stable medical conditions like diabetes mellitus, hypertension, or chronic heart disease. Mild symptoms were characterized with presence of cough, weakness, sore throat, low grade fever 38.5^{0}C, respiratory rate (RR) not more than 22/min, resting SpO_2 >95%, normal highly sensitive C-reactive protein (HS-CRP) (<10mg/L) with no signs of dehydration, sepsis or shortness of breath. Patients with history of respiratory failure, hepatic or renal failure or chronic renal disease, upper gastrointestinal hemorrhage, disseminated intravascular coagulation were excluded from this trial. Similarly, patients that were under the treatment for asthma, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, asbestosis and other such chronic lung conditions that could compromise SpO_2 and RR were also excluded. Also, excluded were pregnant or lactating women and patients history of drug abuse or alcohol dependency.

Out of these 124 screened patients, 118 were found eligible based on the inclusion-exclusion criteria. These 118 subjects were instructed to take three soft gels (3400 mg) of either ViraCide or Placebo soft gels twice a day with ambient temperature water for 14 days daily. The published research data [6-20] of the non-clinical and clinical studies on use of ingredients of ViraCide and dosing, along with information available for marketed ingredients, supported the dose rationale for this study. A comparison of the active and placebo treatment arms was undertaken, with changes in results from baseline to the end of study, being summarized by treatment.

Statistical analysis

All safety and efficacy analyses were performed on the Intent to treat population (ITT), which consists of all randomized subjects who have received at least one dose of study medication and have at least one post-baseline efficacy measurement. Reduction in NEW Score and reduction in 7 point ordinal score were compared between the active and placebo group by using Chi Square test. The TTCI with respect to negative RT-PCR test was compared between the two groups by using Student 't' test.

Results

The primary end points of the study were to determine the TTCI i.e. time taken for clinical improvement based on NEWS and 7 point ordinal score. However, due to the changing regulations for discharge the patients were discharged early, largely on 7th day and hence, meaningful analysis was not possible based on the time i.e. TTCI for NEWS and 7 point ordinal scale. Therefore with the inputs from medical monitor, Ethics committee and statisticians, the reduction in NEWS and 7 point ordinal from baseline to discharge was considered as primary end points for the study. Also time taken for clinical improvement with respect to negative RT-PCR was analyzed as part of efficacy analysis.

The efficacy of the study was evaluated based on below parameters;

1. Reduction in NEWS
2. Reduction in 7-point ordinal scale score
3. TTCI using Negative RT-PCR test day

Table 3. *Comparison Of Changes In Proportion Of Cases With NEWS Between Two Groups*

Scores	Proportion of cases with NEW Score							
	Active (N = 59)				Placebo (N = 59)			
	Baseline		Visit 3		Baseline		Visit 3	
	No	%	No	No	%	No	No	%
0	-	-	44	74.6	-	-	29	49.2
1	-	-	5	8.5	-	-	1	1.7
2	6	10.2	8	13.5	10	16.9	11	18.6
3	53	89.8	*02	3.4	49	83.1	@* 18	30.5

By Chi Square Test P < 0.05, *Significant @Between groups P = 0.0002, Significant

Table 4. *Comparison Of Changes In Proportion Of Cases With 7-Point Score Ordinal Between Two Groups*

Scores	Proportion of cases with 7-Point Ordinal Score											
	Active (N = 59)						Placebo (N = 59)					
	Screening		Baseline		Visit 3		Screening		Baseline		Visit 3	
	No	%	No	%	No	%	No	%	No	%	No	%
1	-	-	*45	76.3	59	100	-	-	@*28	47.5	59	100
2	-	-	14	23.7	-	-	-	-	31	52.5	-	-
3	59	100	-	-	-	-	59	100	-	-	-	-

By Chi Square Test P < 0.05, *Significant @Between groups P = 0.0013, Significant

These parameters were compared from baseline (treatment start day) to discharge day. Efficacy parameters were also compared between the two arms, Placebo control and ViraCide.

Reduction in NEWS

The results showed statistically significant difference in the treatments (Active v/s Placebo) for reduction in NEWS (74.6% of cases had score "0" at visit 3 v/s 49.2% among Placebo group which had score "0" at visit 3). So there was a significant difference of 25.4% among the groups. (Table 3)

Hence, significantly more number of patients on the active group achieved the score 0 on visit 3. So this analysis shows that ViraCide is more effective in reducing the symptoms on visit 3 from baseline as determined on basis of NEWS score.

7-point ordinal scale score

The results showed statistically significant difference in the treatments (Active v/s Placebo) for reduction in 7-point ordinal scale score (76.3% of cases had score "1" at visit 3 v/s 47.5% among Placebo group had score "1" visit 3). So there was a significant difference of 28.8% among the groups. (Table 4)

Hence, significantly more number of patients on the active group archived the score 1 on visit 3. So this analysis shows that ViraCide is more effective in reducing the symptoms on visit 3 from baseline as determined on basis of 7 point ordinal scale score.

TTCI using Negative RT-PCR

The results showed statistically significant difference in the treatments (Active v/s Placebo) for average duration for RT PCR negative (5.47 days among Active v/s 6.97 days among Placebo group). The difference was of 1.5 days i.e. the patients on active group showed negative RT-PCR result 1.5 days earlier than that of the placebo group. (Table 5)

There are few studies and no references available to predict the difference is significant from the clinical perspective. More studies on the RT-PCR negative timeline would be required to establish a standard for comparison for this efficacy parameter.

The secondary objective of the study was to assess safety of ViraCide through monitoring and follows ups of adverse events and evaluation of deranged lab parameters.

During the course of study, no major AEs that could be causally related to the treatment were found. (Table 6) The laboratory parameters including biochemistry parameters didn't show any significant change in the pre-treatment v/s post treatment arm. (Table 7)

7 subjects experienced adverse events that were mild to moderate in nature. The adverse events were seen in active group as well as the placebo group. Hence the adverse events were not found to be linked or associated with the Investigational product i.e. ViraCide. Also an independent analysis from the PI concluded that the adverse event was not causally related to ViraCide.

This study validated the potential efficacy of ViraCide against mild COVID-19 symptoms, while being safe for use in humans.

Discussion

The time for negative RT PCR for the subjects on ViraCide group was less than that of the placebo. The difference was of approximately 1.5 days and this was seen to be statistically significant. It remains to be seen if this difference can be considered clinically significant. More studies with primary objective of time frame to negative RT PCR would be required.

Also the time frame reduction demonstrated here gives a hint about the anti-viral activity of ViraCide. Hence this antiviral activity of ViraCide needs to be confirmed through further research.

Table 5. *Comparison Of Mean Duration For RT-PCR Negative Between Two Groups*

Parameters	Mean TTIC	
	Active (N = 59)	Placebo (N = 59)
Mean	5.47	6.97
SD	0.49	0.61
Range	5.00 – 6.00	6.00 – 9.00
Median	5	7

By Student 't' test p-value is < .00001, Significant

Table 6. *Profile Adverse Events*

	Viracide (N = 59)		Placebo (N = 59)	
Adverse Events	No.	%	No. %	
Mouth Ulcer	1	1.7	2	3.4
Nausea	2	3.4	1	1.7
Vertigo	-	-	1	1.7
Total No. of Events	3	--	4	--
Total No. of Patients	3	5.1	4	6.8

By Chi Square Test P > 0.05, Not Significant

Table 7. *Listing of Individual Laboratory Measurements*

Parameters	Mean (X ± SD)			
	Viracide (N = 59)		Placebo (N = 59)	
	Screening	Visit 3	Screening	Visit 3
Hemoglobin (g/dl)	11.51 ± 1.69	11.91 ± 1.65	11.45 ± 1.37	11.38 ± 1.26
Hs CRP (mg/l)	07.86 ± 1.64	03.43 ± 1.60	07.92 ± 1.66	03.59 ± 1.30
Hematocrit - PCV (%)	38.53 ± 4.80	41.67 ± 4.85	38.12 ± 4.67	40.22 ± 5.15
WBC Count (/cmm)	5931.22 ± 2944.00	6817.97 ± 964.55	5557.12 ± 2479.87	6801.53 ±945.54
RBC count (mil/cmm)	03.73 ± 0.59	03.80 ± 0.66	03.68 ± 0.55	03.64 ± 0.48
Platelet Count (/cmm)	02.12 ± 0.41	02.09 ± 0.33	02.06 ± 0.43	02.07 ± 0.42
ESR	18.14 ± 4.02	09.78 ± 4.39	18.66 ± 4.82	10.10 ± 5.53
Serum Creatinine	00.99 ± 0.25	00.98 ± 0.25	01.09 ± 0.28	01.09 ± 0.27
Bun / Urea	12.92 ± 4.60	12.69 ± 4.30	13.84 ± 3.81	12.57 ± 3.90
Alkaline Phosphatase	67.15 ± 13.24	69.09 ± 16.04	72.81 ± 18.68	74.64 ± 18.44
Bilirubin-Total	02.06 ± 10.32	00.77 ± 0.21	00.72 ± 0.25	02.24 ± 11.23
Bilirubin-Direct	00.22 ± 0.32	00.18 ± 0.07	00.18± 0.09	00.19 ± 0.09
Bilirubin-Indirect	00.48 ± 0.24	00.46 ± 0.20	00.45 ± 0.25	00.47 ± 0.24
Total Proteins	06.05 ± 0.92	06.11 ± 0.83	06.03 ± 0.86	06.12 ± 0.83
LDH	209.53 ± 50.93	160.20 ± 43.05	225.53 ± 58.90	163.92 ± 40.75
Total Cholesterol	199.27 ± 34.08	185.47 ± 32.28	202.80 ± 34.46	193.23 ± 39.27
Triglycerides	217.15 ± 53.27	191.52 ± 33.40	230.06 ± 66.63	213.58 ± 54.83
Random Blood Sugar	162.95 ± 81.84	137.36 ± 35.94	168.02 ± 48.91	150.00 ± 59.71
AST	36.07 ± 13.52	33.41 ± 10.80	35.45 ± 13.02	34.46 ± 12.16
ALT	34.84 ± 10.57	34.92 ± 9.27	34.41 ± 14.21	34.99 ± 10.18
Alkaline Phosphatase	67.09 ± 13.46	68.44 ± 15.99	74.87 ± 19.37	74.64 ± 18.51
Serum Sodium	134.37 ± 7.04	136.66 ± 5.35	135.07 ± 6.34	136.41 ± 4.62
Serum Potassium	03.80 ± 0.56	03.95 ± 0.51	03.68 ± 0.64	03.89 ± 0.58
Calcium	07.43 ± 0.81	07.99 ± 0.91	07.32 ± 0.82	07.80 ± 0.84
Uric Acid	05.81 ± 2.33	05.13 ± 1.58	06.56 ± 2.19	05.49 ± 1.92
Chloride	97.93 ± 6.66	98.44 ± 5.76	98.32 ± 8.26	97.87 ± 6.64
pH	06.58 ± 0.59	06.61 ± 0.55	06.63 ± 0.61	06.61 ± 0.62

For the patients in the active group i.e. patients on ViraCide drastic reduction in NEWS score were seen on visit 3. NEWS score was designed for evaluating clinical response of patients with lung alignments or respiratory issues. Hence the effectiveness of ViraCide for respiratory symptoms arising from other infections / Asthma / COPD remains a topic of further research.

During the course of the study, it was also found out that certain laboratory parameters like hemoglobin, random blood sugar, triglycerides and bilirubin levels were improved in the active group by end of the study. There are several clinical studies which support the hypothesis that improvement in these laboratory parameters has positive effects on progression of COVID in patients.

A retrospective cohort study found the elevated bilirubin associated with progression to more severe COVID-19 in patients [21]. Decrease in bilirubin after using ViraCide can be an indicator of how ViraCide may be effective in controlling progression of this disease. Reduction in triglycerides and blood sugar levels may also prove to be beneficial in controlling COVID-19 in patients as hyperglycemia is associated with compromised immunity in patients. An Observational cross-sectional study including 1411 hospitalized patients with COVID-19 found that the lipid profile measured during hospitalization showed that a severe outcome was associated with higher triglycerides [22].

Another retrospective cohort study in Wuhan, China found that a higher median glucose level during hospital stay or after critical diagnosis (≥6.1 mmol/L) was independently associated with increased risks of progression to critical cases/death among non-critical cases, as well as in-hospital mortality in critical cases [23]. Decrease in blood glucose level after using ViraCide, hence should be further explored with more subjects for a longer duration. Increase in hemoglobin levels in patients that were given ViraCide may also be an indicator of improvement in COVID-19 patients as hemoglobin is the oxygen carrier in blood. Although significant improvement in these laboratory parameters was seen in this study, the study was not specifically designed to explore these parameters. In addition to that, these parameters may also have been affected by SOC or combination of SOC and ViraCide. Hence, further clinical trials are required to establish efficacy of ViraCide in management of COVID-19.

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