Virgin Coconut Oil as Adjunctive Therapy for Hospitalized COVID-19 Patients in a Tertiary Referral Hospital: A Randomized Controlled Trial

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ABSTRACT

Background. Virgin coconut oil (VCO) has anti-viral and anti-inflammatory properties, making it a potential therapeutic candidate against COVID-19 infection.

Objective. To determine the efficacy and safety of VCO as adjunctive therapy for hospitalized patients with COVID-19.

Methods. We conducted a randomized, open-label controlled trial involving laboratory-confirmed COVID-19 patients admitted at the Philippine General Hospital. The study participants were randomized to the intervention group who received virgin coconut oil with local standard of care, or to the control group who received local standard of care alone.

Results. We enrolled 39 participants into the VCO group and 38 participants into the control group. Significantly fewer participants in the VCO group had abnormal CRP levels at the end of treatment compared to control. (relative risk [RR] 0.75, 95% confidence interval [CI] 0.58 to 0.95; p=0.02) No significant difference was found in the duration of hospital stay (mean 9.33 days for VCO vs. 10.29 days for control; p=0.45) and time to symptom resolution (mean 6.8 days for VCO, vs. 6.74 days for control; p=0.91). Although the proportion of patients who developed the secondary outcomes of mortality, need for ICU admission, need for invasive ventilation, and negative viral conversion was lower in the VCO group, results did not reach statistical significance. The VCO group had larger reduction in the inflammatory markers ferritin, lactate dehydrogenase, TNF-alpha, IP-10 and IL-6, but results did not reach statistical significance. Adverse events were significantly higher in the VCO group (RR 4.87, 95% CI 1.14 to 20.79; p=0.03).

Conclusion. This clinical trial on hospitalized patients showed significant benefit in CRP levels of participants given VCO compared to control. There was no significant benefit in the use of VCO as adjunctive therapy in reducing duration of hospital stay. Larger studies are needed to conclusively demonstrate the effect of VCO on other clinical outcomes and inflammatory markers.

Keywords: virgin coconut oil, COVID-19, clinical trial

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been recognized to cause a severe inflammatory response in a portion of affected patients. Agents with both anti-viral and anti-inflammatory properties could pose as potential therapeutic candidates against COVID-19 infection.

Virgin coconut oil (VCO) has antiviral and immunomodulatory properties that make it a potential candidate as an adjunctive treatment for COVID-19. It is naturally extracted from fresh coconut flesh without the use of chemical or thermal treatment. It is rich in medium chain fatty acids, with lauric acid being the major fatty acid.[1]

In vitro, animal and human researches have demonstrated the anti-viral characteristics of virgin coconut oil (VCO).[2] Lauric acid and its derivative, monolaurin, exhibit antiviral effects through disruption of viral proliferation by disintegrating the virus envelope of RNA and DNA viruses through destabilization of the lipid bilayer.[3] It can also inhibit virus maturation by reducing viral glycoproteins and increasing triacylglycerols in the host plasma membrane.[4] VCO has also been demonstrated to interfere with virus binding with host cells.[5] Lauric acid and monolaurin has demonstrated activity against human immunodeficiency virus (enveloped ssRNA virus), Semliki Forest virus (enveloped ssRNA virus), herpes simplex virus (enveloped DNA virus), and papillomavirus (non-enveloped DNA virus).[6]

Lauric acid also has immunomodulatory effects, as it has been shown to have anti-inflammatory effects and can cause an increase of CD4+ T cell counts.[7,8] In vitro studies show that VCO suppresses inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interferon-γ (IFN-γ), and interleukin-6 (IL-6).[9] Studies on rats show decreased levels of TNF-α, IL-6, and nitric oxide (NO), with attenuated inflammatory cell infiltration and edema formation after VCO treatment.[7,10]

SARS-CoV-2 is an enveloped ssRNA virus. Some individuals infected with this virus develop cytokine release syndrome, characterized by systemic hyperinflammation and greatly increased pro-inflammatory cytokine levels, resulting in significant morbidity and mortality. Current standard of treatment for severe COVID-19 disease include corticosteroids to attenuate the inflammatory response.[11]

A randomized controlled trial evaluating the role of VCO for treatment of COVID-19 was published in 2021. This trial involved 63 adults in the Philippines with suspected or probable COVID-19. Results showed that significantly more participants in the VCO group had normal c-reactive protein (CRP) levels after treatment compared to the control group (relative risk [RR] 0.40, 95% confidence interval [CI] 0.16 to 0.99). VCO was also observed to shorten the duration of symptoms when used in conjunction with standard therapy for COVID-19, with resolution of symptoms in all patients by day 18 of illness in the VCO group compared to day 23 in the control group.[12] However, patients in this study were not laboratory-confirmed COVID-19 patients and the study was restricted to patients in community isolation facilities. A randomized controlled trial conducted in Indonesia showed that VCO use among confirmed COVID-19 hospitalized patients led to significant reduction in IL-1β, IL-2, IL-6, TNF-α, and IFN-β levels.[13]

Safety trials on VCO use show no significant adverse effects in electrolytes, liver function tests, and kidney function tests among volunteers given 30 mL of virgin coconut oil daily for four weeks. Some studies report that VCO can cause mild diarrhea, abdominal pain, nausea, and vomiting. The effect of VCO on lipids is still to be fully elucidated, as some studies report increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), while other studies report no significant adverse changes in lipid profile. One study conducted in the Philippines reported increase in fasting blood sugar (FBS) and creatinine among healthy volunteers given 15 mL of virgin coconut oil three times daily for six weeks.[6]

The use of VCO as an adjunctive therapy among hospitalized patients with COVID-19 has not been fully explored. This study aimed to determine the safety and efficacy of VCO as an adjunctive therapy among hospitalized COVID-19 patients. With the continuous emergence of new variants of COVID-19, the need to explore new treatment options for COVID-19 that is effective, safe, and locally available remains to be of utmost importance in scientific research.

METHODS

Study Design

This study is a randomized controlled trial among hospitalized patients admitted at the Philippine General Hospital (PGH) with COVID-19. Patients aged 18 years old and above with laboratory-confirmed (i.e., reverse transcription polymerase chain reaction [RT-PCR] positive) COVID-19, and able to take food and medicines enterally, were invited to participate in the study. The exclusion criteria were: 1) uncontrolled or newly diagnosed diabetes mellitus; 2) chronic heart disease; and 3) elevated lipid profile at hospital admission. The conditions specified in the exclusion criteria confer a higher risk of adverse events from VCO intake based on review of related literature. Other comorbidities were not excluded so as not to limit the applicability and generalizability of the results of the study.

Eligible patients were randomized with an allocation ratio of 1:1 to the treatment group receiving VCO along with local standard of care, or the control group receiving standard care only.

Interventions

The VCO used in the study was analyzed by the Laboratory Services Division of the Philippine Coconut Authority

(PCA). The composition of VCO are as follows: lauric acid (47.96%), myristic acid (20.26%), palmitic acid (9.08%), caprylic acid (6.99%), capric acid (6.49%), oleic acid (5.18%), stearic acid (3.11%), linoleic acid (0.81%), and caproic acid (0.12%). The VCO used in the study was administered within six months from the date of manufacture. The VCO was supplied in unmarked polyethylene terephthalate (PET) bottles and were coded before administration. The VCO was kept at room temperature, away from sunlight until use. Standardized VCO formulation was based on published reports.[2]

Participants in the treatment group received 15 mL of VCO given thrice a day after meals for two weeks, administered orally or via nasogastric tube. This dose was the established VCO dose used in previous human trials.[14,15]

Outcomes

The primary outcomes of this study were the duration of hospital stay and time to recovery/resolution of symptoms. Secondary outcomes included mortality, need for intensive care unit (ICU) admission, time to first ICU admission, need for invasive ventilation, time to first receiving invasive ventilation, conversion of RT-PCR result after two weeks, adverse events, and change in laboratory parameters, including white blood cell (WBC) count, ferritin, CRP, lactate dehydrogenase (LDH), IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10 IL-18, TNF-α, IFN-γ, IFN-γ inducible protein 10 (IP-10) and anti-spike protein immunoglobulin G (IgG) levels.

Peripheral blood was collected from each participant at baseline and weekly thereafter until the end of study participation. Safety monitoring of study participants included measurement of their lipid profile, FBS, and creatinine using serum specimens. Elevation in lipid levels (TC >300 mg/dL) or FBS (>126 mg/dL) was considered grounds to discontinue VCO administration. Another criterion for discontinuation is development of adverse effects including diarrhea, abdominal pain, and vomiting assessed by the attending physician as severe enough to warrant VCO discontinuation. Appropriate treatment for the adverse effects was instituted by the attending physician with the cost incurred by the study. VCO administration was also discontinued among participants who became unable to tolerate enteral intake. Participants who discontinued VCO intake were still followed up to ascertain their outcomes. These participants were included in the intention-to-treat analysis.

There were no changes made to trial outcomes upon the commencement of the study.

Sample Size

The estimated mean hospital stay of 15 days was taken from the observed national trend for Philippine patients with COVID-19 on local standard of care during May 2020.[16] This observed trend ranged from 12 to 15 days. We assumed a variability of about three days. Using these estimates, we computed that a total sample size of 74 (group n=37) is adequate to detect a difference of at least two days or greater between the two groups using a two-sided independent t-test at an alpha of 0.05 and beta of 0.2.

Randomization

The principal investigator facilitated the randomization of the study participants using a randomization module in Research Electronic Data Capture (REDCap) software. REDCap (https://www.project-redcap.org/) is a secure, web-based application used worldwide by a consortium of more than 3,000 research institutions in 126 countries, including Harvard (https://catalyst.harvard.edu/services/redcap/), Yale (https://redcapportal.yale.edu/), and Oxford (http://www.imsu.ox.ac.uk/services/redcap) for collecting and managing research and administrative data, and facilitating collaborative research activities. Simple randomization was done. The allocation sequence was created by an independent biostatistician, who was not part of the study group. This was encoded and concealed in the REDCap software, which was only accessible to a few co-investigators (FMMC). The allocation sequence was not accessible to the research staff in charge of participant enrolment and assignment to interventions.

Blinding

This was an open-label trial. Oil-based placebo was not used as this may confound outcomes. Study participants and the attending physician were aware of treatment assignments. Outcome assessors were blinded to treatment allocation.

Statistical Methods

Study results were reported and summarized as mean ± standard difference (SD), counts (n), percentages (%), or median and interquartile range (IQR), whichever was appropriate. Statistical significance was computed using the Mann-Whitney U test for the primary outcomes.

Both per-protocol and intention-to-treat analyses were conducted. Participants with an intake of at least 10 days of VCO (70% of the total recommended dose) were included in the per-protocol analysis.

Secondary outcomes comparing continuous data and change in values of laboratory parameters, or values at the last day of the study between the two groups were compared using Mann-Whitney U Test. Secondary outcomes measured as binary data or nominal data were analyzed using Fisher's exact test.

Registration

The study protocol was registered at clinicaltrials.gov (NCT04849637) on April 19, 2021 and the Philippine Health Research Registry (PHRR210303-003392). The full protocol is available upon request from the corresponding author.

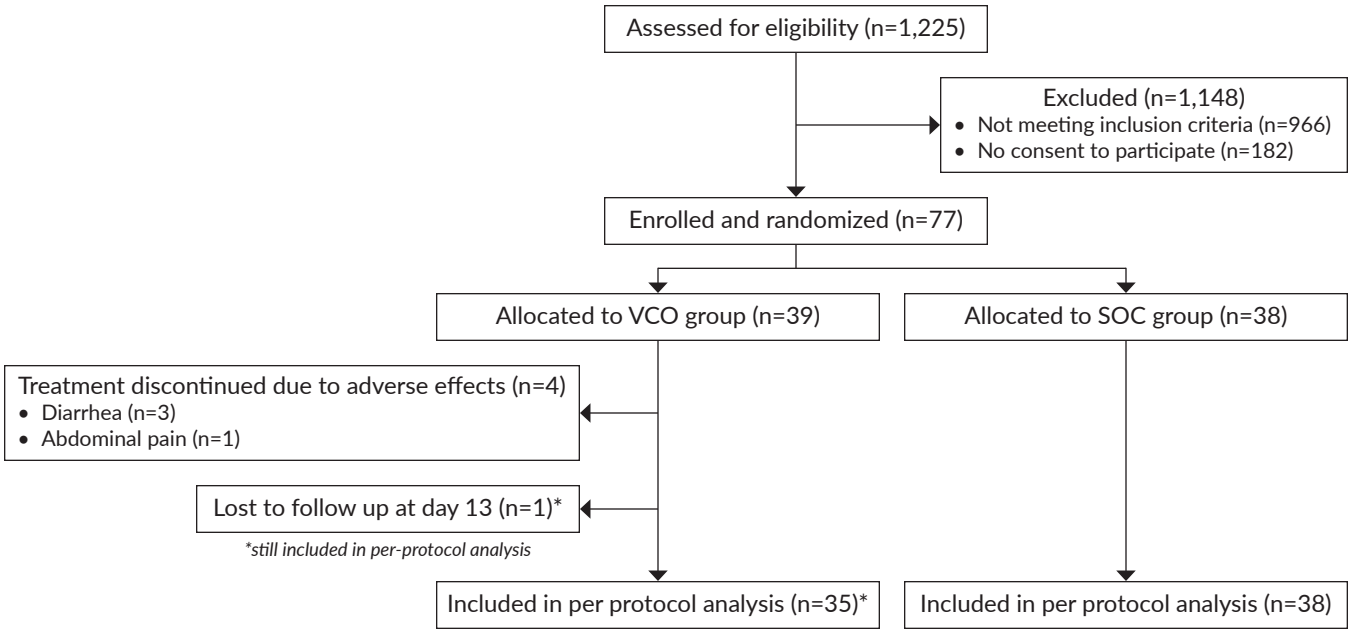

Figure 1. Study participants flow diagram.

Ethical Consideration

This study received approval from the UP Manila Research Ethics Board (UPMREB 2020-0306-01v).

RESULTS

Study Participants

From October 2020 to July 2021, 1,225 patients were screened for eligibility, of which 966 did not meet the inclusion criteria and 182 did not consent to participate. A total of 77 participants were enrolled in the study. There were 39 participants randomized into the treatment group and 38 participants randomized into the control group. Study participants were followed up for two weeks. Of the 39 participants in the treatment group, one was lost to follow-up by Day 13. There were four patients who discontinued VCO due to adverse events. All 77 participants were included in the intention-to-treat analysis. A total of 73 participants were included in the per-protocol analysis. The four study participants who discontinued treatment due to adverse effects were excluded from the per-protocol analysis. The study participant flow diagram is shown in Figure 1.

This flow diagram shows the number of participants assessed for eligibility, enrolled and randomized to the treatment and control group, and included in the data analysis. VCO = virgin coconut oil, SOC = standard of care alone

The baseline clinical characteristics of the study participants in the treatment and control groups are shown in Table 1. There was no significant difference between the two groups. The baseline laboratory parameters are shown in Table 2. The study participants in the VCO group had higher HDL levels (mean 37.87 mg/dL) compared to the control group (mean 32.75 mg/dL), p=0.04. There was no statistically significant difference between the two groups for the rest of the laboratory parameters.

Primary Outcomes

There was no significant difference in the duration of hospital stay between the VCO group (mean 9.33 days, SD 5.21) and the control group (mean 10.29 days, SD 5.38), with p-value 0.45, using intention-to-treat analysis. Excluding the three asymptomatic patients from the analysis, there was still no significant difference in the duration of hospital stay (mean 9.55 days vs 10.67 days, p=0.36). Analysis by COVID-19 severity on enrolment showed no significant difference in duration of hospital stay in all disease severity levels, including those with asymptomatic (p=0.22), mild (p=1.00), moderate (p=0.21), severe (p=0.12), and critical disease (p=0.11). The results are summarized in Table 3.

There was also no significant difference in time to symptom resolution (combined endpoint) between the VCO group (mean 6.80 days, SD 3.58, range 1-16) and control group (mean 6.74 days, SD 3.34, range 1.5-14; p=0.91). Analyzing the individual symptoms, there was no significant difference for all COVID-19-related symptoms (Table 4). No significant difference was noted in the proportion of patients who reported symptom resolution within 14 days between the VCO and control group (Table 5).

In the per-protocol analysis where the study participants with VCO intake of fewer than 10 days were excluded, there was still no significant difference in duration of hospital stay (mean 9.29 days vs 10.29 days, p=0.44) and time to symptom resolution as a combined endpoint (mean 6.50 days vs 6.73 days, p=0.67). The results are shown in Table 6.

Secondary Outcomes

Although there were more deaths in the control group (3 out of 38 participants, 8%) compared to no deaths in the VCO group, the difference did not reach statistical significance (p= 0.07).

No participants in the VCO group needed ICU admission, while there was one participant (2.6%) in the control group that needed to be admitted to the ICU. However, the difference did not reach statistical significance (p=0.50). The time to ICU admission was six days for the study participant in the control group.

No participants in the VCO group necessitated invasive ventilation, while there were three in the control group (8%). However, the difference again did not reach statistical significance (p= 0.12). The mean time to first receiving invasive ventilation among the participants in the control group was 3.67 days (SD 3.06).

The proportion of participants who achieved viral conversion to negative RT-PCR after 14 days was lower in the VCO group (22%) compared to the control group (29%). However, results did not reach statistical significance (p=0.59). The cycle threshold (CT) values among the study

Table 1. Baseline Clinical Characteristics of Study Participants

Parameters	VCO (n=39)	Control (n=38)	*p*-value
Age, mean (SD)	51 (14)	53 (17)	0.65
Males, n (%)	26 (67)	25 (66)	1.00
Symptomatic, n (%)	36 (92.3)	34 (89.5)	0.667
With comorbidity, n (%)	22 (66)	25 (56)	0.40
Diabetes	3 (8)	5 (13)	0.48
Hypertension	17 (44)	14 (37)	0.64
Heart Disease	0	1 (3)	0.49
Liver Disease	0	2 (5)	0.24
Kidney Disease	1 (3)	0	1.00
Asthma	2 (5)	1 (3)	1.00
Tuberculosis	0	1 (3)	0.49
Cancer	2 (5)	0	0.49
COVID Severity on enrolment, n (%)			
Asymptomatic	1 (3)	2 (5)	
Mild	1 (3)	1 (3)	0.99
Moderate	10 (26)	10 (26)	
Severe	15 (38)	13 (34)	
Critical	12 (31)	12 (32)	
Oxygen support on enrolment, n (%)			0.46
No oxygen support	11 (28)	13 (34)	
Low flow oxygen	17 (44)	18 (47)	
High flow oxygen	11 (28)	6 (16)	
Invasive ventilation	0 (0)	1 (3)	
Week of illness on enrolment, n (%)*			0.52
Week 1	20 (53)	18 (50)	
Week 2	18 (47)	16 (44)	
Week 3	0 (0)	2 (6)	
Symptoms, n (%)*			
Cough	36 (95)	31 (86)	0.26
Difficulty breathing	33 (87)	28 (78)	0.37
Weakness	11 (29)	16 (46)	0.15
Loss of appetite	11 (29)	11 (31)	1.00
Ageusia/dysgeusia	6 (16)	3 (8)	0.48
Anosmia/hyposmia	3 (8)	2 (6)	1.00
Diarrhea	3 (8)	0	-
Fever	1 (3)	1 (3)	1.00
Colds	1 (3)	1 (3)	1.00
Myalgia	0	2 (6)	-
Sore throat	1 (3)	0	-
Nausea	1 (3)	0	-
Vomiting	1 (3)	0	-
Other treatment received, n (%)			
Steroids	28 (72)	29 (76)	0.80
Remdesivir	22 (56)	23 (61)	0.82
Tocilizumab	21 (54)	19 (50)	0.82

**Excludes asymptomatic study participants*

Table 2. Baseline Laboratory Parameters of Study Participants

Laboratory Parameters	VCO, Mean (SD)	Control, Mean (SD)	*p*-value
White blood cell count (x 10^9 cells/L)	8.74 (3.94)	9.72 (5.00)	0.48
Ferritin (ng/L)	1136.99 (885.06)	1234.24 (1169.57)	0.84
C-Reactive Protein (mg/L)	82.85 (61.99)	68.25 (70.51)	0.15
Lactate Dehydrogenase (U/L)	436.39 (218.10)	462.37 (449.10)	0.48
Creatinine (umol/L)	114.18 (201.78)	82.80 (101.42)	0.16
Aspartate aminotransferase ((U/L)	72.27 (44.37)	71.78 (42.81)	0.92
Alanine transaminase (U/L)	75.10 (40.12)	86.78 (73.59)	0.93
Albumin (g/L)	35.59 (8.00)	33.27 (8.36)	0.17
Fasting blood sugar (mg/dL)	97.98 (22.32)	94.44 (22.11)	0.45
Total cholesterol (mg/dL)	155.43 (25.03)	148.63 (38.88)	0.67
High-density lipoprotein (mg/dL)	37.87 (12.67)	32.75 (14.89)	0.04
Low-density lipoprotein (mg/dL)	94.26 (24.07)	92.92 (25.77)	0.96
Triglycerides (mg/dL)	119.98 (37.95)	142.01 (63.02)	0.16
Total bilirubin (umol/L)	11.64 (6.00)	12.58 (7.36)	0.95
Direct bilirubin (umol/L)	5.00 (3.06)	5.2 (3.77)	0.77
Indirect bilirubin (umol/L)	6.89 (4.69)	7.62 (4.87)	0.67
IFN-gamma (pg/mL)*	54.64 [8.87-98.50]	19.46 [7.38 - 44.02]	0.33
TNF-alpha (pg/mL)*	41.74 [24.87 - 78.67]	45.69 [29.36 - 193.30]	0.33
IP-10 (pg/mL)*	2670.43 [556.41 - 6702.84]	2390.20 [420.30 - 8151.08]	0.83
IL-1B (pg/mL)*	33.00 [17.16 - 127.44]	24.54 [4.89 - 84.53]	0.42
IL-2 (pg/mL)*	1.74 [0.19 - 5.03]	0.66 [0.30 - 6.86]	0.85
IL-4 (pg/mL)*	3.04 [0.20 - 131.61]	209.90 [0.02 - 222.74]	0.51
IL-6 (pg/mL)*	72.39 [31.31 - 241.75]	50.99 [10.91 - 211.21]	0.39
IL-8 (pg/mL)*	208.32 [127.20 - 314.51]	236.75 [77.47 - 305.41]	0.67
IL-10 (pg/mL)*	18.81 [1.81 - 96.39]	50.61 [16.02 - 629.27]	0.26
IL-18 (pg/mL)*	119.65 [49.97 - 206.56]	144.93 [80.07 - 295.26]	0.19
Anti-spike protein IgG (U/mL)*	0.09 [0.07-0.13]	0.10 [0.07 -0.15]	0.57

**reported as median [IQR]*

Table 3. Duration of Hospital Stay– Intention to Treat Analysis

Duration of hospital stay (days)	VCO			Control			*p*-value
	Mean (SD)	Range	n	Mean (SD)	Range	n	
All study participants	9.33 (5.21)	1-25	39	10.29 (5.38)	3-25	38	0.45
Symptomatic study participants	9.55 (5.10)	2-25	38	10.67 (5.27)	4-25	36	0.36
Asymptomatic	1	-	1	3.5 (0.5)	3-4	2	0.22
Mild	4	-	1	24	-	1	1.00
Moderate	9.2 (2.3)	2-25	10	11.7 (1.9)	4-22	10	0.21
Severe	8.3 (1.1)	4-19	15	9.5 (0.7)	7-15	13	0.12
Critical	11.8 (0.9)	7-18	12	9.9 (1.6)	4-25	12	0.11

Table 4. Time to Symptom Resolution – Intention to Treat Analysis

Time to symptom resolution (days)	VCO		Control		*p*-value
	Mean (SD)	n	Mean (SD)	n	
All symptoms – combined endpoint	6.80 (3.58)	38	6.74 (3.34)	36	0.91
Cough – median (IQR)	7.5 (4-13)	36	7.5 (5.5-11.5)	32	0.88
Difficulty of breathing – median (IQR)	8 (4-13)	38	6 (3-11)	29	0.05
Weakness– median (IQR)	4 (2-6)	11	5 (2-7.5)	16	0.72
Loss of appetite – median (IQR)	4 (2-6)	11	5 (2-7)	11	0.72
Ageusia/dysgeusia – median (IQR)	3 (2-4)	6	4 (1-7)	3	0.60
Anosmia/hyposmia – median (IQR)	2 (2-4)	3	5 (3-7)	2	0.24
Fever - median, (IQR)	7	1	1	1	0.32
Colds – median (IQR)	2	1	1	1	0.32

Table 5. Proportion of Participants with Symptom Resolution within 14 days – Intention to Treat Analysis

Symptoms, n/N	VCO	Control	RR (95% CI)	*p*-value
No symptoms within 14 days	2/38	5/36	0.38 (0.08, 1.83)	0.26
Cough	34/36	32/32	0.95 (0.86, 1.04)	0.50
Difficulty breathing	30/38	29/29	0.80 (0.67, 0.94)	0.24
Weakness	10/11	16/16	0.90 (0.72, 1.13)	0.41
Loss of appetite	10/11	11/11	0.91 (0.72, 1.17)	1.00
Ageusia/dysgeusia	6/6	3/3	1.00 (0.65, 1.53)	-
Anosmia/hyposmia	3/3	2/2	1.00 (0.53, 1.87)	-
Fever	1/1	1/1	1.00 (0.32, 3.10)	-
Colds	1/1	1/1	1.00 (0.32, 3.10)	-
Diarrhea	3/3	0/0	-	-
Myalgia	0/0	2/2	-	-
Sore throat	1/1	0/0	-	-
Nausea	1/1	0/0	-	-
Vomiting	1/1	0/0	-	-

**VCO (n = 36); Control (n=35)*

Table 6. Primary Outcomes – Per-Protocol Analysis

Primary Outcome	VCO			Control			*p*-value
	Mean (SD)	Range	n	Mean (SD)	Range	n	
Duration of hospital stay (days)	9.29 (5.29)	1-25	35	10.29 (5.38)	3-25	38	0.44
Time to symptom resolution - combined endpoint (days)*	6.50 (3.50)	1-16	34	6.73 (3.30)	1.5-14	36	0.67

**Excludes asymptomatic patients*

Table 7. Secondary Outcomes

Secondary Outcomes	VCO (n=39)	Control (n=38)	RR (95% CI)	*p*-value
Mortality - n (%)	0 (0)	3 (8)	0.14 (0.01, 2.61)	0.07
Need for ICU admission - n (%)	0 (0)	1 (2.6)	0.33 (0.01, 7.74)	0.50
Time to first ICU admission - narrative	-	6 days	-	-
Need for invasive ventilation - n (%)	0 (0)	3 (8)	0.14 (0.01, 2.61)	0.12
Time to first receiving invasive ventilation - mean (SD)	-	3.67 days (3.06)	-	-
Viral conversion to negative RT-PCR - n (%)*	8 (22)	10 (29)	0.78 (0.35, 1.74)	0.59

**VCO (n = 36); Control (n=35)*

participants who remained RT-PCR positive after 14 days were compared between the VCO group (n=28) and the control group (n=25). The mean CT value for ORF1 AB region in the VCO group was 36.5 (SD 3.0), while the mean value for the control group was 36.0 (SD 2.6). The results were not statistically different (p=0.16). The mean CT value for N Gene was 36.0 (SD 3.4) in the VCO group, while the mean value was 35.0 (SD 2.9) in the control group. Results were again not statistically different (p=0.07). The secondary outcomes are summarized in Table 7.

There was no significant difference in the mean change in the inflammatory markers between VCO and control groups from baseline to the end of the 14-day treatment, as shown in Table 8. The mean reduction in the levels of inflammatory markers including ferritin, CRP, and LDH in the VCO group was larger compared to control; however, results did not reach statistical significance.

Analysis of the inflammatory markers as binomial data (normal or abnormal value) showed that significantly fewer study participants in the VCO group had abnormal CRP levels at the end of treatment compared to the control. In the VCO group, 70% (23 out of 33 study participants, six participants had no data available) had abnormal CRP values at the end of treatment, compared to 94% in the control group (29 out of 31 study participants, seven participants had no data available), with RR of 0.75, 95% CI 0.58 to 0.95, p=0.02. There was no significant difference in the proportion of study participants with abnormal LDH at the end of treatment in the VCO group (57% or 20 out of 35 study participants, 4 with no data available) and control group (39% or 12 out of 31 study participants, 7 with no data available), with an RR of 1.48, 95% CI 0.87 to 2.50, p=0.15. There was also no significant difference in the proportion of study participants with abnormal ferritin at the end of treatment in the VCO group (58% or 21 out of 36 study participants, 3 participants with no data available) and control group (65% or 20 out of 31 study participants, 7 participants with no data available), with an RR of 0.90, 95% CI 0.62 to 1.32, p=0.60.

There was a larger reduction in TNF-alpha, IP-10, and IL-6 from baseline to end of treatment in the VCO group compared to control, but results did not reach statistical significance. The results are in Table 9.

The change in anti-spike protein IgG levels is shown in the time series analysis in Figure 2. The confidence intervals of the VCO and control group overlap widely, indicating no significant difference between the two groups. The median and IQR levels of the anti-spike protein IgG are reported in Table 10 similarly demonstrating wide overlap in the IQR levels.

The change in anti-spike protein IgG levels shown in the time series analysis demonstrate wide overlap in the confidence intervals and no significant difference between the two groups.

Safety monitoring

Adverse events were significantly higher among those who received VCO (25%) compared to control (5%), with p-value of 0.03. The most common adverse events reported were diarrhea and abdominal pain. There were four study participants who discontinued VCO administration due to adverse events. Two of these study participants developed diarrhea after two doses of VCO (day 1 of administration), while one study participant developed abdominal pain after two doses of VCO. Hence, VCO administration was discontinued on day 1 for these three study participants. One study participant developed abdominal pain and diarrhea on the second day of VCO administration. Initially, the symptoms were tolerated by the patient. However, due to escalating severity of adverse events, VCO was discontinued by day 6 of administration. Adverse events that were observed are summarized in Table 11.

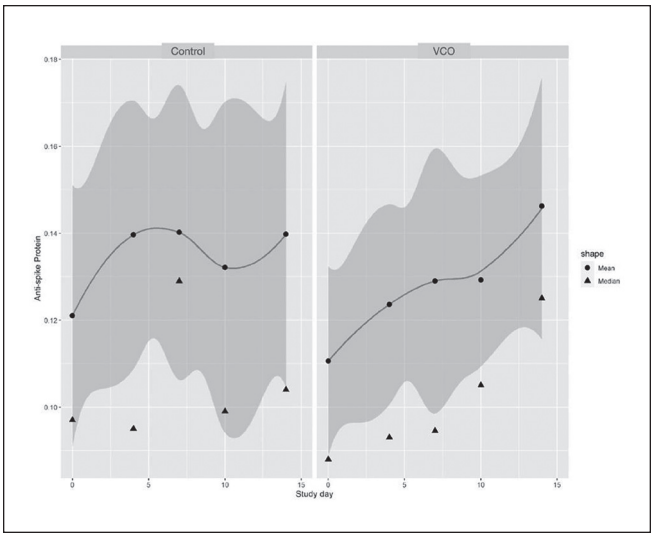

Figure 2. Time series analysis of anti-spike protein IgG levels of VCO and control group.

Monitoring of liver and kidney function showed no significant difference in the mean change of creatinine, AST, ALT and albumin from baseline to end of the 14-day treatment for the VCO and control group. Although the LDL for the VCO group had a mean increase of 17.05 mg/dL compared to a mean reduction of 0.22 mg/dL in the control group, values were not statistically different (p=0.08). There was also no significant difference in the mean change in fasting blood sugar (p=0.15), total cholesterol (p=0.59), HDL (p=0.27), and triglycerides (p=0.30). Laboratory parameters for safety monitoring are shown in Table 12.

Table 8. Change in Inflammatory Markers

Laboratory Parameters	VCO			Control			*p*-value
	Mean difference	SD	n	Mean difference	SD	n	
WBC count (x 10^9 cells per liter)	-0.36	3.53	36	-1.42	5.42	34	0.19
Ferritin (ng/L)	-421.59	622.01	33	-170.34	983.87	30	0.50
CRP (mg/L)	-76.13	64.71	31	-60.01	75.34	29	0.13
LDH (U/L)	-164.66	178.76	32	-133.43	176.36	30	0.39

Table 9. Change in Cytokine Levels

Cytokine Levels	VCO			Control			*p*-value
	Median difference	IQR	n	Median difference	IQR	n	
IFN-gamma (pg/mL)	0.00	-26.55 to 17.83	10	0.00	-1.79 to 34.26	9	0.74
TNF-alpha (pg/mL)	-8.63	-33.04 to 18.73	16	0.00	-18.19 to 21.95	14	0.59
IP-10 (pg/mL)	-756.37	-6393.69 to -6.39	24	-4.49	-5981.14 to 114.66	21	0.57
IL-1B (pg/mL)	97.16	-172.19 to 342.86	4	0.00	-21.15 to 16.80	6	0.34
IL-2 (pg/mL)	-0.07	-0.74 to 0.00	7	0.16	0.00 to 0.16	5	0.29
IL-6 (pg/mL)	-5.36	-104.28 to 67.49	25	2.94	-8.39 to 22.97	21	0.38
IL-8 (pg/mL)	139.97	-147.45 to 578.97	25	334.69	0.00 to 751.36	21	0.42
IL-10 (pg/mL)	0.00	-1.77 to 131.81	3	1.94	-843.01 to 9.83	4	1.00
IL-18 (pg/mL)	10.44	-14.94 to 28.39	22	18.05	-66.94 to 81.43	16	0.53

Table 10. Anti-spike Protein IgG Levels

Anti-spike protein IgG (U/mL)	VCO			Control		
	Median	IQR	n	Median	IQR	n
Baseline	0.09	0.07 – 0.13	39	0.10	0.07 – 0.15	37
Day 4	0.09	0.07 – 0.16	35	0.10	0.08 – 0.16	35
Day 7	0.09	0.07 – 0.17	20	0.13	0.09 – 0.18	29
Day 10	0.11	0.08 – 0.16	25	0.10	0.09 – 0.18	23
Day 14	0.13	0.11 – 0.17	20	0.10	0.07 – 0.16	27

Table 11. Adverse Events

Adverse events - n (%)	VCO (n=39)	Control (n=38)	RR (95% CI)	*p*-value
Diarrhea	6 (15)	1 (3)	5.85 (0.74, 46.30)	0.11
Abdominal pain	4 (10)	0	8.78 (0.49, 157.62)	-
Fever	1 (3)	1 (3)	0.97 (0.06, 15.02)	-
Loss of appetite	1 (3)	0	2.92 (0.12, 69.64)	-
Vomiting	1 (3)	0	2.92 (0.12, 69.64)	-
Combined adverse events*	10 (25)	2 (5)	4.87 (1.14, 20.79)	0.03

**Count of individuals with at least 1 adverse events*

Table 12. Laboratory Parameters for Safety Monitoring

Laboratory Parameters	VCO		Control		*p*-value
	Mean difference	SD	Mean difference	SD	
Creatinine (umol/L)	-17.89	83.41	13.47	117.65	0.71
AST (U/L)	-40.55	69.04	-9.55	64.07	0.53
ALT (U/L)	34.80	45.21	-7.27	74.20	0.09
Albumin (g/L)	2.90	10.53	2.52	10.27	0.94
FBS (mg/dL)	-13.23	32.25	-8.6	22.12	0.15
Total cholesterol (mg/dL)	53.87	71.43	45.10	58.66	0.59
HDL (mg/dL)	19.69	15.19	15.29	15.54	0.27
LDL (mg/dL)	17.05	45.18	-0.22	37.50	0.08
Triglycerides (mg/dL)	61.23	71.64	130.01	156.22	0.30

DISCUSSION

This randomized controlled study on hospitalized patients with RT-PCR-confirmed COVID-19 infection showed no significant benefit of VCO administration in clinical outcomes, including duration of hospital stay, time to symptom resolution, mortality, need for ICU admission, need for invasive ventilation, and negative viral conversion.

There were significantly more participants in the VCO group who had normal CRP levels after treatment compared to the control group. Our results are similar to the published study of Angeles-Agdeppa et al. which reported that more participants in the VCO group had normal CRP levels after treatment compared to the control group (p=0.035).[12] This finding is consistent with the anti-inflammatory properties of VCO.[5] However, the anti-inflammatory properties of VCO may not be robust enough to cause an observable benefit in the various clinical outcomes measured in this study.

Another possible explanation is that the study was not powered enough to detect significant benefit in the secondary outcomes. The sample size of this study was computed to power the primary outcome of duration of hospital stay and time to recovery. A larger sample size is required for the secondary outcomes. The proportion of patients in the VCO group who developed the secondary outcomes of mortality, need for ICU admission, need for invasive ventilation, and negative viral conversion was observed to be lower in the VCO group compared to control. The mean reduction in the inflammatory markers ferritin, LDH, and CRP, as well as the inflammatory cytokines TNF-alpha, IP-10, and IL-6 was larger in the VCO group compared to control. IP-10 has been demonstrated to be an excellent predictor for the progression of COVID-19.[17] IL-6 and THF-alpha are predictors of disease severity and death.[18]

There was a significantly increased risk for adverse events among those given VCO, with diarrhea and abdominal pain being the most commonly reported symptoms. Four study participants experienced adverse events (abdominal pain and diarrhea) severe enough to necessitate discontinuation of VCO administration. This finding is consistent with the safety trials on VCO that reported gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain as the most commonly reported adverse events, and these were most often observed in the first week of administration.

The main limitation of this study is the open-label study design, due to the difficulty in procuring a suitable placebo that will not confound study outcomes. Although the open-label design may predispose to certain biases such as reporting bias of subjective outcomes from the study participants and possible co-interventions provided by the clinicians, the study aimed to minimize such bias by blinding the outcome assessors. There was also no significant difference in the treatments provided to the study participants in the VCO and control group, particularly the number of study participants who were given steroids, remdesivir, and tocilizumab. Furthermore, the results of this study are consistent across the different clinical outcomes, including both objective and subjective outcomes, as there was no significant benefit for VCO observed in all measured clinical outcomes.

The study participants in this RCT included hospitalized confirmed COVID-19 patients, with varying disease severity (asymptomatic, mild, moderate, severe, critical) and varying oxygen requirements (no oxygen support, low-flow oxygen, high-flow oxygen, invasive ventilation). The results of this study can be applied to hospitalized COVID-19 patients regardless of disease severity and oxygen requirements.

The relative risk for mortality, need for ICU admission, need for invasive ventilation, proportion of participants with symptom resolution, and viral conversion showed potential for benefit with VCO, but the wide confidence intervals preclude definite conclusions to be made. Inflammatory markers and cytokines also demonstrated a trend towards greater reduction among the VCO group compared to control. Larger studies are needed to conclusively determine the effect of VCO on these outcomes.

CONCLUSION

This clinical trial on hospitalized patients did not demonstrate significant benefit in the use of VCO as adjunctive therapy in reducing duration of hospital stay for COVID-19 patients, with significantly increased risk for adverse events. Larger studies are needed to conclusively demonstrate the effect of VCO on other clinical outcomes such as mortality, need for ICU admission, need for invasive ventilation, proportion of participants with symptom resolution, and viral conversion, and the effect on levels of inflammatory markers and cytokines.

Recommendation

Larger studies are needed to conclusively determine the effect of VCO on other clinical outcomes mentioned above. RCTs that evaluate the possible difference in effect of VCO based on patient characteristics, including sex, age (young adults compared to older adults), and presence or absence of co-morbidities may be done to further explore the possible effect of VCO on COVID-19.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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