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RESEARCH ARTICLE

Efficacy of Quinine Sulfate in Patients with Mild-To-Moderate COVID-19: A Randomized Controlled Trial

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Abstract

BACKGROUND: Before WHO revoked the emergency use authorization for Chloroquine (CQ) and Hydroxychloroquine (HCQ) because of their side effects, it was suggested to use these two drugs for COVID-19 therapy. In addition, another derivate of quinine, namely Quinine Sulfate (QS), showed good in *silico* and *in vitro* antiviral activity against SARS-CoV-2. Prior the WHO revocation, this study was conducted to evaluate the efficacy of QS in mild-to-moderate COVID-19 patients.

METHODS: This was an adaptive, controlled, multicenter, randomized, double-blind clinical trial involving mild-to-moderate COVID-19 patients in Indonesia. The participants were divided into 2 groups: the control group (standard COVID-19 treatment + placebo) and the treatment group (standard COVID-19 treatment + QS). The primary outcome was the efficacy of QS based on clinical status using a 7-point ordinal scale. The secondary outcomes were the efficacy of QS in terms of the incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay.

RESULTS: No significant difference in the efficacy parameters studied was found between the control group and the treatment group. The difference in the mean oxygen saturation was also measured and the results showed a significant difference where the treatment group had higher mean oxygen saturation than the control group (p=0.001).

CONCLUSION: Although not significant, the treatment group showed better therapy outcomes compared to the control group.

KEYWORDS: clinical trials, efficacy, quinine, chloroquine, hydroxychloroquine

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Introduction

The infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) were a global health threat.(1) COVID-19 was spreading rapidly worldwide, with high morbidity and mortality rates.(2) During this progression, the virus mutated rapidly, forming new variants continuously (3), and more potent variants have emerged in each country independently (4). The World Health Organization (WHO) has defined the most infectious subtype that has spread across borders as the variant of concern or variant of interest.(5)

Various countries have taken steps to eradicate this disease, one of which is vaccination.(6) Vaccines have been proven to be very effective and have caused a significant decrease in the number of infections for a while.(7,8) However, as the virus continues to mutate, the effectiveness of vaccines continues to decrease.(9-11) In Australia, for example, cases of infection with the omicron variant continue to increase despite the vaccination level and implementation of effective control measures.(12) Likewise, in Japan, vaccination history is not associated with the number of new positive cases.(13) The virus's rapid mutation outpaces the vaccine's ability to contain it, which means the virus may still remain contagious even after administering a third vaccine dose.(14) In addition, immunization is not effective in preventing long COVID-19, *i.e.*, a disease with long-lasting symptoms.(15,16)

Therefore, research on COVID-19 drugs was pursued. At the beginning of the pandemic, chloroquine (CQ) and hydroxychloroquine (HCQ) were included in the guidelines for the treatment of COVID-19, especially in Indonesia. CQ and HCQ are derivatives of quinine, a natural ingredient from the Cinchona bark extract that is commonly used to treat fever in malaria.(17,18) Quinine has antibacterial and antiviral activities for influenza, dengue, and herpes simplex virus infections.(14,19,20) Another derivate of quinine, namely Quinine Sulfate (QS) showed good *in silico* and *in vitro* antiviral activity against SARS-CoV-2. Therefore, a clinical trial study was conducted to evaluate the efficacy of QS in adults who were hospitalized for COVID-19 and received standard treatment + placebo compared with adults who received standard treatment + QS. Although, later studies indicated some serious side effects with CQ and HCQ, leading to revocation by WHO on the emergency use authorization for CQ and HCQ (21), this clinical trial results should be important for enrichment in medical science.

Methods

Study Design

This adaptive, controlled, multicenter, randomized, double-blind clinical trial evaluated the efficacy of QS in adults who were hospitalized and diagnosed with mild-to-moderate COVID-19 by real time polymerase chain reaction (PCR) and clinical symptoms. The study was conducted at Gatot Soebroto Army Central Hospital, Jakarta, and Hasan Sadikin General Hospital, Bandung. The participants were divided into 2 groups: the control group that received standard COVID-19 treatment + placebo; and the treatment group that received standard COVID-19 treatment + QS. Randomization was performed randomly with a 1:1 ratio for the control group and treatment group.

The drug regimen used refers to the COVID-19 Treatment Management Protocol (4th Edition, 2022) applicable in Indonesia.(25) In the control group, both mild and moderate cases receive standard COVID-19 treatment + placebo. In the treatment group with mild cases, subjects received standard COVID-19 treatment + QS 1×400 mg for 5 days. For moderate cases, subjects received standard COVID-19 treatment + QS 2×400 mg on the first day and 1×400 mg on the next day for 5-7 days.

Subjects Recruitment

The clinical trial lasted for a period of one year, from March 2021 to February 2022. The study involved 25 male and female adult patients aged 18-50 years who were hospitalized for mild-to-moderate COVID-19 based on clinical symptoms and confirmed by a positive PCR. Subjects with mild symptoms included: symptomatic patients without evidence of viral pneumonia or without hypoxia; symptoms that appear such as fever, cough, fatigue, anorexia, shortness of breath, myalgia; other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia) or loss of taste (ageusia); elderly and immunocompromised patients with atypical symptoms such as fatigue, decreased consciousness, decreased mobility, diarrhea, loss of appetite, delirium, and no fever; oxygenation status : SpO_2 >95% with room air. Meanwhile, subjects with moderate symptoms are patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including SpO_2 ≥93% with room air.(25)

Subjects were eligible to participate in this study if they fulfilled the following criteria: aged ≥18 years (up to 50 years); hospitalized for COVID-19 with mild to moderate symptoms; willing to randomly accept one of the drug groups (control group or treatment group); were not participating in other research studied at the time of the present study; signed the information sheet and subject consent/informed consent.

Subjects were excluded if they: received QS, CQ, HCQ, lumefantrine, or mefloquine within 30 days prior to this study; had received treatment for COVID-19 prior to this study; had contraindications to QS; were unable to swallow pills or other reasons related to adherence to medical regimens; were pregnant and/or breastfeeding; had underlying severe illness for which treatment and follow-up were not beneficial based on the judgment of the physician;

their platelet count was less than 150,000 and more than 450,000 cells/μL; were to be transferred to a non-study hospital within 72 hours.

Outcomes

The primary outcome was the efficacy of QS based on clinical status using a 7-point ordinal scale as follows: 1, mortality; 2, hospitalization with invasive mechanical ventilation or extracorporeal membrane oxygenation; 3, hospitalization with non-invasive ventilation or high-flow oxygen device; 4, hospitalization, requires supplemental oxygen; 5, hospitalization, does not require additional oxygen; 6, not hospitalization with activity restrictions; 7, no hospitalization and no activity restrictions.(26) The clinical status of the subjects was assessed every day until day 10.

The secondary outcome was the efficacy of QS in terms of the incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and duration of hospitalization (length of stay).

Statistical Analysis

The T-independent difference test was conducted to determine the efficacy of QS in the control and treatment groups in terms of the primary (clinical status of subjects based on the 7-point ordinal scale) and secondary (incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay) outcomes.

Results

Initially, 27 subjects, but 2 subjects were excluded because they did not meet the pre-determined inclusion criteria; thus, a final of 25 subjects were included in the study. Then, the subjects were randomly assigned to the control group, which was given standard COVID-19 treatment alone (n=11), and the treatment group, which was given standard COVID-19 treatment + QS (n=14). As shown in Table 1, the random distribution of the subjects in the control and treatment groups showed that the two study samples did not initially

Table 1. Baseline data of subjects' demographics and clinical characteristics.

Variable	Control Group (n=11)	Treatment Group (n=14)	*p*-value
Sex, n			
Male	7	5	0.165
Female	4	9	
Age (year), mean±SD	33.45±12.27	37.93±8.95	0.698
Weight (kg), mean±SD	62.55±13.34	12.99±8.98	0.629
Height (cm), mean±SD	163.55±6.17	7432.83±7.70	0.308
Laboratory parameters, mean±SD			
Hematocrit (%)	41.85±2.58	37.93±3.93	0.009*
Hemoglobin (g/dL)	14.53±1.35	12.99±1.55	0.016*
White blood count (WBC) (10^3/μL)	5140.89±2766.16	7432.83±5265.75	0.251
Platelet (10^3/μL)	225818.18±49785.17	269285.71±66105.31	0.083
Creatinine (mg/dL)	0.81±0.10	0.81±0.15	0.979
ALT/SGPT (U/L)	26.40±11.79	22.36±7.62	0.358
AST/SGOT (U/L)	24.30±7.41	24.27±7.68	0.993
Bilirubin (mg/dL)	47.25±10.37	36.00±14.14	0.319
Urea (BUN) (mg/dL)	25.90±7.95	21.09±8.48	0.197
Clinical status, mean±SD			
Body temperature (°C)	36.35±0.26	36.50±0.39	0.266
Heart rate (/minute)	82.45±7.51	79.71±8.14	0.397
Respiratory rate (/minute)	20.18±0.60	19.86±0.53	0.167
Systolic (mmHg)	117.09±8.09	108.29±10.21	0.028*
Diastolic (mmHg)	77.09±5.45	73.07±6.03	0.098
Oxygen saturation (%)	97.91±0.83	98.50±1.02	0.133

*Considered significant if $p<0.05$, tested with T-independent difference test.

have different demographic characteristics; thus, whether QS was effective against COVID-19 requires continued research. Hematocrit (p=0.009) and hemoglobin (p=0.016) levels were found to be slightly lower in treatment group compared to control. These indicated that at starting point, some subjects in treatment groupwere slightly clinically worse. The systolic blood pressure was also lower in the treatment group (p=0.028) but still in the normal range.

The clinical efficacy of QS in adult subjects with mild-to-moderate COVID-19 symptoms compared with the control group was assessed considering the clinical status of the subjects based on a 7-point ordinal scale, incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay.

The primary outcome was the clinical efficacy of QS based on the clinical status of the subject according to the 7-point ordinal scale. The statistical test results were shown in Table 2. The average increase in the score of the subject's clinical status on days 0-10 were shown in Figure 1. Based on the results of the difference test between the control and the treatment group, the clinical status of the two groups on days 0-10 did not show a significant difference (p>0.05). However, the average change started on days 6-10, with higher improvements in the treatment group than in the control group (-0.30 *vs.* 0.15), and on day 10 (0.33 *vs.* 0.43), the treatment group had better clinical status and improved clinical condition than the control group.

The secondary outcomes included clinical efficacy based on the incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay. The incidence and duration of oxygen therapy was presented in Table 3. Furthermore, the average oxygen saturation was shown in Table 4. The results of the statistical analysis showed no significant difference between

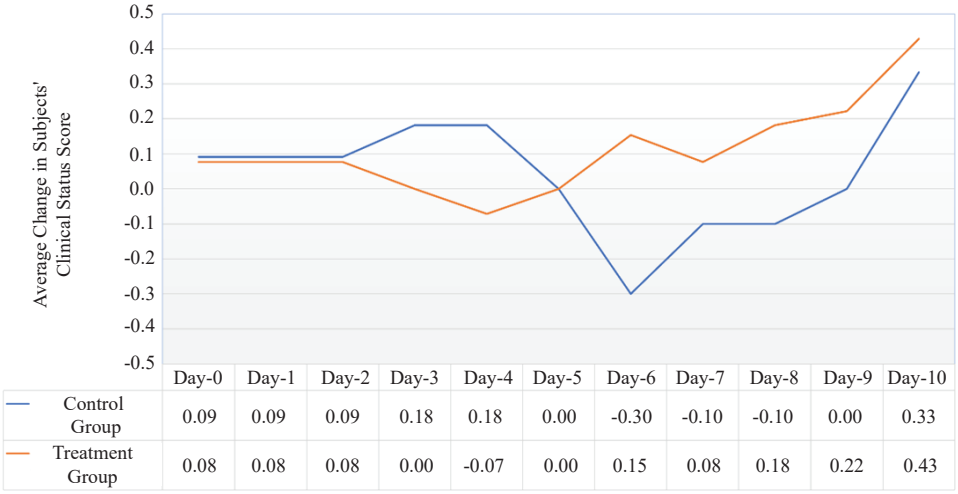
Table 2. Average change in subjects' clinical status score on day-0 to day-10.

Time (Day)	Mean±SD		*p*-value
	Control Group (n=11)	Treatment Group (n=14)	
0	0.09±0.30	0.08±0.28	0.907
1	0.09±0.30	0.08±0.28	0.907
2	0.09±0.30	0.08±0.28	0.907
3	0.18±0.75	0.00±0.39	0.442
4	0.18±0.75	-0.07±0.47	0.314
5	0.00±1.18	0.00±0.55	1.000
6	-0.30±1.06	0.15±0.38	0.165
7	-0.10±0.57	0.08±0.28	0.335
8	-0.10±0.57	0.18±0.40	0.203
9	0.00±0.67	0.22±0.44	0.409
10	0.33±1.12	0.43±0.79	0.851

Tested with T-independent difference test.

the control and treatment groups regarding the incidence and duration of oxygen supplementation. Descriptively, 5 (35.7%) subjects in the treatment group received oxygen therapy, whereas only 2 (18.2%) in the control group received oxygen therapy. However, the duration of oxygen therapy in the treatment group was shorter than that in the control group (8.9% *vs.* 16.8%). Therefore, the treatment group (standard COVID-19 treatment + QS) experienced better clinical efficacy than the control group in terms of duration of oxygen therapy.

In addition, as an adaptive design study, we have also included another efficacy parameter, which was the average oxygen saturation. The average oxygen saturation in the treatment group was higher than that in the control group (98.20 *vs.* 97.34), and the difference in oxygen saturation



	Day-0	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	Day-8	Day-9	Day-10
Control Group	0.09	0.09	0.09	0.18	0.18	0.00	-0.30	-0.10	-0.10	0.00	0.33
Treatment Group	0.08	0.08	0.08	0.00	-0.07	0.00	0.15	0.08	0.18	0.22	0.43

Figure 1. Average change in subjects' clinical status score on days 0-10.

Table 3. Incidence and duration of oxygen supplementation.

Variable		n (%)		*p*-value
		Control Group	Treatment Group	
Oxygen therapy (n)	No	9 (81.8)	9 (64.3)	0.332
	Yes	2 (18.2)	5 (35.7)	
	Total	11 (100.0)	14 (100.0)	
Duration of oxygen supplementation (day)	No	89 (83.2)	102 (91.1)	0.080
	Yes	18 (16.8)	10 (8.9)	
	Total	107 (100.0)	112 (100.0)	

Tested with T-independent difference test.

was significant (p=0.01). This shows that the treatment group (standard COVID-19 treatment + QS) experienced better clinical efficacy than the control group in terms of oxygen saturation.

Furthermore, the results of the analysis of the clinical efficacy of QS in adult subjects with mild-to-moderate COVID-19 symptoms based on the incidence of mechanical ventilation are shown in Table 5. Based on the test results, the difference in the incidence of mechanical ventilation between the control group and the treatment group was not significant (p>0.05). Only 1 subject in the control group required mechanical ventilation, which was for 2 days.

The results of the analysis on the clinical efficacy of QS in adult subjects with mild-to-moderate COVID-19 symptoms based on the length of stay are shown in Table 6. The length of stay was not significantly different between the control group and the treatment group (p=0.353). However, the average length of stay in the treatment group was shorter (11.86 days) than that of the control group (12.55 days). As shown in Table 7, the number of subjects with a length of stay less than 10 days was higher in the treatment group (43%) than in the control group (27%). This means that the treatment group will recover faster than the control group.

In this study, as an adaptive design, we also analyzed the final status of the subjects as shown in Table 8, which was divided into "discharged recovered" and "requires hospitalization." The results did not show a significant difference between the two groups. However, 1 subject in the control group required hospitalization, and the proportion of subjects in the treatment group who were discharged in a recovered condition was higher than that in the control group (100.0% *vs.* 90.0%).

Table 4. The average oxygen saturation.

Group	n	Mean±SD	*p*-value
Control group	107	97.34±2.39	0.001*
Treatment group	112	98.20±1.01	

*Considered significant if p<0.05, tested with T-independent difference test.

Discussion

Quinine is an alkaloid compound found in Cinchona bark.(27) Quinine, quinidine, synconin, and synconidine are the most abundant compounds found in Cinchona plants. This plant is extensively utilized as a rich source of bioactive chemical compounds used in drug manufacturing, particularly quinine compounds renowned for their antimalarial properties. Quinine, the primary constituent of secondary metabolites found in Cinchona, continues to be employed as a reasonably potent drug for combating malaria. (27) Various studies have indicated that the alkaloids present in quinine exhibit additional potential activities, including anti-obesity, anticancer, antioxidant, anti-inflammatory, antimicrobial, and antiviral effects.(28-30)

QS has the potential to fight SARS-CoV-2, as evidenced by several *in silico* and *in vitro* studies. *In silico*, QS can bind strongly to the angiotensin-converting enzyme-2 (ACE2) receptor, which is the entry point of SARS-CoV-2, and has stronger binding than CQ and HCQ. (23) Several *in vitro* studies have also shown that QS has antiviral activity against SARS-CoV-2.(24,31)

Clinical efficacy was evaluated based on the clinical condition of the subjects according to the 7-point ordinal scale, incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay. In the primary outcome, the treatment group showed an average improvement in clinical condition on 7 ordinal scales better than the control group, especially on days 6 to 10, as seen in Figure 1. This is related to the mechanism of QS as an antivirus that can accelerate the improvement of

Table 5. The incidence of mechanical ventilation.

Variable		n (%)			*p*-value
		Control Group	Treatment Group	Total	
Non invasive ventilation (BIPAP/CPAP)	Yes	0 (0)	0 (0)	0 (0)	1.000
	No	11 (100)	14 (100)	25 (100)	
Not using non-invasive ventilation (BIPAP/CPAP)	Day-1	11 (100)	14 (100)	25 (100)	1.000
	Day-2	11 (100)	14 (100)	25 (100)	1.000
	Day-3	11 (100)	14 (100)	25 (100)	1.000
	Day-4	11 (100)	14 (100)	25 (100)	1.000
	Day-5	11 (100)	14 (100)	25 (100)	1.000
	Day-6	11 (100)	14 (100)	25 (100)	1.000
	Day-7	11 (100)	14 (100)	25 (100)	1.000
	Day-8	11 (100)	14 (100)	25 (100)	1.000
	Day-9	11 (100)	14 (100)	25 (100)	1.000
	Day-10	11 (100)	14 (100)	25 (100)	1.000
Invasive ventilation	Yes	0 (0)	1 (7.1)	1 (4)	0.336
	No	11 (100)	13 (92.9)	24 (96)	
Not using invasive ventilation	Day-1	11 (100)	14 (100)	25 (100)	1.000
	Day-2	11 (100)	14 (100)	25 (100)	1.000
	Day-3	11 (100)	14 (100)	25 (100)	1.000
	Day-4	11 (100)	14 (100)	25 (100)	1.000
	Day-5	10 (90.9)	14 (100)	25 (100)	0.250
	Day-6	11 (100)	14 (100)	25 (100)	1.000
	Day-7	11 (100)	14 (100)	25 (100)	1.000
	Day-8	11 (100)	14 (100)	25 (100)	1.000
	Day-9	11 (100)	14 (100)	25 (100)	1.000
	Day-10	11 (100)	14 (100)	25 (100)	1.000

Tested with T-independent difference test.

clinical conditions in COVID-19 patients. QS has antiviral activity by increasing the synthesis of retinoic acid-inducible gene I (RIG-I) and interferon (IFN)-α. Subsequently, both will block virus mRNA translation through the activation of Protein Kinase R (PKR) and degrade viral poly mRNA by activating RNAse (L), preventing the synthesis of viral proteins.(32) Furthermore, a study investigated the effects of QS, CQ, and HCQ on inhibiting SARS-CoV-2 replication in

Table 6. Length of stay.

	Control Group	Treatment Group	*p*-value
Mean±SD	12.55±4.55	11.86±5.05	0.353
Minimum	5	6	
Maximum	21	21	

Tested with T-independent difference test.

Table 7. Categories of the length of stay.

Category Length of Stay	n (%)		
	Control Group	Treatment Group	Total
≤10 days	3 (27)	6 (43)	9 (36)
>10 days	8 (73)	8 (57)	16 (64)
Total	11 (100)	14 (100)	25 (100)

Table 8. Final status of the subjects.

Final Status of Subjects	n (%)			*p*-value
	Control Group	Treatment Group	Total	
Out of the hospital in recovering condition	10 (90.9)	14 (100.0)	24 (96.0)	0.250
Requires hospitalization	1 (9.1)	0 (0)	1 (4.0)	
Total	11 (100.0)	14 (100.0)	25 (100.0)	

Tested with T-independent difference test.

Vero B4 cells. Inhibiting SARS-CoV-2 virus replication by QS was more effective than CQ and HCQ, with 10 μM QS reducing virus replication by 90%, while HCQ only reduced it by 50%.(33) The antiviral properties of QS are associated with the better average change in clinical conditions in the treatment group compared to the control group, although not statistically significant.

In the secondary outcome, which includes the incidence and duration of oxygen supplementation, mechanical ventilation, and length of stay, there were no significant differences between the control and treatment groups. We also analyzed the difference in oxygen saturation levels, the results showed that there was significant difference between the control and treatment groups, with the treatment group having a better average oxygen saturation compared to the control group.

ACE2 is found in nearly all human organs, predominantly in type II alveolar epithelial cells of the lungs, while being less pronounced in surface epithelial cells of the oral, nasal, and nasopharyngeal mucosa. This indicates that the lungs are the primary target of SARS-CoV-2.(34,35) The viral entry and replication process heavily relies on endosomal-lysosomal acidification and the function of various host endosomal proteases, which are also active in acidic pH conditions.(36,37) QS is a weak base and causes an increase in the pH of acidic intracellular organelles, thus disrupting the SARS-CoV-2 fusion process in cells.(38,39) Therefore, the inhibition of SARS-CoV-2 fusion against these cells can reduce the worsening of lung damage. This is evidenced by the better oxygen saturation value in the treatment group than in the control group.

In vitro studies, QS showed antiviral activity against SARS-CoV-2 and this activity occurred in several TMPRSS2+ human cancer cell lines.(24) TMPRSS2 is a co-receptor that mediates viral entry by facilitating S protein cleavage resulting in membrane fusion and viral particles enter endocytically.(40) This mechanism shows that the antiviral activity of QS against SARS-CoV-2 is one of them by interfering with the attachment of the virus to its receptor via TMPRSS2.(24)

Several studies have investigated the effects of quinine on the lower respiratory tract, particularly in modulating inflammation and bronchoconstriction. Quinine can reduce inflammatory cell infiltration and decrease excessive mucus accumulation in a mouse model of asthma.(41,42) Under COVID-19 conditions, excessive inflammation can lead to excessive mucus production, resulting in airway obstruction and recurrent respiratory infections, which can even lead to further obstruction.(43,44) Other studies have also shown that quinine can reduce bronchoconstriction and airway remodeling because of smooth muscle relaxation.(42) The final status of the subjects who were given QS also showed good results 100% discharged in a recovered condition, while in the control group only 90% were discharged in a recovered condition. So even though statistically the efficacy of the QS was not significantly different between the control group and the treatment group due to the insufficient number of subjects the treatment group showed better results than the control group and considering the fact that QS can improve respiratory function. This clinical trial study only involved small number of sample sample size, which may have reduced the ability to detect statistically significant differences among of the primary or secondary outcomes.

Conclusion

Although not significant, descriptively, the treatment group showed better results than the control group in terms of clinical status based on the 7-point ordinal scale, incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay. The difference in the mean oxygen saturation between the control group and the treatment group was significant, where the treatment group had a better mean oxygen saturation than the control group. The final percentage of subjects who were "discharged from the hospital in a recovering condition" in the treatment group reached 100%, whereas only 1 subject in the control group required hospitalization.

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Authors Contribution

IRL, KL, MIB and AM were involved in Research Conception/Design. IPS and ES performed the measurements and data acquisition. IRL, IPS and ES processed the experimental data and performed the data analysis. CBK, II and KL aided in interpreting the results. IRL, MIB, AM and KL drafted the manuscript. IRL designed the figures and/or table design. MIB, AM and KL performed the critical revision of the manuscript. All authors discussed the results and commented on the manuscript.

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