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PVP-I and Iota-Carrageenan Improve Subjective Clinical Symptoms In COVID-19 Emergency Hospital Wisma Atlet, Indonesia: A Single-Blind Randomized Clinical Trial

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Keywords:
COVID-19, iota-carrageenan, PVP-I, symptom.

ABSTRACT

COVID-19 caused various symptomatic manifestations in humans. Viral reservoirs are found at naso-oropharyngeal areas and challenge the dentist to reduce the virus using antiseptics, such as PVP-I and Iota-carrageenan (IC). Clinical trials of the above regimes on COVID-19 patients have never been carried out. Aim: To evaluate subjective clinical symptoms in COVID-19 patients after using PVP-I 1% mouthwash and IC nasal spray. Method. A single-blind randomized clinical trial was done in Wisma Atlet emergency hospital. Recruitment of subjects obtains from those who fulfilled the inclusion criteria under informed consent. Eighty-nine subjects who received standard drug of COVID-19 were then divided into Group-A that received PVP-I for 14 days, IC for seven days, and Group-B, who did not receive. Data collections were recorded at the beginning and end of observation for 17 subjective clinical symptoms. Chi- square was used to find the correlation among groups. Results. Male, 19-30 y.o were dominant in both groups. The mean duration of PVP-I and IC used was 5.6 and 5.51 days, respectively. The five frequent symptoms were anosmia, dry cough, fever, slimed cough, and headache. On the 8th day, there was a significant difference in symptoms between-group in dry cough (P=0.003), fever (P=0.024), and sore throat (P=0.001), and dysgeusia (P=0.042) on the 14th day. Conclusions. Using PVP-I mouthwash six times/day and iota-carrageenan nasal spray three times/day for 5 to 6 days may reduce several subjective clinical symptoms.

1. INTRODUCTION

The COVID-19 pandemic caused by the β-type coronavirus (SARS-CoV-2) has a vast impact on the

national health system, not only in Indonesia but in the world. Reported that 41% of COVID- 19 patients occurred due to nosocomial transmission [1]. WHO states that this disease spreads through droplets, splatter, or aerosols from the mouth or nose [2]. The mean SARS-CoV-2 virus in saliva was found to be 3.3 x 106 copies / mL [3]. Therefore, the mouth and nasopharynx are considered as a source (reservoir) of transmission of COVID-19.

Povidone-iodine (PVP-I), which was first discovered in 1955, has antimicrobial properties in the presence of the free iodine (I2) ion. In the free ionic form, iodine will enter rapidly into the plasma membrane of microbes and disrupt the protein and nucleic acid structure to be oxidized so that microorganisms die. According to [4], PVP-I has broad-spectrum effectiveness against various oral pathogens such as *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Tannerella forsythensis, Prevotella intermedia*, and *Streptococcus anginosus*. Its effectiveness can be achieved in less than 15 seconds of exposure. Against biofilm formation, PVP-I can also suppress the formation of oral mucosal biofilms to reduce plaque formation and dental caries in children [5]. Research at Duke University Singapore reported in vitro that exposure to 30 seconds of PVP-I 0.5-1% could kill the SARS-CoV-2 virus by four log10 with an effectiveness of 99.99% [6]. The study results at TIDREC Malaysia showed that PVP-I 0.5% or 1% was able to reduce >5 log10 virus titers within 30 seconds with effectiveness of 99,99% [7]. The effectiveness of PVP-I against viruses is more effective than chlorhexidine gluconate and benzalkonium chloride [8], [9]. PVP-I is effective against SARS-CoV, which causes SARS infection [10], MERS-CoV [11], Modified Vaccinia Virus Ankara (MVA), the new European test virus for enveloped viruses [12], and Avian Influenza [13]. The use of PVP-I, of 0.23% for 2 minutes, reduced the quantity of SARS-CoV-2 virus to undetectable levels. Meanwhile, for MERS-CoV, it was found that PVP- I with a concentration of 1% used for 30 seconds was able to reduce viral activity by more than 99.99% but not at a concentration of 0.1% [12]. PVP-I can suppress TNF-α, which acts as an inflammatory regulator in many chronic diseases [14]. PVP-I also effectively reduces the severity and accelerates the duration of upper respiratory tract infections such as common cold influenza, and tonsillopharyngitis [15], [16] Besides, the use of PVP-I in critically ill patients on a ventilator prevents the development of ventilator-associated pneumonia [17].

The toxicity of PVP-I is much less than that of iodine tincture. Therefore, WHO recommends using PVP-I with a concentration of 0.7-10% as a safe and surgical antiseptic [18]. Besides, the use of PVP-I can reduce the risk of bacteremia significantly (1.5 to 3 times) compared with sterile water [19]. Allergic response to PVP-I is scarce and was only found in 2 out of 500 subjects who used the substance [20] and no cases of resistance to PVP-I [15].

The use of PVP-I in children has also been studied in Japan. PVP-I gargling for upper respiratory tract infection prevention 4-5 times per day for 2-3 months did not find any side effects [21]. According to [22], public health interventions in preventing the spread of COVID-19 infection can be carried out by gargling and nasal spray using PVP-I as an additional regimen for personal protective equipment (PPE). In its guidelines in August 2020, WHO recommended PVP-I 0.2% or hydrogen peroxide 1% as a mouthwash before examining various procedures involving the mouth area to reduce oral microbial titers, including SARS-CoV-2 [23].

Several research protocols were carried out to inhibit SARS-CoV-2 in the oral cavity and including the nasopharynx. One of them is an intervention in the nasal area using Iota-carrageenan. This material is reported to have the ability to eradicate various types of viruses, including the OC43 and 229E coronavirus types [24]. Iota-carrageenan is a polymer derived from red algae that have been shown to reduce viral load

in nasal secretions and adult and pediatric patients [24], [25]. The mechanism of action of iota-carrageenan is not systemic. Iota-carrageenan does not penetrate the nasal mucosa, and its antiviral effect is based on its physical mechanism of action. It forms a mucoadhesive layer in the nasal cavity. This mucoadhesive layer will envelop the germs and prevent germs from sticking to the nasal mucosa [26] analyzed two randomized placebo-controlled clinical trials on using the iota-carrageenan nasal spray in children and adults with a common cold caused by viruses. It showed that using the iota-carrageenan nasal spray in the early days of common cold symptoms decreases the duration of illness to 2 days, increases viral clearance, and decreases the recurrence rate of common cold symptoms. Both studies also show that the tolerability of the iota-carrageenan nasal spray is good. There were no severe or non-serious adverse events that occurred in association with using the iota-carrageenan nasal spray. Iota-carrageenan was able to eradicate 99% of the viral load in the nasal secretions in pediatric and adult patients. These include eradicating human coronavirus types OC43 and 229E, influenza virus type A, human metapneumovirus, respiratory syncytial virus, and parainfluenza type 3 [16]. In the results of a study by [27] on human and animal influenza type A viruses, it was found that iota-carrageenan effectively inhibited viral replication with or without other antiviral drugs even after 72 hours after infection.

Various clinical trials have been carried out to find drugs that can help prevent the transmission of the virus that causes COVID-19. There are no clinical trial reports regarding the use of PVP-I mouthwash and Iota-carrageenan nasal spray to date, as a continuation of the various in vitro test results from various countries that have been carried out. The study was conducted to determine the benefits of using these two ingredients to reduce symptoms caused by SARS-CoV-2 infection in patients at COVID-19 Emergency Hospital (RSDC) Wisma Atlet Jakarta. Wisma Atlet is one of the COVID-19 Emergency Hospitals designated by the government as independent isolation for patients with mild and moderate symptoms. It is hoped that the study will contribute to the benefits of PVP-I and iota-carrageenan in reducing mild to moderate subjective clinical symptoms due to SARS-CoV-2 infection to help control the transmission of COVID-19, which sources mainly come from the mouth and nose area.

2. METHOD

A single-blind randomized clinical trial was carried out in RSDC Wisma Atlet on September-October 2020. Subjects were recruited after receiving an explanation from the researcher and filling in the informed consent. Ninety-five subjects were recruited based on inclusion and exclusions criteria. A total of 89 subjects were included in the study. Inclusion criteria were patients with positive PCR results for COVID-19, were still conscious and able to carry out their activities, were willing to use mouthwash and nasal sprays that had been provided, aged over 18 years, the longest being treated at RSDC was not more than three weeks, willing to fill out the monitoring application provided. Exclusion criteria were no allergy history-related PVP-I or equivalent substance (alkylphenol ether sulfate (ammonium salt), and disodium hydrogen phosphate dodecahydrate), no history of thyroid disease or disturbance, not in pregnancy period, and unable to gargle. All subjects received standard treatment for COVID-19 patients. The subject was divided into two groups, A and B. Group A consisted of 45 subjects who received standard treatment, 1% PVP-I mouthwash six times a day for 14 days, and iota-carrageenan nasal spray three times a day for seven days. Group B consist of 44 subjects who received only standard treatment for COVID-19. One percent PVP-I mouthwash (Betadine®, PT. Mundhipharma Laboratories, Indonesia) and 1.2mg/mL iota-carrageenan (Betadine Cold Defense Nasal Spray®, PT. Mundhipharma Laboratories, Indonesia) were used in this study. Symptoms COVID-19 were defined as subjective symptoms according to the subject that was recorded daily using an online application provided.

The single-blind method was used in this study and numbers of subjective symptoms based on the case

report monitoring by WHO [28] such as sore throat, slimed cough, dry cough, fever, runny nose, difficulty breathing, anosmia, dysgeusia, dry mouth, muscle pain, joint pain, malaise, headache, abdominal pain, diarrhea, nausea/vomiting, and skin rash. All symptoms recorded were then classified into three categories improve, the same condition, and worsen. Any adverse events were recorded and managed by the medical team in RSDC Wisma Atlet. Ethical clearance was received from Ethical Commission RSDC Wisma Atlet No. Sprin/3274/VIII/2020/RSDCWA. All subjects were under medical surveillance of clinical trial by RSDC Wisma Atlet medical team. Data were analyzed descriptively based on the proportion of subjects.

3. RESULT

This study was done from September until October 2020, when the population of COVID-19 patients in Jakarta reaching the highest number in Indonesia, compared to other provinces. RSDC Wisma Atlet Jakarta only treated a patient with minimal to moderate symptoms, while severe symptoms patients were treated in another hospital. Most of the subjects treated at RSDC Wisma Atlet had mild symptoms or were said to have conditions without symptoms or people without symptoms. One of the criteria for moderate symptoms is shortness of breath and accompanied by radiological evidence of moderate to severe pneumonia. In such conditions, RSDC has regulations to transfer the patient to a designated COVID-19 hospital immediately. The shortness of breath symptoms reported in this study are subjective, so the radiological data is no longer taken as the screening has been done before patient admission. Table 1 shows the characteristic of the subject population among groups. All subjects have completed the study without adverse events reported, and all subjects took both drugs; none used only one drug.

Table 1. Characteristic of COVID-19 patients in RSDC Wisma Atlet.

Variables	**Group**	
	A **n (%)**	**B** **n (%)**
Sex		
Male		
19-30 years old	22 (11%)	18 (9%)
31-40 years old	6 (3%)	13 (6.5%)
>40 years old	3 (1.5%)	5 (2.5%)
Female		
19-30 years old	6 (3%)	2 (1%)
31-40 years old	5 (2.5%)	4 (2%)
>40 years old	3 (1.5%)	2 (1%)
Domicile		
DKI Jakarta	31 (15.5%)	33 (16.5%)
Bodetabek	10 (5%)	8 (4%)
Others	4 (2%)	3 (1.5%)
Job		
Student	3 (1.5%)	3 (1.5%)
Police/Army	0	2 (1%)
Government employee	1 (0.5%)	3 (1.5%)
General employee	33 (16.5%)	32 (16%)
Entrepreneur	5 (2.5%)	2 (1%)
Unemployment	3 (1.5%)	2 (1%)
Exposure to COVID-19		
Contact with other	17 (8.5%)	22 (11%)
Travel abroad	0	2 (1%)
Do not know	25 (12.5%)	18 (9%)
No answer	3 (1.5%)	2 (1%)

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Table 2. Duration of COVID-19 treatment in RSDC Wisma Atlet between groups.

Duration (days)	Group	
	A	B
Standard COVID-19 treatment		
Mean	12	11.30
Mouthwash treatment for 6 times/day		
Mean	5.6	-
Range (min-max)	1 – 14	
Nasal spray treatment for 3 times/day		
Mean	5.51	-
Range (min-max)	2 - 7	

Both groups showed a similar mean duration of receiving a standard COVID-19 regime in RSDC Wisma Atlet (Table 2). The mean mouthwash and nasal spray use duration among groups A and B was 5.6 days and 5.51 days, respectively. During follow-up, it was noted that none of the patients reported discontinuation of mouthwash and nasal sprays in the middle of the study. Of the 14 days prescribed to use mouthwash and seven days for nasal spray, the subjects only used mouthwash for 5.6 days and nasal spray for 5.51 days.

Table 3 shows the distribution of subjects who experienced changes in subjective symptoms, namely changes in symptom improvement, remained the same, or worsened. The five initial subjective symptoms most frequently reported at RSDC Wisma Atlet in groups A and B were anosmia, dry cough, fever, and slimed cough, and headache. A total of 50 - 100% of subjects who received mouthwash and nasal spray reported improvement in subjective symptoms of all symptoms. It also occurred in 75-100% of group B subjects. In group A, 5% reported no change in anosmia before and after using both drugs. Likewise for dry cough symptoms by 9%, dysgeusia and headaches by 10%, joint pain by 14%, fever by 25%, and abdominal pain by 50%.

In contrast, those who experienced worsening were only found in group A at 10% for symptoms of slimed cough. In group B, 10% of subjects reported no change (the same) in sore throat symptoms at the beginning and the end of the observation, while 18% reported worsening diarrhea symptoms. There was a significant difference between groups A and B in the subjective symptoms of dry cough (P=0.003), fever (P=0.024), sore throat (P=0.001) on the 8th day of drug use; and dysgeusia (P=0.042) on the 14th day. On day 8th, It was shown that there were significant differences in some subjective symptoms. It might be because the subject received two regimes (PVP-I and IC) that act in the naso-oropharynx, which is the reservoir of the virus. Whereas on the 14th day, the nasal spray has been stopped, and the use of mouthwash can only reduce the symptoms of dysgeusia which are prominent in the oral cavity of COVID-19 patients. On the other hand, it is also possible due to the characteristic of the SARS-CoV-2 virus that will naturally subside within two weeks.

Table 3. Percentage of subjective clinical symptoms severity distribution among groups.

Subjective Clinical symptoms	Beginning Observation (%)		End Observation (%)						Day-8		Day-14	
			Improve		No different		Worsen		X^2	P	X^2	P
	A	B	A	B	A	B	A	B				
Anosmia	42.22	25	40	25	2.22	-	-	-	NA		3.516	0.06
Dry cough	24.44	29.55	22.22	29.55	2.22	-	-	-	8.391	0.003**	0.335	0.562
Fever	22.22	29.55	22.22	29.55	-	-	-	-	5.064	0.024*	1.433	0.231
Slimed cough	22.22	18.18	20	18.18	-	-	2.22	-	3.6	0.057	0.72	0.396

Sore throat	20	18.18	20	15.91	-	2.27	-	-	9.919	0.001**	0.562	0.453
Headache	22.22	11.36	20	11.36	2.22	-	-	-	2.142	0.143	2.4	0.121
Runny nose	17.78	18.18	13.33	18.18	4.44	-	-	-	1.333	0.248	0	1
Dysgeusia	20	25	17.78	25	2.22	-	-	-	NA		4.104	0.042*
Difficulty breathing	20	6.82	20	6.82	-	-	-	-	0.8	0.371	NA	
Nausea/vomit	20	4.55	20	4.55	-	-	-	-	NA		NA	
Malaise	17.78	11.36	17.78	11.36	-	-	-	-	NA		NA	
Joint pain	15.56	4.55	13.33	4.55	2.22	-	-	-	NA		1.147	0.284
Dry mouth	13.33	6.82	13.33	6.82	-	-	-	-	NA		NA	
Muscle pain	13.33	9.09	13.33	9.09	-	-	-	-	NA		NA	
Diarrhea	6.67	11.36	6.67	9.09	-	-	-	2.27	NA		NA	
Abdominal pain	4.44	0	2.22	0	2.22	-	-	-	NA		NA	
Skin rash	2.22	2.27	2.22	2.27	-	-	-	-	NA		NA	

* P<0.05; ** P<0.01

4. DISCUSSION

The clinical trial study of PVP-I and Iota carrageenan in COVID-19 patients at RSDC Wisma Atlet Kemayoran refers to in vitro data from various studies [6], [7], [9], and the first study done in Indonesia. During the research, the profile characteristics of COVID-19 patients at RSDC represent a portion of COVID-19 patients profile in Jakarta (available on http://corona.jakarta.go.id), which is composed of a combination of data from all health care facilities.

Based on the results of this study, the number of men infected with SARS-CoV-2 was more than women. According to [29], gender can indeed affect the possibility of exposure to infectious diseases to fellow individuals, which is influenced by several factors such as the work environment, attitudes or behavior, type of work (which is at risk), the ability and habits of individuals to seek treatment, responsibility in-home or work [30]. In a meta-analysis report by [31], it was found that based on the proportion of patients confirmed COVID-19, there was no sex difference, but the number of males was higher than females in terms of the number of patients requiring intensive care. The study results at RSDC Wisma Atlet Kemayoran are similar to a meta-analysis of 57 studies in the world, and it was found that the prevalence pool of COVID-19 in men vs. women was 55 vs. 45 (P <0.001) [32].

Based on the age group among males and females, the most infected is the 19-30 year-old group, while in the Jakarta population data pool, the most age group is 30-39 years old. It is probably due to the RSDC Wisma Atlet Kemayoran only a small part of the location where COVID-19 patients are distributed in Jakarta.

Most of the COVID-19 patients (68%) at RSDC are domiciled in Jakarta, followed by Tangerang (8%), which is closest to RSDC Wisma Atlet Kemayoran. Meanwhile, other cities (Bekasi, Bogor, Depok) may have independent isolation locations closer to the patient's domicile. Most (69.5%) COVID-19 patients treated at RSDC are private employees.

Most of the research subjects came with unknown history of COVID-19 exposure; meanwhile, 40% of subjects had a history of contact with COVID-19 patients. Most of these subjects are private employees and entrepreneurs who are likely to have more activities outside the home and use public transportation. Based on the research results by [33], it is concluded that the transmission of COVID-19 due to work at the beginning of the pandemic is more often found in jobs related to community services, including public

services, drivers, construction workers, and religious leaders. The average time to stay at the RSDC was 12 days in contrast to the study results by [34], which reported the median length of treatment for COVID-19 patients from 55 hospitals designated as COVID-19 care centers in Jakarta was 24 days. The fundamental background of differences in duration above due to those who came and treated at RSDC Wisma Atlet was mainly mild to moderate symptoms.

Based on the research design, the drug administration intervention was planned for 14 days. However, most subjects did not reach that duration because most were being treated for around 12 days. The average of mouthwash and nasal spray was used only 5-6 days. It might be due to several factors, such as no other subjective symptoms related to COVID-19, and the patient's viral load has reached CT> 35, with no potential of transmission.

The significant difference of clinical symptoms between groups A and B showed on days 8th and 14th. The reason was that the subject in group A received two types of drugs (mouthwash and nasal spray) for the first whole week that worked at the naso and oropharynx area, known as the reservoir of the virus. Meanwhile, on day 14th, when the patient has stopped the nasal spray since day 8th, mouthwash reduced the symptoms of dysgeusia. Apart from that, it could also be because the characteristics of the COVID-19 infection will subside within two weeks in immunocompetent people. [34] reported that the symptoms of COVID-19 hospitalized patients were fever, malaise, shortness of breath, which were categorized as asymptomatic or mild symptoms.

The subjective symptoms were analyzed individually. Group A experienced more subjective symptom improvement than group B. It might be due to the intervention of the drug's active ingredients (I2 and iota-carrageenan) on the cell membranes of the SARS-CoV-2 virus. According to [35], the oral mucosa has ACE2 receptors, especially the tongue mucosa, compared to another oral mucosa. SARS-CoV-2, which has a high affinity for the ACE2 receptor, will increase its viral titer in the oropharyngeal and nasopharyngeal areas if not prevented [36]. Povidone-iodine has high effectiveness against the SARS-CoV- 2 virus within 30 seconds in vitro [6], [7], affects the number of subjective symptoms reported in the two groups of observations. Iota-carrageenan contained in nasal sprays is known to become a mucosal barrier so that the SARS-CoV-2 virus cannot bind to its receptors. The results of this study are also in line with clinical trials conducted in Singapore to evaluate the relationship between some commercial mouthwash and CT levels of the SARS-CoV-2 virus. This study found that mouthwash containing PVP-I and CPC (cetylpyridium chloride) significantly reduced viral CT within 5 minutes, while chlorhexidine gluconate was ineffective [9]. The mechanism of using mouthwash and nasal sprays to improve subjective systemic symptoms such as joint pain, shortness of breath, other symptoms are not fully known and still requires further research concerning viral CT and systemic indicators.

There are several limitations of this study. The average duration of mouthwash and nasal sprays used in this study cannot be established as the duration of general use, as the treatment of subjects in RSDC merely follow the length of treatment at the RSDC Wisma Atlet Kemayoran. Some subjects might be admitted more than 14 days as the recruitment day was not on the first day of admission. The study did not analyze a model for reducing the risk of spreading COVID-19 infection through salivary droplets or aerosols due to the absence of supporting data of susceptible subjects, laboratory analysis data required for the pathogenesis. There is a tendency to decrease clinical symptoms among groups, while the study only used a pragmatic approach to avoid researchers' daily active drug intervention. Proper education and instructions before drug administration are essential, and the application of a drug schedule reminder in this study was beneficial to determine the level of patient adherence [37].

5. CONCLUSION

Using both 1% PVP-I and Iotaa carrageenan nasal spray can reduce mild subjective symptoms complained of by COVID-19 patients at RSDC Wisma Atlet Jakarta. Using PVP-I mouthwash six times per day and iota-carrageenan nasal spray three times per day for average 5-6 days may reduce subjective clinical symptoms.

6. ACKNOWLEDGEMENT

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7. ETHICS APPROVAL

This study was reviewed and approved by the Ethics Committee of the Emergency COVID-19 Hospital Wisma Atlet Kemayoran Jakarta, Indonesia.

8. AUTHOR CONTRIBUTION

Amtha, Gunardi, and Hidayat did the concept and designed the paper's structure, counted the result, and reviewed the paper. Amtha, Gunardi wrote the paper. Dewanto, Gunardi and Muhammad collected and analysis the data. All authors have read and approved the final manuscript.

9. CONFLICT OF INTEREST

No conflict of interest in the study.

10. FUNDING

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