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Effectiveness of Benzydamine Hydrochloride + Cetylpyridinium Chloride (Difflam®) Lozenges in Alleviating Sore Throat among COVID-19 Patients: A Real-World Evidence Study in the Clinical Practice

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Abstract

Objective: *Since the start of the pandemic, the SARS-CoV-2 which causes COVID-19 infection, has aggressively taken a toll on millions of lives worldwide. Recent studies have shown that newer variants consistently present with a greater frequency of sore throat. This study explored the real-world effectiveness of benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge in alleviating sore throat of Filipino patients, under condition of routine medical practice.*

Study Design: *Observational, uncontrolled study design*

Setting: *Ambulatory / out-patient health facilities*

Method: *This study included patients with mild to moderate COVID-19 infection in a real-world setting confirmed either with rapid antigen test (RAT) or positive real-time polymerase chain reaction (RT-PCR), who manifested with symptoms and signs of dysphagia / odynophagia. They were prescribed with Difflam® lozenge as an adjunct to standard care, in accordance with the respective local prescribing information and routine clinical practice.*

Results: *A decreasing trend was observed in the median visual analogue scale (VAS) pain scores from baseline up to the seventh day. The difference from the baseline VAS score was significant in all observation period from day 1 to day 7 ($p<0.001$). The greatest difference was seen on day 4 and 5 (median VAS scores of 1 and 0, respectively). The mean duration of symptoms before total resolution of sore throat (VAS score = 0) was 4.4 SD ± 1.9 days with majority of participants (87 %) reporting resolution at the end of seven days observation. The mean length of time before negativity of COVID-19 RAT was 3.9 SD ± 1.6 days. Majority did not experience adverse events, and if so, were generally mild.*

Conclusion: *The benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge reduced the duration of COVID-19 (RAT negative) and completely alleviated symptoms of dysphagia and odynophagia among patients with mild to moderate COVID-19 infection within four to five days of initiation of therapy.*

Keywords: Benzydamine Hydrochloride, Cetylpyridinium Chloride, Sore Throat, COVID-19

1. Background

The SARS-CoV-2 pandemic has presented sore throat as one of the basic clinical presentations of the disease [1, 2]. Recent studies have shown that newer variants, in particular the Omicron strain, consistently present with a greater frequency of sore throat [3]. Though mild to moderate COVID-19 infections are generally self-limiting, it is imperative to address COVID-19 symptoms, including concerns on throat irritation [4]. Increasing oral fluid intake may soothe throat soreness, and lozenges can also alleviate throat pain by keeping the upper airways moist and by stimulating saliva production [4].

One study enumerates the 'ideal' features of over-the-counter options in the treatment of simple sore throat cases [5]. Their mechanism of action must directly target both the virus and the inflammation produced by providing local pain relief, fast onset and prolonged duration of action, as well as a good safety profile [5]. Lozenges offer relatively rapid delivery of active ingredients, prolonged activity, slower rates of clearance and therefore, have a sustained effect [6]. Moreover, they are easy to administer, for they do not require water intake for administration. It also avoids first-pass metabolism and therefore has increased bioavailability. It has a pleasant taste, with better patient compliance in patients with difficulty swallowing [6, 7].

The oral cavity is believed to play an important role in the pathogenicity and transmission of SARS-CoV-2, the causative agent for COVID-19 infection. The identification of targeted anti-viral mouth preparations that reduce salivary viral load may contribute to lessening the incidence of COVID-19 infection. While awaiting the results of significant clinical studies, which to date do not exist, the commercial availability of topical mouth preparations leads the medical community to search for chemicals and molecules that have specific anti-viral properties with respect to SARS-CoV-2. Because SARS-CoV-2 is an enveloped virus, many reagents target the outer lipid membrane. Moreover, some of these therapeutic agents are hypothesized to act on the capsid by denaturing proteins. Until now, there has been no robust scientific evidence to recommend topical mouth preparations with an anti-SARS-CoV-2 effect to control the viral load in the buccal cavity [8].

This real-world scenario observational, uncontrolled study determined the effectiveness of benzydamine and cetylpyridinium chloride (Difflam®) lozenge on alleviating throat pain of Filipino patients who were diagnosed with mild to moderate COVID-19 infection under condition of routine medical practice.

2. Methods

This study was conducted from October 2022 until April 2023, aligned with various guidelines and recommendations for good epidemiological practice for non-interventional studies and internationally accepted guidelines [9-12].

Physicians from several ambulatory and out-patient health facilities throughout the Philippines were tapped to recruit study subjects. As part of their routine medical care, the study subjects were prescribed with benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge and were given for free as a supplement for the management of these conditions, in accordance with the respective local prescribing information and routine clinical practice. The study subjects were also given RAT kit and were instructed to perform daily testing.

Patient eligible for participation in this study were aged 12-60 years old, who were recognized with mild to moderate COVID-19 infection based on the Department of Health operational definition, diagnosed either through RT-PCR or a RAT kit, presenting with sore throat (i.e., odynophagia or dysphagia) [13]. Participants were excluded if they had a history of status asthmaticus or with a previous history of intubation / intensive care unit admission secondary to bronchial asthma exacerbations; with a history of severe renal impairment (eGFR 15-29 mL/min/1.73 m2); with a history of severe liver impairment (Child-Pugh C); pregnant and breastfeeding women; with known hypersensitivity to benzydamine hydrochloride or cetylpyridinium chloride; have taken molnupiravir; have used any other oral preparations like povidone iodine, hexetidine, chlorine dioxide, carbenezolone, dichlorobenzyl alcohol, amymetacresol, hexylresorcinol, xylitol, etc. within the last 48 hours prior to initiation of treatment; and diagnosed cases of oral cavity malignancy or those with chronic non-healing pathologies in the oral cavity.

There were 154 patients initiated with benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge. No monetary compensation was given. They were instructed to take one lozenge slowly every one to two hours, with a maximum of 12 lozenges per day. Duration of treatment should not exceed seven (7) days. Patients were asked to continue taking hydrochloride + cetylpyridinium chloride (Difflam®) lozenge at least once a day for the subsequent second to seventh days. During the course of the study, patients were allowed to use other prescribed medications, except different mouth preparations, as deemed medically appropriate by their attending physician. Patients were followed up until the total resolution of the sore throat or up to a maximum of seven (7) days. The development of adverse effects was monitored for a total duration of seven (7) days.

Since this was an observational, uncontrolled study, there were no special protocol-mandated visits or procedures associated with the study. However, whenever applicable, evaluations documented in the case report form (CRF) were expected to be aligned with the local prescribing information recommendations and individual clinician practice. During the course of the study, patients could discontinue if they were given another oral mouthwash / gargle preparation. However, these patients would still remain in the study, and data were captured at the time of this change in treatment. For patients who voluntarily withdrew from the study for any reason at any time, their data would also be captured at the time of the withdrawal.

Demographic profile and vital signs were collected on all patients, and these included age, sex, vaccination status, nature of work / profession and frequent use of voice at work. Data on relevant medical history / current medical conditions were also gathered. If possible, diagnoses (and not symptoms) were likewise recorded. The choice of treatment, as well as the decision to discontinue treatment, were at the sole discretion of the pre-

scribing physician and the patients, and were independent from participation in this study. Key selected adverse events (AE), their duration, intervention (if any), and time of resolution were also recorded.

Data were analyzed using Stata version 13 software. Continuous variables were expressed as mean ± SD or median (minimum and maximum) for non-normally distributed data. Categorical variables were expressed as percentages. Significant differences in visual analogue scale (VAS) scores between baseline and each succeeding day up to 7 days were determined using Wilcoxon signed rank test. A p-value <0.05 was accepted to be statistically significant.

3. Results and Interpretation

A total of 154 individuals were recruited to participate in the study. Eight cases had no subsequent data for VAS scores and other outcome measures (i.e., number of lozenges consumed, time to resolution of symptoms, RAT results and adverse events) and were considered as drop-outs. Analysis was carried out on 146 valid responses. There were 51.4% females and 45.9% males. The mean age was 34.2, SD ± 10.7 years, the youngest being 12 years old and the oldest being 60 years old. Forty percent (40%) received Sinovac as their primary vaccination against COVID-19, while Pfizer BioNTech was given as the primary vaccination in 46.6%. Almost all received the required doses for each vaccine type. Frequent use of voice was observed more among those with white-collared (50.0 %) than blue-collared jobs (43.7 %) (Table 1).

Gender (n, %)	**n = 146**		**Age in years (mean, sd)**	
Male	67 (45.9)		34.2, 10.7	
Female	75 (51.4)			
No response	4 (2.7)			
Vaccine type	With first dose No. (%) n=146		With second dose No. (%) n=146	
Sinovac	58 (39.7)		20 (13.7)	
Sinopharm	-		17 (11.6)	
Astra Zeneca Oxford	18 (12.3)		10 (6.8)	
Pfizer BioNTech	44 (30.1)		68 (46.6)	
Moderna	15 (10.3)		18 (12.3)	
Janssen	8 (5.5)		NA	
Gamaleya Sputnik	1 (0.7)		1 (0.7)	
No response	2 (1.4)		4 (2.7)	
Nature of Work	Does your job require frequent use of your voice?			
White-collared	Yes (%)	No (%)	No response	Total
(businesswoman, physician, nurse, midwife, IT, BPO, customer service rep, office clerk, etc.)	36 (50.0)	31 (43.1)	5 (6.9)	72
Blue-collared	14 (43.7)	3 (9.4)	15 (46.9)	32
Self-employed	3 (30.0)	7 (70.0)	0	10
Unemployed	1	-	-	1
No response	-	-	-	10

Table 1: Demographic Profile of Study Subjects

Heart rate, respiratory rate, blood pressure, temperature and oxygen saturation were within normal in most of the participants who had vital sign measurements. Mild to moderate fever was noted in 58 participants out of 107 who had temperature readings (54.2%). Majority (76.2%) did not have medical co-morbidities. Allergic rhinitis and hypertension were the most common co-morbidities, with study subjects allegedly taking their maintenance medications with good adherence.

Vital Signs	No.(%)
Heart Rate (beats / minute) (n=33)	
Normal (60-100)	33 (100.0)
Respiratory Rate (breaths / minute) (n=33)	
Normal (12-20)	21 (63.6)
Tachypneic (>20)	12 (36.4)
Systolic Blood Pressure (mmHg) (n=32)	

Normal (90-130)					30 (93.8)	
Elevated (>130)					1 (3.1)	
Low (<90)					1 (3.1)	
Diastolic Blood Pressure (mmHg) (n=32)						
Normal (60-100)					32 (100.0)	
Temperature (oC) (n=107)						
Afebrile (<37.6)					49 (45.8)	
Low-Grade Fever (37.6 - 37.9)					25 (23.4)	
Moderate-Grade to High-Grade (≥38)					33 (30.8)	
Oxygen Saturation (n=34)						
>95%					32 (94.1)	
≤95%					2 (5.9)	
Comorbidities	Total No. (%)	With Maintenance Medications			Compliance with Medications	
		Yes	No	No response	Good	Poor
Allergic rhinitis	17 (11.6)	6	6	5	6	-
Bronchial asthma	1 (0.7)	-	1	-	-	-
Dyslipidemia	1 (0.7)	1	-	-	1	-
Hypertension	18 (12.3)	15	-	3	15	-
Pulmonary tuberculosis	1 (0.7)	1	-	-	1	-
Cervical pathology	1 (0.7)	-	-	1	-	-
None	111 (76.2)					

Table 2: Clinical Profile of Study Subjects.

At baseline, the median VAS score was 7.5, the lowest being 1 and the highest being 10. There was a gradual decreasing trend in VAS scores from baseline to bedtime of Day 1. This trend progressed until VAS scores dropped to 0 on day 5 where the largest difference from baseline was seen. Nonetheless, the difference from baseline was significant at each time point up to the end of the study period ($p<0.0001$). The median number of Difflam lozenges consumed likewise decreased from 10 lozenges on day 1 to 3 lozenges on day 7. The difference in the number of lozenges consumed between day 1 and each successive treatment day was also significant ($p<0.0001$) (Table 3).

Time	VAS Scores		p-value*	Number of Lozenges Consumed		p-value*
	Median	Min, Max		Median	Min, Max	
Day 0 (baseline)	7.5	1, 10				
After 30 minutes	7	1, 10	<0.0001	10	0, 12	
After 60 minutes	6	0, 10	<0.0001			
After 6 hours	6	0, 9	<0.0001			
After 12 hours	6	0, 9	<0.0001			
At bedtime of Day 1	5	0, 9	<0.0001			
Day 2	4	0, 8	<0.0001	9	0, 12	<0.0001
Day 3	3	0, 8	<0.0001	6	0, 12	<0.0001
Day 4	1	0, 7	<0.0001	5	0, 12	<0.0001
Day 5	0	0, 5	<0.0001	4	0, 12	<0.0001
Day 6	0	0, 5	<0.0001	3	0, 12	<0.0001
Day 7	0	0, 4	<0.0001	3	0, 12	<0.0001

*Wilcoxon signed-rank test

Table 3: VAS Scores from Baseline to Day 7 and Corresponding Lozenges Consumed.

The mean duration of symptoms before total resolution of sore throat, which meant having a VAS score equal to 0 with no recurrence of throat pain, was 4.4 SD ± 1.9 days. It was on day 5 when sore throat resolved in most of the participants (24.7%). Nineteen participants (13%), though, still had symptoms beyond 7 days (Table 4).

Duration of sore throat before complete resolution in days (mean, sd)	
Hour / Day of Complete Resolution of Sore Throat	Number of Resolved Cases (%)
< 1 day	
1 hour	3 (2.1)
6 hours	5 (3.4)
12 hours	3 (2.1)
1 day	2 (1.4)
2 days	5 (3.4)
3 days	12 (8.2)
4 days	26 (17.8)
5 days	36 (24.6)
6 days	13 (8.9)
7 days	22 (15.1)
> 7 days (~treatment failure)	19 (13.0)

Table 4: Duration of Sore Throat before Complete Resolution and Proportion of Resolved Cases.

With time, the proportion of those positive on RAT decreased with a consequent increase in the proportion of those negative on RAT (Table 5).

Time	**RAT Positive**	**RAT Negative No. (%)**	**Number of Resolved Cases (%)**
No. (%)	RAT Negative	14 (9.6)	14 (9.6)
No. (%)	No Information	24 (16.4)	10 (6.8)
Day 1	132 (90.4)	14 (9.6)	0
Day 2	120 (82.3)	24 (16.4)	2
Day 3	94 (64.4)	48 (32.9)	4
Day 4	54 (37.0)	85 (58.2)	7
Day 5	21 (14.4)	118 (80.8)	7
Day 6	11 (7.5)	128 (87.7)	7
Day 7	4 (2.7)	135 (92.5)	7

Table 5: Distribution of RAT results through time

The mean length of time before resolution of COVID-19 infection, which was the day when the self-administered salivary COVID-19 RAT yielded a negative result, was 3.9 SD ± 1.6 days. Unexpectedly, a negative RAT result was observed as early as Day 1, but a greater proportion of participants were negative on RAT by Day 4 (25.3%) (Table 6).

Adverse Events	**Total**	**Severity**			**Duration (Days)**	**Action**			**Outcome**	
		Mild	**Moderate**	**No response**		**None**	**Others**	**No response**	**Resolved**	**No response**
Taste Disturbance	48	33	3	12	1.8	38	Observation (1)	9	42	6
Altered Sense Of Taste	42	29	2	11	1.5	29	Observation (2)	11	37	5
Dry Mouth	35	22	2	11	2	28	Warm Saline Gargle (1)	6	30	5
Oral Burning Sensation	26	15	1	10	1.5	20		6	25	1

Thirst	12	7		5	2.8	11		1	11	1
Warm Feeling In Mouth	7	6		1	1.5	7			7	
Nausea	3	1		2	2	1		2	2	1
Dizziness	1	1			1			1	1	
Drowsiness	1	1			2	1				1
Others: Numbness	2	2			3.8	2			2	

Table 6: Adverse Events.

4. Discussion

The predominant variant in the Philippines during the implementation of the study was the Omicron [14]. There was an increase in the number and proportion of the Omicron subvariant BA.5 since July 2022, while different Omicron subvariants which were flagged by the World Health Organization (WHO) or European Centre for Disease Prevention and Control (ECDC) was on a continuous uptrend starting September 2022 [14].

This variant is more transmissible, less severe, and commonly presents with sore throat and odynophagia [15]. This is consistent with the results of the current study, as all participants presented with sore throat, with only 54.2% complaining of fever episodes, and vital signs were documented to be within normal limits in most of the participants who had measurements [15]. Nonetheless, genetic sequencing was not performed; hence, it could only be surmised that majority of the study subjects were infected with the Omicron variant, based on clinical manifestations and local epidemiologic statistics.

All of the participants were fully vaccinated with the primary series of COVID-19 vaccine which may have reduced the severity and the duration of symptoms. As of March 2023, a total of 179 million doses of COVID-19 vaccine were administered in the Philippines, with 80 million completed dose, and 25 million booster dose [16].

Since the study was an observational, uncontrolled study, the presence of comorbidities was not evaluated which could potentially influence the prognosis of the COVID-19 infection. It was notable that majority (76.2%) of the study participants had no medical co-morbidities. Those with co-morbidities reported hypertension and allergic rhinitis, and they alleged they were taking their maintenance medications with good compliance. Previous reports showed that hypertension, the most common comorbidity, could potentially exacerbate the severity of COVID-19 patients, mainly through increasing inflammation [17], whereas allergic rhinitis increases severity and risk of hospitalization [18].

Moreover, the study focused primarily on the ambulatory out-patient clinics. All patients only required supportive medical management, including prescription with benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge as an adjunct for the management of their condition [13].

The baseline median VAS of the participants was 7.5, where in a 1 to 10 severity scale, 0 to 3 referred to mild symptoms, 4 to 6 pertained to moderate symptoms, and 7 to 10 referred to severe symptoms. This value is higher than the baseline median VAS of 5 in the study using Difflam-C® solution and higher than the pain severity seen in a world-wide survey involving the Philippines, ranging between 1-6 (63%) [19]. Sore throat and voice hoarseness were the two symptoms consistently more prevalent among Omicron than among Delta cases, regardless of vaccination status [3]. Furthermore, study conducted in Poland showed mean severity of 4.27 on VAS scale which was 3.23 lower from the baseline median VAS of the study participants [20].

With the use of the Difflam® lozenge, there was a decreasing trend in the VAS from baseline up to the seventh day of observation with the greatest difference seen in Days 4 and 5. Moreover, there was a noticeable shortening of the course of the sore throat. The current study showed throat irritation resolution by Day 5, as compared to seven to ten days when no active medical intervention was prescribed [21]. Similarly, data on Difflam-C® oral solution revealed comparable result where throat irritation resolution by Day 5 [19]. Moreover, the mean length of time before resolution of COVID-19 infection (COVID-19 RAT negative result) was four days, as compared to the two weeks clinical recovery noted in mild to moderate cases [22]. Likewise, a progressive decrease in positivity in the swab samples was observed in another study where bactericidal products Phytorelief, in two formulations, baicalin, rifampin and benzydamine produced the disappearance of positivity in most subjects at three to seven days [23]. Thus, the Difflam® lozenge could be viewed as a promising remedy for patients with odynophagia and confirmed cases of COVID-19 infection.

In the prevention of infection, viral load reduction is done at the level of the respiratory tract mucosa, and medical experts continue to explore therapeutic agents that can potentially achieve this end goal [24].

Benzydamine is a topical non-steroidal anti-inflammatory drug (NSAID), with analgesic, antipyretic and local anesthetic activity [25]. It has been approved for the symptomatic treatment of acute sore throat and oropharyngeal mucositis due to radiation therapy. Around 82% of patients diagnosed with pharyngitis of various etiologies and prescribed with benzydamine derived moderate or better relief from pain and dysphagia, compared to subjects given the placebo [25]. The pharmacological activity of benzydamine is mainly related to the inhibition of pro-inflammatory cytokine synthesis, although it also shows anesthetic ac-

tivity by modulating neuronal excitability [26]. It inhibits prostaglandin synthesis, as well as its ability to prevent the release of pro-inflammatory cytokines, without affecting other inflammatory cytokines, and, importantly, anti-inflammatory cytokines [26].

The local anesthetic properties of benzydamine are most likely due to the structural features it shares with local anesthetics, including an aromatic ring structure linked to a basic tertiary amine group by a short alkyl chain. Therefore, like local anesthetics, it reversibly blocks nerve conduction when applied topically in appropriate concentrations. Benzydamine blocks voltage-gated sodium currents in the dorsal root ganglion neurons; thus, modulating nociceptor excitability. In a clinical trial performed on 87 healthy subjects, it has been shown to be extremely useful in the treatment of painful conditions of the mouth and throat, primarily due to rapid pain relief [26, 27]. In this study, as early as 60 minutes, there were three participants whose sore throat pain were relieved at use of the Difflam® lozenge which persisted until end of the study. In a similar study using Difflam-C® oral solution, as early as 30 minutes, there were two participants whose sore throat pain was relieved at first use of the solution which persisted until bedtime [19].

Cetylpyridinium chloride (CPC), a quaternary ammonium compound (QAC), is an antiseptic with the actions and uses typical of cationic surface-active agents [28]. In addition to its emulsifying and detergent properties, QACs show bactericidal activity against gram-positive and, in higher concentrations, versus some gram-negative bacteria [28]. It penetrates the bacterial cell membrane, causing the lysis of cellular components, metabolic disorder, and inhibition of cell growth, thereby eventually leading to bacterial death [28]. QACs, including CPC, also have variable antifungal activity and are effective allegedly against some viruses [28]. Their virucidal activities are not widely documented, although some reports against enveloped viruses have been presented in the literature relating to surface disinfection [28]. Among this group of compounds, CPC has recently been shown to be active against influenza, both *in vitro* and *in vivo*, through a direct attack on the viral envelope, with an *in vitr*o EC50 of 5-20 µg/ml. CPC is usually used in medicated oral rinses, throat lozenges, and sprays [28].

One study evaluated the in vitro efficacy of benzydamine hydrochloride (BH) + cetylpyridinium chloride (CPC) lozenge as a virucidal agent in reducing viral titers of COVID-19. There was a faster virucidal effect seen in the combination BH/CPC as a lozenge, when compared to CPC as a free active substance, in terms of high concentrations with a 4-log reduction in virus titer after one minute of exposure [29]. Samples that were exposed to a high concentration of test products, CPC as a free active substance or a BH/CPC lozenge presented with the destruction of the viral envelope resulting to the loss of viral infectivity [29].

There were preliminary findings on BH/CPC lozenges, based on testing in a defined and controlled laboratory environment designed to mimic the conditions of the oral cavity, which found strong virucidal activity against SARS-CoV-2 [28]. In fact, some clinicians concluded that BH/CPC, in higher concentrations, could rapidly destroy viruses and reduce viral concentration by as much as 99% in approximately one minute. This could be quite promising since BH/CPC could potentially address the speedy rate of transmission of the Omicron variant.

The combination of BH/CPC has antiseptic, antimicrobial, anti-inflammatory, and analgesic properties [30]. Other researchers have investigated whether the fixed combination in the form of lozenges is therapeutically equivalent to the oro-soluble tablet formulation in a randomized, parallel, partially double-blind, three-arm, placebo controlled clinical trial in patients with sore throat due to upper respiratory tract infection [30]. The therapeutic equivalence between the lozenges and oro-soluble tablets formulation of BH/CPC was demonstrated in terms of sore throat pain intensity reduction, sore throat pain relief, percent of responders, and time to the pain relief onset after the initial dose, and in terms of the disease resolution after four and seven days of treatment. Results showed that both formulations were superior to placebo and had a similar safety profile to placebo [30].

Despite the potential benefit of Difflam® lozenge, 19 (13%) study participants reported that their sore throat did not completely resolve even after seven days (median 1, range 1-4), which demonstrated similar results with the use of Difflam-C® oral solution (i.e., 4% of study participants, median 2, range 1-4) [19]. Such can be explained by poor adherence with medicine intake (i.e., only seven out of 19 treatment failures had good compliance), other potential etiologic agents for the odynophagia / dysphagia (i.e., bacterial species), and the lingering clinical manifestations of long COVID-19 syndrome.

There is no clear definition of long COVID-19 syndrome; however, in general, it is an illness described among patients who have recovered from COVID-19 but still have ongoing symptoms or among those who continued to have symptoms for longer than normally expected [31]. Small proportion of COVID-19 patients may experience symptoms for protracted periods, or even possibly have recurrence of other clinical manifestations such as fatigue, headache and upper respiratory complaints (i.e., shortness of breath, sore throat, persistent cough and loss of smell), despite being labeled as COVID-19, recovered [32].

The most common adverse effect experienced by the participants in this study was taste disturbance, followed by altered sense of taste, dry mouth, and oral burning sensation. These were expected and could possibly be explained by the inherent chemical constituents of benzamidine and cetylpyridinium chloride [33-35]. In a similar study using Difflam-C® oral solution, data showed mucosal numbness as the most common adverse effect of the solution which was expected with the use of benzamidine [19]. In this study, these adverse events were not disabling for the patients to discontinue usage, and the reported adverse events spontaneously resolved, without requiring any additional intervention.

5. Conclusion

Among Filipino patients aged 12-60 years presenting with odynophagia given benzydamine hydrochloride + cetylpyridinium chloride (Difflam®) lozenge, 87% experienced complete relief

of throat pain at the end of seven days of treatment. In addition, Difflam® lozenge shortened the duration of COVID-19 evidenced by RAT negative results (81%), and relieved the sore throat (63%) to just four to five days.

Limitations

The nature of the medical consultation (i.e., face-to-face vs. tele-consult) curtailed thorough physical examination of the buccal cavity and other pertinent organ systems (i.e., respiratory tract). More so, given the public health burden of COVID-19 in the country, on top of the popularity of other over-the-counter medications as COVID-19 therapy, it would be difficult to ascertain the effectiveness of a monotherapy regimen, like that of benzydamine and cetylpyridinium chloride lozenge, in addressing the sore throat.

This is a real-world effectiveness study, and all well-known limitations of such an epidemiologic design may be evident. Nonetheless, this study has provided local data on primary care management of COVID-19 odynophagia.

Data Availability Statement

RPS & FL are employed with iNova. JMN, RMJ, MPA, KMR have received consultancy honoraria from iNova.

Conflicts of Interests

RPS is employed with iNova. JMN, RMJ, MPA, KMR have received consultancy honoraria from iNova.

Authors' Contributions

JMN, RMJ, MPA, KMR, RPS; all the authors, conceptualized the study, acquired and analyzed data, drafted and revise the paper, and approved the version to be published.

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