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Research Article

The Role of an Oral Spray of a Formulation Containing 8.4% Sodium Bicarbonate in Preventing COVID 19 and Other Influenza Like Illness in Humans

Kshitij Mody* and Sankeerth Thoota

Department of Orthopaedics, Welcare Hospital, India

***Corresponding Author:** Kshitij Mody, Department of Orthopaedics, Welcare Hospital, India.

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Abstract

Background: A prospective, double arm, placebo control, single blinded, investigator led research study was performed to assess the strength of an oral spray formulation, containing 8.4% sodium bicarbonate as its active ingredient, in offering a barrier to the development of Influenza Like Illnesses (ILI) including Covid-19 infection and to evaluate the safety and tolerability of the spray in subjects with repeated daily use for 28 consecutive days.

Methods: 350 subjects were enrolled, 175 in the active product group and 175 in the placebo control group. Randomisation was achieved by block randomisation technique. Subjects in the active product group were given the Investigational Product (IP) and subjects in the placebo control group were given the Placebo Product (PP). Monitoring of recruited subjects was done based on a USFDA approved Patient Reported Outcome Measure (PROM) methodology. Subject Diaries were issued to all subjects to record data and daily monitoring was carried out by telephone. All subjects were monitored in person on Day 1, Day 15 and Day 28.

Results: It was seen that a significantly lower number of subjects using the Investigational Product recorded any ILI symptoms as compared to the subjects using Placebo Product.

Conclusion: The results establish that the oral spray formulation used in this study is effective in mitigating SARS-CoV-2-enveloped virus-related activity by creating an alkaline pH environment in the oropharyngeal spaces.

Keywords: Covid-19; Sodium Bicarbonate; Oral Spray

Abbreviations

ASL: Airway Surface Liquid; IP: Investigational Product; PP: Placebo Product; PROM: Patient Reported Outcome Measure; RT-PCR: Reverse Transcription Polymerase Chain Reaction; SB: Sodium Bicarbonate; SD: Subject Diary; USFDA: United States Food and Drug Administration

Introduction

The human population of the world is currently facing a pandemic of respiratory infection. We know that such diseases can be caused by various microbes, including bacteria and fungi as well as viruses [1]. These organisms require certain environmental conditions to thrive and cause damage via the infection. A key factor amongst these conditions is the local pH. The pH of the environment where these microbes harbour can significantly influence bi-

ological activity including enzyme actions, reaction rates, protein and nucleic acid stability [2,3].

The present pandemic of Covid-19 is caused by a novel member of the Corona group of viruses, namely SARS-CoV-2;2019-nCoV. There is evidence in literature that viruses belonging to the Corona group need a low pH environment to allow the first connectivity of the virus to a cell wall [4-6]. It therefore follows that if the infection lowers the pH, and in turn supports viral proliferation, any elevation of the pH of oropharyngeal environment to an alkaline medium may disrupt the virus and its activity.

It is now well established and reported that high viral loads are detected in the nose and throat areas of infected patients regardless of whether or not they are symptomatic [7].

The infectivity of SARS-CoV-2 depends on the ability of this virus to invade cells. Since the oral cavity is a primary interface between the external environment and body, there is a high likelihood that this pathway of viral entry and colonization is critical for the onset of Covid-19 [8,9].

The question which needs to be examined is whether the oral cavity is relevant in the development of SARS-CoV-2 disease pathology?

Scientific rationale

Respiratory infections are caused by bacteria, viruses, fungi, and parasites [12]. These microbes require for their growth a particular range of external pH which affects their many biological actions such as enzyme activity, reaction rates, protein stability and structure of nucleic acids [13,14].

The airway surface liquid (ASL) contains a complex mixture of antimicrobial factors that kill inhaled or aspirated organisms and act as a first line of defence. The composition of ASL is critical for antimicrobial effectiveness. Changes in the ASL, such as local acidosis, occur with inflammation or infection [15,16].

Recent scientific evidences suggest a role of the oral cavity as a portal into the body for SARS-CoV-2. In the first 10 days after the transmission, when the patient usually remains asymptomatic but is highly contagious, the virus accumulates in the nasal, oral, and pharyngeal mucosa, and only later will further accumulate in the lungs [10].

This possible role of the oral cavity, both as portal of entry of the virus into the body and as the viral reservoir, may be potentially put to a good use. Any possible benefit here from manipulation of the local environment could become even more relevant in the context of the foreseen evolution of the pandemic, which suggests that in spite of the implementation of hygienic measures and social distance, SARS-CoV-2 may not be eradicated up to 2024 [11].

Further, vaccinating a sizable proportion of the world population is a daunting task for all governments and is likely to take a few years. The efficacy of these vaccines in terms of long-lasting protection is yet to be confirmed. The ability of the virus to undergo substantial mutation resulting in escaping the effects of the vaccination can be an additional challenge.

In view of all the above factors, the possibility of a simple yet effective preventive measure with established food grade material is an extremely important and attractive option.

In the presence of respiratory tract infections caused by bacteria, viruses, fungi, and mycobacteria, there is an expected local acidic medium in the secretions. Changing the local pH of respiratory tract secretions to alkaline by adding Sodium Bicarbonate (SB) 8.4% can affect growth and pathogenicity and/or may be lethal for the respiratory tract pathogens [17].

There is evidence in literature that viruses belonging to the Corona group need a low PH environment to allow the first connectivity of the virus to the cell wall [16-18]. It has also been observed that viruses thrive at a pH level of 6 and a body temperature of 37 degrees [19]. It has been shown that saliva has a pH normal range of 6.2 - 7.6 with 6.7 being the average pH [20]. This presently allows the virus to enter the cells and then multiply.

If one can stop the ability of the virus to multiply in the initial stages in the upper respiratory tract by modulating the pH of the environment and thus creating a barrier, one can expect that its serious sequelae may be either prevented or minimized.

If the pH of the oropharynx can be raised to an alkaline level of pH 8 or more, then it would be logical to expect that any member of Corona group of viruses which gain access to this area of the body will not be able to gain entry into the tissue cells of this area.

Denying entry into the cells, by implication, also means denying the virus an opportunity to multiply. Further, logic would also suggest that slowing down or stopping the multiplication of the virus may translate into a reduced rate of further transmission to other humans, and equally importantly would also prevent the development of the disease pathology.

Sodium Bicarbonate inhalations (4.2% and 8.4%) have been used to treat respiratory conditions such as cystic fibrosis and chlorine gas inhalations. Its safety, tolerability and efficacy in improvement in those clinical conditions have been well established [21,22].

The oral sprays in the present study have been formulated using compounds already approved by regulatory bodies in the U.K. Europe, the U.S.A. and India. The materials are already widely used in medicines and food products.

Materials and Methods

We carried out a prospective, double arm, placebo control, single blinded, investigator led research study. The subjects were adults aged 18 or more and in good general health.

The study was scrutinised by the local ethics committee, and subjects were given a volunteer information document and signed an informed consent prior to enrolment.

After approval of the local ethics committee and registration of the study on Clinical Trials Registry of India with registration number (CTRI/2021/02/030957), written consent was obtained from all subjects following detailed explanation of the study protocol.

Study objective

To study a food grade formulation having 8.4% sodium bicarbonate as its main active ingredient, proposed to be used in the form of a spray administered to the oropharynx area, to assess the strength of the formulation in offering a barrier to the development of Influenza Like Illnesses (ILI) including Covid-19 infection and also to evaluate its safety and tolerability.

Study methodology

350 subjects were enrolled, 175 in the active product group and 175 in the placebo control group. Randomisation was achieved by block randomisation technique. Subjects in the active product group were given the Investigational Product (IP) and subjects in the placebo control group were given the Placebo Product (PP).

The monitoring of the recruited subjects was conducted utilising Patient Reported Outcome Measure (PROM) methodology. It has been shown that diagnosis of ILI based on clinical diagnostic criteria recorded through a PROM method can have an accuracy of 77% of adults [23,24]. The US Food and Drug Administration released a guidance document "Patient- Reported Outcome Measures: Use in Medical Product Development to support labelling claims in December 2009 [23,25].

We used a PROM device called FluPro - Plus (trademark) licenced from Leidos Biomedical Research Inc. FluPro – Plus is a PROM device developed as per the USFDA guidance document on this subject [26-32].

Study subjects were recruited as per the inclusion and exclusion criteria listed.

Inclusion criteria

Only subjects who met all of the following criteria were included in the study:

1. Age: Adult 18 years inclusive and above at the time of consent.
2. Sex: Adult, healthy males and non-pregnant/non-lactating females.
3. Subjects are in good general health as determined by the Investigator on the basis of medical history reported by subjects including absence of symptom or signs of Covid-19 infection or any other ILI.
4. Subjects must be able to understand and provide written informed consent to participate in the study.
5. Subjects with no relevant findings in medical history or on physical examination which would suggest to the P.I. that the subject is unsuitable for inclusion in the study.
6. Subjects who are willing to allow the Investigator to register volunteer details with a confidential database (The Over-Volunteering Protection Service) to prevent concurrent entry into clinical studies/trials.
7. Subjects who are able and willing (in the Investigator's opinion) to comply with all the trial requirements.

Exclusion criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subjects who have a clinically significant active Oral Cavity disease.
2. Subjects who have a history of recent Oral ongoing treatment.
3. Subjects who have a condition or are taking medication(s) which, in the judgment of the Investigator or Designate, makes the subject ineligible or places the subject at undue risk.
4. Subjects who have received treatment (chemotherapy, radiation, immune suppressant medications) for any type of cancer within the last 6 months.
5. Subjects who are currently participating in any another study related to Oral applications.
6. Subjects who are currently participating in any clinical study, which in the judgment of the Investigator, could potentially affect responses in either study or have participated in a clinical study in the recent past up to three months.
7. Subjects who have a known sensitivity or allergy relating to the substance(s) being evaluated.
8. Subjects who are Pregnant, lactating or have the intention to become pregnant during trial period as determined by questioning the subject.
9. Subjects with any pharyngeal, or laryngeal finding which precludes bronchoscopy.

Subjects were issued the FluPro Plus questionnaire in the form of Subject Diaries (SD). They were asked to fill in the questionnaire on a daily basis.

All subjects were issued the Investigational Product (IP) or the Placebo Product (PP) and were given detailed explanation on their administration. A demonstration of the method was provided and all subjects were informed of the frequency with which the product was to be used. 2 bottles of 50 ml each were given to each subject.

Telephone based monitoring of all subjects was carried out once in three days to ascertain the appropriate use of the product. Physical monitoring in the form of a personal meeting was conducted on Day-1, Day-15 and Day-28. At each of these three meetings the subject was asked to demonstrate the use of spray pump to ensure that the IP was being administered correctly. The sputum was checked for its pH one minute after the administration of the product and the pH was recorded in the SD. This ensured that the primary purpose of creating an alkaline status with a pH of 8 or more was being achieved.

The SD's were checked on Day-15 and Day-28 to ensure that the data/answers to the questionnaire was captured on a daily basis.

The Centers for Disease Control and Prevention (CDC) from USA has published a document dated October 19, 2020 and titled "Duration of Isolation and Precautions for Adults with COVID- 19". They have reviewed the entire literature and evidence available to date and summarized the key findings. The document has the following opening statement, "Accumulating evidence supports ending isolation and precautions for persons with COVID-19 using a symptom-based strategy". It is based on this comprehensive review of evidence that we chose the study duration of 28 days. There is adequate evidence in the world literature to establish that the COVID-19 infection has a total natural life cycle of active infectivity for a period of 21 days in the overwhelming majority of cases.

To ensure that our study did not overlook any subject wherein the symptoms may develop a few days after this 21 day window following first contact with the virus, whilst the virus is still in active replication mode, we added 6 more days for the administration of the IP and reserved Day-28 for the final review. This provides the rationale and justification for the chosen study period of 28 days.

At the end of the study period the data was analysed to ascertain the results.

Oral spray (Test A)

Sr. No.	Material Name	Label Claim	Suggested Limit
1	Sodium Bicarbonate	8.40%	4.2 - 8.4
2	Glycerine	8.00%	4.0 - 12.0
3	Propylene glycol	5.00%	3.0 - 8.0
4	Xylitol	5.00%	3.0 - 8.0
5	Benzalkonium chloride	0.01%	0.01 - 0.04
6	Polo Mint Flavour	0.01%	0.01 - 0.04
7	Neotam Sweetener	QS	-
8	Brilliant Blue	QS	-
9	Water	-	-

Table A

Oral spray (Placebo B)

Sr. No.	Material Name	Label Claim	Suggested Limit
1	Glycerine	8.00%	4.0 - 12.0
2	Propylene glycol	5.00%	3.0 - 8.0
3	Xylitol	5.00%	3.0 - 8.0
4	Benzalkonium chloride	0.01%	0.01 - 0.04
5	Polo Mint Flavour	0.01%	0.01 - 0.04
6	Neotam Sweetener	QS	-
7	Brilliant Blue	QS	-
8	Water	-	-

Table B

Statistical analysis

The statistical analysis of data was done using R software version 4.0.3. Categorical variables were presented with numbers and percentages. Continuous data was presented descriptively with mean, median, and standard deviation (SD). All the statistical tests performed were two-sided with a level of significance of 5%.

Chi-square (or Fisher's Exact Test when needed) was used to compare the proportion of subjects with ILI symptoms between the active treatment and the placebo groups. A logistic regression model was also run to find out the effect of any covariates on the response variable (presence or absence of ILI symptoms). For continuous variables, the comparison between active and placebo group was done using two-sample t-test.

Results

Characteristics	Active (N = 162)	Placebo (N = 158)	Overall (N = 320)	P-value
Age (years)				
N	162	158	320	0.6573
Mean	43.44	42.68	43.07	
SD	15.65	14.73	15.18	
Median	42.00	41.50	42.00	
Min; Max	(18, 78)	(18, 79)	(18, 79)	
Height (cm)				
N	162	158	320	0.1903
Mean	159.64	158.15	158.90	
SD	9.22	11.03	10.17	
Median	159.00	157.50	158.00	
Min; Max	(142, 179)	(134, 184)	(134, 184)	
Weight (Kg)				
N	162	158	320	0.6230
Mean	60.86	60.22	60.55	
SD	11.55	11.81	11.67	
Median	59.50	60.00	60.00	
Min; Max	(34, 101)	(35, 106)	(34, 106)	
Gender, n (%)				
Female	70 (43.2)	72 (45.6)	142 (44.4)	0.6710
Male	92 (56.8)	86 (54.4)	178 (55.6)	
Race, n (%)				
Asian	162 (100.0)	158 (100.0)	320 (100.0)	NA

Table 1: Summary of demographic parameters.

Interpretation: Since none of the p-values are significant in table 1, it shows that all the subjects are equally distributed in the two treatment arms in terms of the baseline characteristics.

Treatment	n (%)	P-value
Active Treatment (N=162)	21 (12.9%)	0.0069*
Placebo (N=158)	39 (24.7%)	

Table 2: Percentage of subjects with symptoms.

*Significant p-value.

p-value is based on chi-square test.

Interpretation: Lower number of subjects with ILI symptoms is observed in the Active treatment arm. Since the p-value is < 0.05 we can say that there is a statistically significant difference in the percentage of subject with ILI symptoms between the two treatment arms.

Interpretation: The logistic regression model was run with ILI Symptoms presence (Yes/No) as the outcome variable and treatment, age and gender as the factors. Since the p-value is corresponding to treatment is < 0.05 we can say that there is a statistically significant difference in the percentage of subject with ILI symptoms between the two treatment arms.

Factor	P-value	Odd Ratio (95% Confidence Interval)
Treatment	0.0079*	Active vs. Placebo 0.45 (0.25; 0.81)
Age	0.6339	1.00 (0.99; 1.0)
Gender	0.9435	Female vs. Male 1.02 (0.56; 1.8)

Table 3: Logistic regression analysis.

*Significant p-value.

The other two factors (age and gender) do not play any significant role in terms of percentage of ILI symptoms.

Factor	P-value	Odd Ratio (95% Confidence Interval)
Treatment	0.0079*	Active vs. Placebo 0.45 (0.25; 0.81)
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Table 3: Logistic regression analysis.

*Significant p-value.

Discussion

Infection by the Covid-19 virus poses significant dangers to a patient's life, and any therapeutic measure that can influence the natural history favourably should be a welcome addition to the therapeutic armamentarium. Whilst vaccines remain in various stages of development, patients continue to present and require treatment beyond the supportive.

Like other coronaviruses (SARS-CoV), entry of SARS-CoV-2 into a host cell seems to be pH dependent, because once a virus fuses with a human cell via S- glycoprotein then its entry inside the cell utilizes a pH-dependent endocytotic pathway [4]. When these endo-lysosome vesicles move towards the nucleus, their pH drops (more acidic), which catalyzes fusion of viral and cell membranes [33]. The studies have mentioned that there is more reduction in viral entry if alkaline conditions are retained in the host cells i.e. pH>7, while as under acidified conditions (pH < 7) there is more viral load inside the host cells [4,34,35]. Therefore, it is evident that novel therapeutic strategies could be designed to raise the pH (alkaline) of endo-lysosomes through infusion of pH raising agents known as lysosomotropic agents. They are defined as weaker bases that have potential to penetrate lysosomes in their protonated form and thus increase their intracellular pH [36]. The use of safer lysosomotropic agents could pave a way to act as one of the effective counter strategies to thwart infection caused by SARS-CoV-2.

This study has attempted to exploit the vulnerability of the virus to an alkaline pH, which may offer a quick, cheap and readily available attempt to influence the course of the disease. Using an oral spray of a formulation containing 8.4% sodium bicarbonate (baking soda), we demonstrated an elevation of the oropharyngeal pH. A similar effect may be expected further down the respiratory tree.

The results of this study appear to validate the basic science findings that the Corona-Sars-2-enveloped virus-related activity can be mitigated by creating an alkaline pH environment in the oropharyngeal spaces. Further, there are recent reports [10] which indicate that combating this virus at the oropharynx level in the early stages of the infection, or perhaps even before the stage of infection is reached, can either prevent the infection or can reduce the severity of the disease.

Conclusion

The results establish that the oral spray formulation used in this study is effective in mitigating SARS-CoV-2-enveloped virus-related activity by creating an alkaline pH environment in the oropharyngeal spaces.

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