EFFICACY EVALUATION OF BD ORAL SPRAY ON THE SYMPTOMS AND COURSE OF COVID-19 PATIENTS IN THE CLINICAL HOSPITAL

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Abstract: A prospective randomized, open-label, single-blinded clinical trial was conducted to evaluate the efficacy of BD on the symptoms and course of the disease in patients with moderate and severe Covid-19 in the field hospital. 200 hospitalized patients with Covid-19 diagnosis were enrolled. The patients were randomized into 100 patients in the interventional group (BD group) and 100 in the control group. The BD group patients were treated with BD oral spray in conjunction with standard Covid-19 treatment protocol. The control group patients were treated with standard of care without BD. Patients of the BD group demonstrated a significantly faster improvement in all Covid-19 related symptoms, resulting in a shorter time for complete recovery than the control group. More remarkably, patients in the BD group showed a shorter time for complete viral clearance. The addition of BD to the standard of care protocol also resulted in significant improvement in the restoration of taste and smell and reduction of lung infiltration. The patients in the BD group also exhibited fewer adverse events related to treatment. BD is a simple-to-use, safe, and effective adjunctive treatment for moderate and severe Covid-19 cases. BD might be effective for Covid-19 symptoms.

Keywords: Covid-19, BD, Viral Infection, Hospital

1. Introduction

The pandemic of Covid-19 had resulted in a high number of hospitalizations, deaths and caused a devastating toll on humans and society. The symptoms of the Covid-19 patients can vary from asymptomatic, mild to life-threatening or even deaths in some cases. This clinical observation suggested the critical role of host innate immunity in disease development and progression. As the first defense barrier against pathogens, the innate immune reaction determines the viral infectiveness, disease progression and outcome. Using natural agents with mucosal and systemic immune-enhancing activities might play a vital role in preventing and treating Covid-19 [1].

Due to the airborne transmission of Covid-19 via exposed infectious respiratory droplets, saliva, or direct contact, it is crucial to control the viral loads in the saliva and respiratory secretions. Thus, it suggested a cost-effective strategy to prevent cross-contamination and community transmission by implementing effective oral and throat hygiene [2].

Several published reviews and meta-analyses have documented the importance of good oral hygiene and the use of chemical antiseptic (disinfectant) agents to prevent respiratory disorders and nosocomial infections [3;5].

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In our prior publication, we have suggested that the possible implementation of zinc iodide in combination with dimethyl sulfoxide could provide a viable solution for preventing and treating Covid-19 [6;8]. The ingredients of this composition have been demonstrated in clinical and experimental studies as safe and effective for antiviral, anti-inflammatory, antimicrobial, antifungal, mucosal, and systemic immune-enhancing activities [9;10].

BD is registered in Vietnam as an oral sanitizer and disinfectant. The formulas have been developed in the BD Pharmaceutical Ltd, Korea. BD has been tested for acute and chronic toxicity, skin and mucosal irritation, and thyroid toxicity by the Pharmacology Department of the National Institute of Drug Quality Control of Vietnam. The testing results showed an excellent safety profile and tolerability. The key ingredients of BD are zinc iodide, ginger extract, propolis extract, natural fruit flavor, xylitol, DMSO and pure water.

In this study, a prospective randomized, open-label single-blinded parallel-group clinical trial was conducted to evaluate the efficacy of BD oral spray in conjunction with standard of care on the symptoms and course of the disease for the patients with moderate and severe Covid-19 patients in the limited resources clinical hospital.

Aim of the study

Our study aimed to evaluate the efficacy and safety of an inexpensive and simple-to-use BD for treatment and prevention of Covid-19 in the clinical hospital. Due to the Covid-19 outbreak resulting in limited medical and human resources, we could only focus on studying and recording the most essential clinical and paraclinical data related to Covid-19 symptoms, disease progression, and substantiating a possible immediate implementation of BD for Covid-19 treatment and prevention.

2. Material and Method

Study materials

BD is registered for use as an oral sanitizer and disinfectant medical device in Vietnam provided it for the clinical hospital as a donation.

Study location and time:

The study was conducted at Son Tay clinical hospital (Son Tay Town, Ha Noi City) from June to September, 2021.

Study design:

The current study was prospective randomized, open-label, single-blinded (the investigators were blinded) using the parallel group method.

Inclusion criteria

Hospitalized patients were laboratory-confirmed Covid-19 infection by RT- PCR positive in the sample collected within 72 hours before the randomization. Male or non-pregnant females were older than 15 years of age at the time of enrollment. Subject with clinical evidence of moderate to severe Covid-19 defined by decision No. 3416/QĐ-BYT.

Exclusion criteria

A subject was not eligible for inclusion in this study if any criteria apply.

- The physician decides that trial involvement was not in the patient's best interest, or any condition did not allow the protocol to be followed safely.
- The patient was already in, or had already been in, another clinical trial of an experimental treatment for Covid-19.
- The patient was associated with a known medical history of allergy to Zn and iodine. The patient already received dialysis (either acute or chronic) or imminent need of dialysis at the time of enrolment.

Study groups

Two hundred moderate and severe Covid-19 patients were randomized into two groups: The interventional group (BD group) and the control group. The 100 patients BD group received BD oral spray 5 to 10 times daily, 5 pushes each time depending on the severity of the disease (moderate: 5 times, severe: 10 times) in conjunction with all other treatments as the standard of care for Covid-19 and comorbidities. Other 100 patients in the control group received only standard of care protocol without BD. BD oral spray was provided for 14 days.

Severity classification:

Moderate cases: Patients who show lower respiratory disease during clinical assessment and chest X-ray examination with clinical features of dyspnea and or hypoxia, SpO2 ≥94% on room air and respiratory rate ≥ 24, but < 30 breaths/minute.

Severe cases: Patients who show lower respiratory disease during clinical assessment and chest X-ray examination with clinical features of dyspnea and hypoxia, SpO2 <94% on room air, a respiratory rate ≥ 30 breaths/minute.

Outcome assessments

The study outcome was assessed by clinical symptomatology progress, time for recovery and symptom clearance, viral clearance rate, chest X-ray examination, and adverse effects of the treatment**.**

Statistical analysis

The statistical analysis of data was performed using software SPSS 25.0. Statistical tests were two-tailed, and p-value<0.05 was considered at a significant level.

Research ethics:

This study protocol was approved by the ethical committee No. 012/QĐ-IMP.

3. Results

3.1. Results of patients information collection

In our study, the proportions of males and females in each group were similar: Control group: Male (57.0%), female (43.0%); BD group: Male (58.0%), female (42.0%).

As presented in Table 1, there were no statistical differences between the age of patients in BD and control groups (p=0.1, p>0.05).

Table. Age of patients in BD group and Control groups

Age	BD group		Control group		Total	
	Number	%	Number	%	Number	%
15-19	5	5	2	2	7	3.5
20-29	20	20	15	15	35	17.5
30-39	15	15	14	14	29	14.5
40-49	16	16	19	19	35	17.5
50-59	17	17	19	19	36	18
60-69	12	12	11	11	23	11.5
≥ 70	15	15	20	20	35	17.5
Tổng	100	100.0	100	100.0	200	100.0

The results in Table 2 showed the most prevalent complications of Covid-19 in the study patients were pneumonia (96.0%) and respiratory failure (39.5%). The most popular pre-existing comorbidity were diabetes (38.5%), COPD (31.5%), hypertension (26.0%), bronchial asthma (16.5%), cardiovascular (15.5%). The complication of Covid-19 and concomitant diseases were comparable across the control and BD groups with the p>0.05.

Table 2. Background medical history information of patients in the study groups

Background disease	BD group		Control		Total	
	Number	%	Number	%	Số lượng	%
Pneumonia	46	46.0	32	32.00	78	39.00
Diabetes	7	7.0	11	11.00	18	9.00
COPD	99	99.0	93	93.00	192	96.00
Cancer	37	37.0	40	40.00	77	38.50
Chronic renal failure	26	26.0	27	27.00	53	26.50
Obesity/overweight	6	6.0	6	6.00	12	6.00
Heart disease	8	8.0	7	7.00	15	7.50
Neuropathy	11	11.0	10	10.00	21	10.50
Blood disease	18	18.0	13	13.00	31	15.50
Asthma	7	7.0	2	2.00	9	4.50
Hypertension	9	9.0	6	6.00	15	7.5
Liver disease	20	20.0	13	13.00	33	16.50
Other disease	23	23.0	29	29.00	52	26.00
Respiratory failure	7	7.0	2	2.00	9	4.50
Tired	12	12.0	10	10.00	22	11.0

According to the results shown in Table 3, the vaccination rates in the two study groups were similar; the difference was not statistically significant ($p>0.05$).

Table 3. Covid-19 vaccinated information of patients in study groups.

Covid-19 vaccinated	**BD group**		**Control**		**Total**	
	Number	**%**	**Number**	**%**	**%**	**%**
1st Dose	31	31.0	29	29.00	60	30.00
2nd Dose	60	60.0	57	57.00	117	58.50
Not yet	9	9.0	14	14.00	23	11.50

The results in the Table 4 include 100 % of patients in two groups had dyspnea, sore throat (87.5 %), and excessive tiredness (81.5%), fever (80.0%), cough (79.0%), taste loss (75.5%), pain and chest tightness (57.5%), runny nose (56.5%), headache (50.0%), muscle pain (42.5%), numbness in limbs (40.0%), diarrhea (38.0%), loss/reduction of smell sensation (36.5%), dizziness, vertigo (22.0%) and vomiting-nausea (20.0%). Despite a higher number of patients in the BD group presenting with vomiting and nausea, there were no statistical differences in the symptomatology prevalence in the BD and control groups at the moment of admission.

Table 4. The symptoms of patients come to clinical hospital

Symptoms	**BD group**		**Control group**		**Total**	
	Number	**%**	**Number**	**%**	**%**	**Ratio %**
Cough	85	85.0	73	73.0	158	79.0
Fever	79	79.0	81	81.0	160	80.0
Tired	85	85.0	78	78.0	163	81.5
Sore throat	85	85.0	90	90.0	175	87.5
Loss of taste	71	71.0	80	80.0	151	75.5

Chest pain	57	57.0	58	58.0	115	57.5
Headache	54	54.0	46	46.0	100	50.0
Numbness in limbs	40	40.0	40	40.0	80	40.0
Shortness of breath	100	100.0	100	100.0	200	100.0
Muscle pain	59	59.0	46	46.0	105	52.5
Runny nose	55	55.0	58	58.0	113	56.5
Smell disorder	40	40.0	33	33.0	73	36.5
Nausea/vomiting	29	29.0	15	15.0	44	22.0
Dizzy	30	30.0	10	10.0	40	20.0
Diarrhea	38	38.0	39	39.0	77	38.0
Other	18	18.0	5	5.0	23	11.5

Add more results in Table 5 shown the levels of severity were comparable in both groups, and the difference was not statistically significant (p>0.05).

Table 5. Disease level of patients in the study group

Condition	BD group		Control		Total	
	Number	%	Number	%	%	Number
Moderate	76	76	72	72	148	74
Severity	24	24	28	28	52	26

Overall, Tables 1-5 showed baseline demographic characteristics of all recruited patients in study groups were compatible. There were no statistically significant differences between the BD and the control group.

3.2. Treatment results with BD

The treatment for Covid-19 patients in study groups adheres to the Vietnamese Ministry of Health's guidelines. The results shown in Table 6, there was no difference in drug usage between the BD and the control group.

Table 6. Medicines to treat Covid-19 patients in groups

Drugs used	BD group		Control group	
	Number	%	Number	Tỷ %
Cough and fever reducer	98	98.0	96	96.0
Underlying disease	64	64.0	67	67.0
Antibiotic	100	100.0	100	100.0
Vitamins and minerals	100	100.0	100	100.0
Anti-inflammatory	100	100.0	99	99.0
Antifreeze	56	56.0	51	51.0
Anti virus	100	100.0	100	100.0
Other	100	100.0	98	98.0
BD oral spray	100	100.0	0	0.0

As Figure 1 showed that 15.5 % of patients got oxygen via glasses, 57.0 % of patients received oxygen through a mask, 25.0% of patients received HFNC, and 2.5% of patients received non-invasive mechanical ventilation. There was no statistically significant difference in oxygen therapy between BD and control groups (p>0.05).

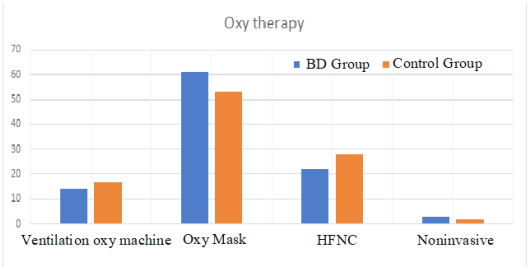


Figure 1. Results of oxygen supply to patients in the study groups

Our study discovered that the number of patients experiencing adverse effects in the BD group was low. Only four patients suffered diarrhea, 3 had dizziness, and 2 had vomiting and nausea. Meanwhile, this rate was higher in the control group. Eighteen patients experienced diarrhea, 6 had dizziness, 3 had vomiting and nausea. The difference in the adverse side effects of treatment was significantly higher in the control group than in the BD group in Table 7.

Table7. Unwanted effects related methods treatment in study groups

Unwanted effects	BD group		Control group		Total	
	Number	**%**	**Number**	**%**	**Number**	**%**
Nausea/vomiting	2	2	3	3	5	2.5
Dizzy	3	3	6	6	9	4.5
Tiêu chảy	4	4	18	18	22	11.0
Táo bón	3	3	2	2	5	2.5
Total	12	12	29	29	41	20.5
	p=0.035, p<0.05. p value for total Unwanted effects					

The results in Figure 2 showed a statistically significant difference in the ratio of patients with Covid-19 related symptoms in BD and the control group after four days of treatment with $p < 0.05$ (p=0.03-0.01). Furthermore, on the fifth day of therapy, only 40.0 % of patients in the BD group had clinical symptoms, while 60 % of patients were symptom-free. By the 7th day, just 1.0 % of the patients in the BD group showed clinical symptoms, while 99.0 % had none. Compared with the control group, the improvement in Covid-19 symptomatology in the BD group was highly statistically different started from day 5th of treatment, and this trend continued to the end of the study.

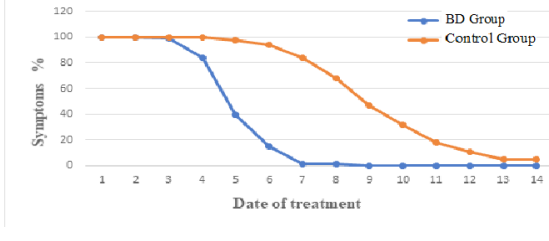
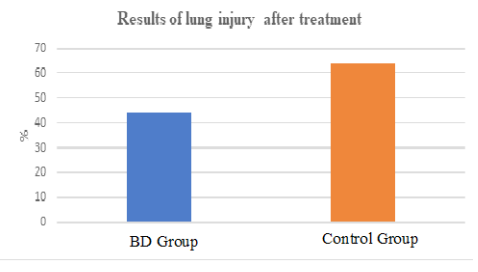


Figure 2. Results of Compare the change of clinical symptoms of Covid-19 patients

Image examination and laboratory test results of study groups

Patients received a chest X-ray weekly. There were 95 vs. 98 patients who needed to take 2nd x-ray and 5 vs. 8 patients who were required to take 3rd X-ray in BD and control groups respectively. From the 2nd and 3rd chest X-ray reports after seven days of treatment, the BD group had 44.0 % with signs of lung damage, while the control group was 66.0 %. BD group exhibited a significant reduction in lung infiltration was shown in Figure 3.



The results shown in Table 8, the initial RT-PCR test showed 100% Covid-19 positive

at admission. The BD group exhibited an 80.0 % negative rate on the 2nd test, which was carried out on the 9th-10th days after admission, whereas the Control group was 73.0 %. The third RT-PCR test was performed for evaluating hospital discharge 48 hours following the second test. The BD group reached 91.0 % negative, whereas the Control group was 81.0 %. The remaining positive cases, whose cycle threshold was not assured as specified, had been evaluated by RT-PCR for the fourth time after 24 hours. The BD group has 98.0 % negative compared to 91% in the Control group. The RT-PCR test results indicated patients in BD group had a faster viral clearance rate when compared with Control group.

Table 8. Results RT-PCR test of patients in study groups

RT-PCR test results		BD group		Control group	
		Number	%	Number	%
1st time	Negative	0	0.0	0	0
	Positive	100	100.0	100	100.0
2nd time	Negative	80	80.0	73	73.0
	Positive	20	20.0	27	27.0
3rd time	Negative	91	91.0	81	81.0
	Positive	9	9.0	19	19.0
4th time	Negative	98	98.0	91	91.0
	Positive	2	2.0	9	9.0
p=0.047, p< 0.05					

4. Discussion

The morbidity, mortality, infectiveness, and spread of Sars-Cov-2 are dependent on the host-pathogen relationship. Given the lack of inexpensive, effective, and safe antiviral drugs for Covid-19, especially in countries of limited resources, it should be more focused on supporting the discovery and implementation of possible complementary therapeutic approaches. Additionally, pathological viruses such as Sars-Cov-2 are constantly mutated into different strains or variants that could make antiviral drugs work less effectively against these viruses. Therefore, research and development of holistic preventive and therapeutic strategies based on boosting innate and adaptive immune defense mechanisms of the human body to combat Covid-19 should be encouraged, especially in a scenario where the virus may become endemic and recurrent seasonal [1;10;11].

Oral therapeutic intervention can have a substantial role in combating the Covid-19 pandemic, as intact oral mucosa circumvents the virus-invade-host theory. Additionally, the oral mucosal membrane with saliva is a primary transmission route of viruses and a potential source of recontamination and community spread of infection [3;4;12].

Viral pathogens such as Sars-Cov-2 can infect the upper respiratory tract for colonization and proliferation for the first few days after entering the body. Our study results strongly indicated the delivery of effective therapeutics for the prevention and treatment of the disease could be achieved via oral and pharyngeal cavities with BD oral spray.

We acknowledge that our current study has limitations. This is a non-funded study conducted in a limited resource field hospital that was recently established in the emergency with Covid-19 breakout in Hanoi City. We were not

able to prepare and use a placebo in the control group, and it was not possible to blind the study groups. We also could not monitor the dynamic of biomarkers for inflammation and coagulation abnormalities in the patients to document possible paraclinical evidence to substantial additional objective therapeutic benefits of BD oral spray.

Despite the limitations mentioned above, in the most practical view of the current global situation with the Covid-19 pandemic, the data of our present study clearly showed the robust therapeutic and possible preventive efficacy of BD oral spray. Besides significant reduction in Covid-19 symptomatology, positive impact on the course of the disease, and viral clearance rate, our current study suggested using BD early in the clinical practice may reduce numbers of patients progressing to severe disease and transmission of Covid-19 in the community.

BD composes well-characterized and proven natural and OTC pharmaceutical ingredients with a favorable safety profile. It is a significant advantage for the development and application of BD against Covid-19 as a repurposed therapeutic product since developing new medications can take many years.

The future larger and well-designed clinical trial is warranted to explore more potential therapeutic activities of BD and promote a possible more comprehensive application of this simple-to-use, inexpensive and effective weapon for Covid-19 treatment and prevention the Covid-19 disease.

5. Conclusion

The current study results demonstrate that BD is an inexpensive, simple-to-use, effective treatment for moderate and severe Covid-19 cases. The data of our study also suggested BD might be effective for primary and secondary Covid-19 prevention.

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