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Original Article:

Clinical Trial of Sinudrain Haft Bahr Solution for Symptom Management in Mild to Moderate COVID-19

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Abstract

Introduction: The COVID-19 pandemic, caused by the coronavirus, has been declared a global health emergency by the World Health Organization (WHO). This virus primarily affects the respiratory system, and affordable treatments for mild to moderate cases are urgently needed. Sinudrain Haft Bahr, a solution with antiseptic properties, was evaluated for its potential to alleviate COVID-19 symptoms.

Materials and Methods: A clinical trial was conducted on 61 COVID-19 patients at Taleghani Hospital, Tehran. After a medical evaluation and analysis of symptoms, participants were randomized 1:1 (intervention vs. control) using admission code parity. The intervention group received Sinudrain, while the control group received routine medications from the national protocol. The drug was administered by gargling the solution three times a day and spraying it inside the nose six times a day. Patients' clinical symptoms were monitored on the first, third, and fifth days.

Results: Sinudrain significantly reduced cough (45%), sore throat (41%), and shortness of breath (32%) versus controls (all $p<0.05$). No effect was observed on fever, loss of smell, or digestive symptoms.

Conclusion: Sinudrain is a promising adjunctive therapy for COVID-19 respiratory symptoms, with advantages in cost, availability, and safety. Further trials are warranted.

Keywords: COVID-19, Sinudrain Haft Bahr, randomized controlled trial, respiratory symptoms, nasal spray, adjunctive therapy

1. Introduction

In December 2019, patients with COVID-19 were identified for the first time in Wuhan, China [1]. The virus rapidly spread worldwide, and in March 2020, the World Health Organization (WHO) declared it a pandemic, recognizing it as one of the greatest health threats in the world [2]. COVID-19 is a contagious disease caused by the coronavirus. It primarily attacks the human

respiratory system, causing a range of symptoms from mild, transient colds to severe acute respiratory syndrome [3,4]. Despite advances in vaccination, affordable and accessible treatments for mild to moderate COVID-19 remain limited, particularly in resource-constrained settings. Sinudrain Haft Bahr, a registered solution in Iran, contains natural antiseptics (e.g., sodium chloride) and has demonstrated efficacy in sinusitis and influenza. Its potential to mitigate COVID-19 symptoms via nasal/oral application warranted investigation.This study aimed to evaluate Sinudrain's efficacy in reducing respiratory symptoms of mild to moderate COVID-19 compared to standard care. The signs and symptoms may differ in each person, and their intensity may vary to the point where some patients do not exhibit any noticeable symptoms [4,5]. Based on the manifestation of their symptoms, individuals are divided into two groups:

Patients without clinical symptoms

According to this classification, patients with COVID-19 without clinical symptoms are referred to as asymptomatic patients or asymptomatic carriers [4,5].

Patients with clinical symptoms

According to factors such as the involved organ, type, and severity of symptoms, these patients are categorized into four subgroups: mild (40% of patients), moderate (40% of patients), severe (15% of patients), and critical (5% of patients). (This classification is based on the 2023 declaration of the WHO and reflects the overall population of patients with COVID-19) [4,6].

Mild disease

Mild disease is characterized by symptoms such as fever, cough, fatigue, loss of appetite, and shortness of breath. Some patients also experience non-specific symptoms like sore throat, nasal congestion, headache, diarrhea, nausea, and vomiting [7-10]. In addition, in some cases, loss of smell or taste has been reported as an early disease symptom [11-13]. However, no cases of viral pneumonia or hypoxia have been reported in this group of patients [4].

Moderate disease

Patients with the moderate type have medical signs similar to pneumonia without severe symptoms of pneumonia and with blood oxygen saturation within the range of 90% ($PO2 \geq 90\%$) [4,6].

Severe disease

Severe disease is characterized by pneumonia-like symptoms such as fever, cough, and shortness of breath. These symptoms may be accompanied by a respiratory rate exceeding 30 breaths per minute, severe respiratory distress, or a blood oxygen saturation level below 90% ($PO2 < 90\%$) [4,6].

Critical disease

In a minority of patients, COVID-19 can progress to a critical stage, leading to serious complications such as acute respiratory distress syndrome (ARDS), structural cardiac abnormalities, arrhythmia, acute renal failure, metabolic disorders, acute thrombotic issues, and other life-threatening complications [4,6]. Due to the broad clinical symptoms and involvement of other vital organs, these patients are more prone to mortality.

The Sinudrain Haft Bahr drug was officially registered with the Iranian Ministry of Health and Medical Education under the registration number 0235-93 in 2013-2014. This medication is a holistic remedy containing elements such as calcium, potassium, zinc, manganese, and sodium. The active ingredient in this medication is sodium chloride, known for its antiseptic qualities; it can disinfect areas it touches, such as the throat, nose, and sinuses. Additionally, it considerably reduces the symptoms of patients with sinusitis, colds, and influenza by draining the infection and moisture from the sinuses and the back of the throat. Given that mild to moderate COVID-19 cases often affect the upper part of the respiratory system, similar to conditions like sinusitis, cold, and influenza, this solution is expected to emerge as a promising candidate for enhancing the treatment of this disease. Therefore, a clinical trial was conducted to examine the effectiveness of this medication for COVID-19 patients with mild to moderate symptoms. The following will explain the outcomes and data obtained from this clinical trial.

2. Materials and Methods

The proposed plan was initially registered in the Iranian Registry of Clinical Trials (IRCT) system, and a confirmation code was obtained (IRCT202 10914052471N1). The project then underwent review by the Research Council of the Vice-Chancellor of Research and Technology at Shahid Beheshti University of Medical Sciences and was subsequently approved by the Ethics Committee (IR.SBMU.R ETECH.REC.1399.1209). This was an open-label, randomized clinical trial conducted at Taleghani Hospital, Tehran. The study was conducted from March 20, 2023, to October 12, 2023, on 61 patients referred to Tehran's Taleghani Hospital with clinical symptoms of COVID-19. After a medical evaluation and analysis of their symptoms, participants were randomized 1:1 (intervention vs. control) using admission code parity. Those with an even admission code were assigned to the intervention group, while those with an odd admission code were placed in the

control group. The inclusion criteria for this trial were a positive PCR test for COVID-19, no underlying cardiac disease, an age range of 17-67 years, oxygen levels above 80%, and pulmonary involvement less than 40%. Patients with severe lung irregularities on X-ray images, persistent symptoms such as shortness of breath and nausea, or no improvement in their overall condition were excluded from the study. The intervention group received only Sinudrain (without concomitant medications), while the control group received routine national protocol medications (acetaminophen, diphenhydramine, etc.). Sinudrain Haft Bahr was manufactured by Sobhan Darou Pharmaceutical Co. (Tehran, Iran) and provided as a standardized solution under institutional collaboration. The drug was administered by spraying the solution inside the nose six times a day and gargling it three times a day. The dosing protocol followed Iranian Ministry of Health guidelines for Sinudrain (Reg. #0235-93) and aligned with prior studies of nasal antiseptics in viral infections. The patient's clinical symptoms were monitored on the first, third, and fifth days. Data were collected using a questionnaire and validated through the Generalized Estimating Equations (GEE) analysis of ranked responses. This study has several limitations, including its open-label design, reliance on remote (telephone-based) follow-up—which may have introduced reporting errors and reduced patient compliance—and a short-term (5-day) observation period without viral load measurements. However, these limitations were partially mitigated by rigorous symptom monitoring and strict adherence to inclusion criteria.

3. Results

The GEE method was used to analyze the symptoms of 61 patients, who were divided into two groups: the intervention group, consisting of 37 patients (60.7%), and the control group, consisting of 24 patients (39.3%). The average age in the intervention group was 40.8 ± 15.2 years, while the control group had an average age of 48 ± 18 years. There was no significant difference in age between the two groups (p = 0.096). The intervention group included 13 women (35.1%) and 24 men (64.9%), while the control group had 12 (50%) women and 12 (50%) men. No significant difference regarding gender was observed between the two groups (p=0.249). The results of rank logistic regression using the GEE method in examining the relationship between the symptoms and the studied groups are reported in Table 1. Considering the correlation between treatment and time in Table 1, the treatment had a significant effect on all symptoms except fever, loss of smell, and digestive symptoms. With each additional unit of time, the intervention group's probability of experiencing cough symptoms decreased by 41% compared to the control group (OR= exp (-0.22-0.31) = 0.59). The intervention group exhibited a significant reduction in symptoms compared to the control group, with a 45% decreased risk of experiencing sore throat symptoms (Odds Ratio, OR = 0.55), a 42% reduced likelihood of body pain symptoms (OR = 0.58), and a 32% lower chance of experiencing shortness of breath (OR = 0.68). Additionally, the probability of headache symptoms decreased by 42% in the intervention group (OR = 0.58).

Table 1. The results of rank logistic regression using the GEE method in examining the relationship between the symptoms and the studied groups

Symptoms		Regression coefficient β	Standard deviation (SD)	P-value	Odds Ratio (OR)
Cough	Treatment effect	.393	.5337	.462	1.481
	Time effect	-.223	.1113	**.045	.800
	Interaction of treatment and time	-.311	.1316	**.018	.733
Sore throat	Treatment effect	3.681	.7381	**.000	39.673
	Time effect	.046	.1119	.679	1.047
	Interaction of treatment and time	-.635	.1560	**.000	.530

Body pain	Treatment effect	1.007	.4896	**.040	2.736
	Time effect	-.136	.0816	.095	.873
	Interaction of treatment and time	-.414	.1289	**.001	.661
Shortness of breath	Treatment effect	-1.330	.4661	**.004	.265
	Time effect	-.136	.0900	.130	.873
	Interaction of treatment and time	-.243	.1203	**.043	.784
Fever	Treatment effect	-2.083	.8499	**.014	.125
	Time effect	-.380	.1201	**.002	.684
	Interaction of treatment and time	-.148	.1886	.433	.863
Headache	Treatment effect	1.836	.4838	**.000	6.268
	Time effect	-.070	.1533	.647	.932
	Interaction of treatment and time	-.482	.1862	**.010	.618
Sense of smell	Treatment effect	3.632	1.1820	**.002	37.777
	Time effect	.297	.3976	.454	1.346
	Interaction of treatment and time	-.521	.4119	.206	.594
Digestive	Treatment effect	.091	.5981	.879	1.095
	Time effect	-.278	.1555	.074	.757
	Interaction of treatment and time	.117	.2047	.566	1.125

** is meaningful at the 0.05 level

Furthermore, the results of the treatment and time interaction in Table 1 demonstrated that the frequencies of all symptoms, except for fever, olfactory symptoms, and digestive symptoms, varied between the two groups at different assessments. Table 2 illustrates the frequency of symptoms for the significant interaction between therapy and time, broken down by group and assessment times. The obtained results show that before starting the medication, the treatment group had higher levels of sore throat, body pain, and headache compared to the control group. However, on the fifth day following treatment, the percentage of all symptoms, except for headache, was significantly lower in the treatment group compared to the control group.

Table 2. The frequency of symptoms(with/without) at different assessment times by group

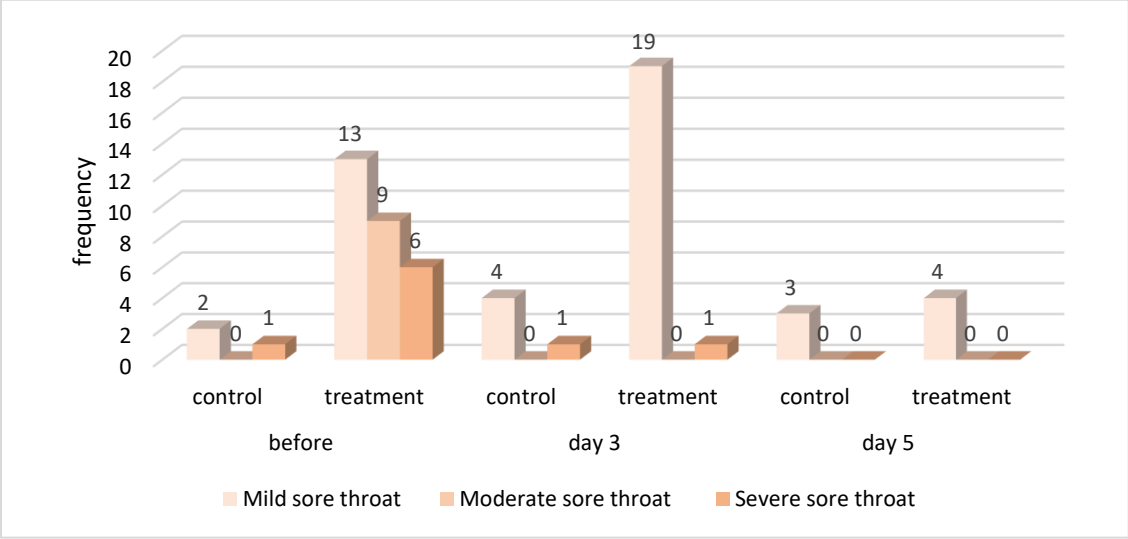
symptoms		Before consumption		Third day		Fifth day	
		control	treatment	control	treatment	control	treatment
Cough	Without symptoms	3(12.5%)	6(16.2%)	1(4.2%)	4(10%)	2(8.3%)	27(73%)
	With symptoms	21(87.5%)	31(83.8%)	23(95.8%)	36(90%)	22(91.7%)	10(27%)
Sore throat	Without symptoms	20(87%)	9(24.3%)	18(78.3%)	16(44.4%)	20(87%)	32(88.9%)
	With symptoms	3(13%)	28(75.7%)	5(21.7%)	20(55.6%)	3(13%)	4(11.1%)
Body pain	Without symptoms	6(25%)	6(16.2%)	6(25%)	13(36.1%)	8(34.8%)	27(73%)
	With symptoms	18(75%)	31(83.8%)	18(75%)	23(63.9%)	15(62.5%)	10(27%)
Shortness of breath	Without symptoms	1(4.2%)	18(48.6%)	2(8.3%)	13(36.1%)	3(13%)	34(91.9%)
	With symptoms	23(95.8%)	19(51.4%)	22(91.7%)	23(63.9%)	20(87%)	3(8.1%)
Headache	Without symptoms	17(73.9%)	10(27.8%)	18(75%)	29(80.6%)	19(82.6%)	29(80.6%)
	With symptoms	6(26.1%)	26(72.2%)	6(25%)	7(19.4%)	4(17.4%)	7(19.4%)

In examining the changes in the severity of symptoms over time, according to Table 3 and the graphs, both groups experienced a decrease in the moderate-to-severe symptoms of cough, sore throat, and shortness of breath on the fifth day following treatment. Among these symptoms, the severity of shortness of breath decreased more significantly in the treatment group than in the control group.

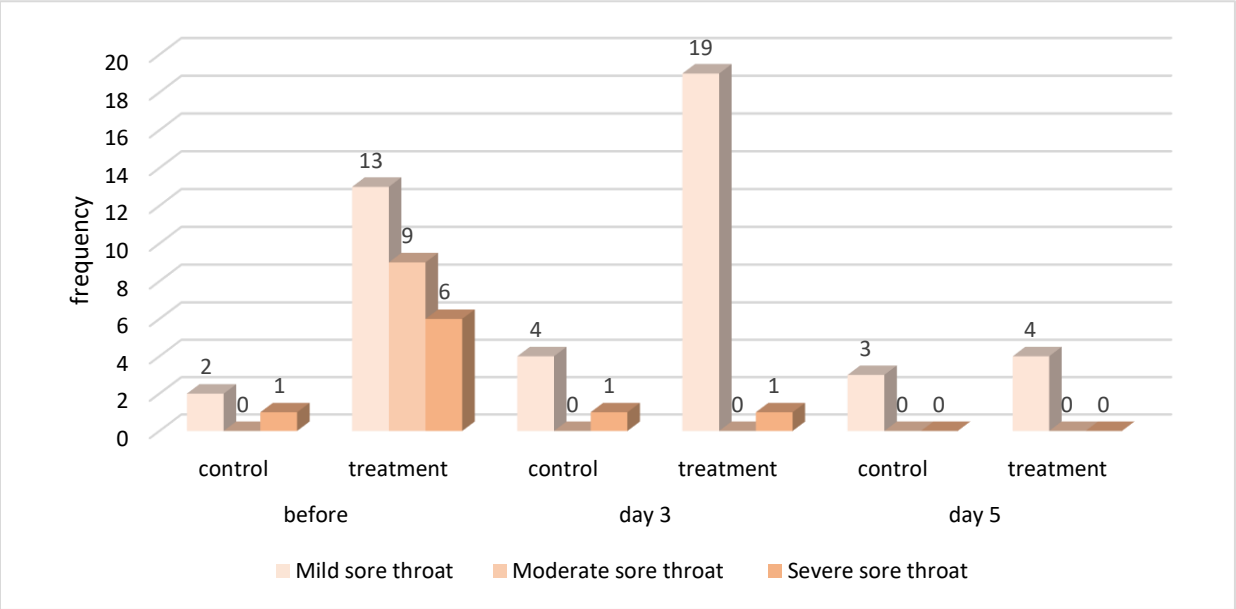
Table 3. Frequency of the severity of symptoms over different assessment times by group

symptoms		Before consumption		Third day		Fifth day	
		control	treatment	control	treatment	control	treatment
Cough	No symptoms	3	6	1	4	2	27
	Mild	9	13	14	12	15	10
	Moderate	11	10	8	20	6	0
	Severe	1	8	0	0	0	0

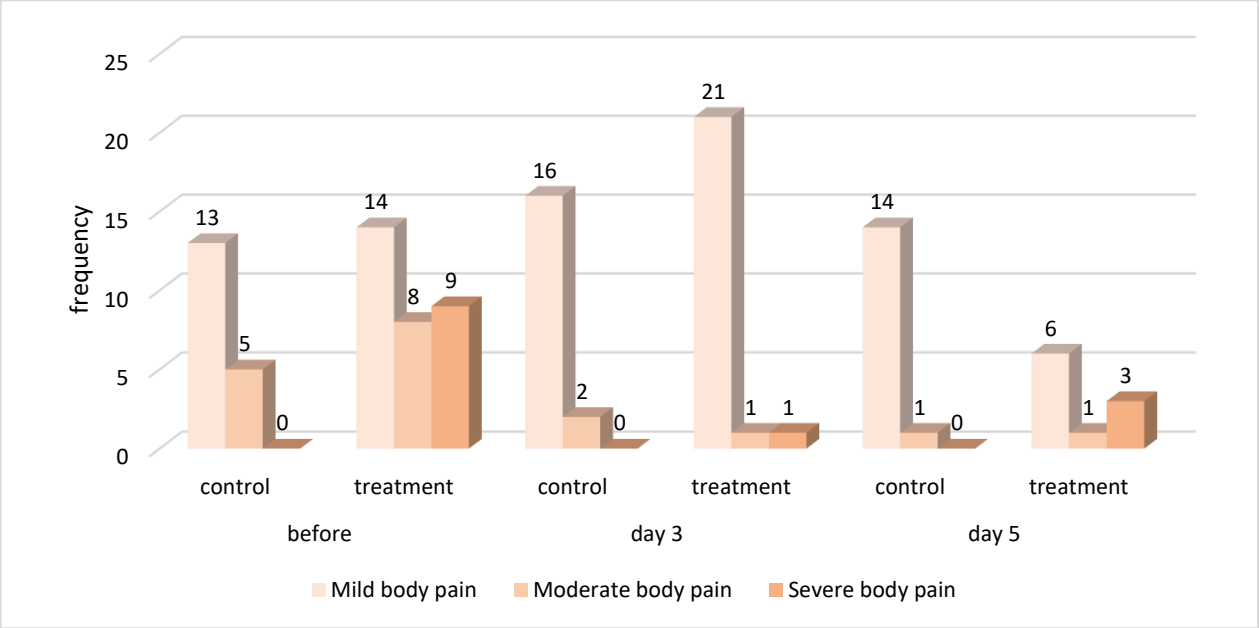
Sore throat	No symptoms	20	9	18	16	20	32
	Mild	2	13	4	19	3	4
	Moderate	0	9	0	0	0	0
	Severe	1	6	1	1	0	0
Body pain	No symptoms	6	6	6	13	8	27
	Mild	13	14	16	21	14	6
	Moderate	5	8	2	1	1	1
	Severe	0	9	0	1	0	3
Shortness of breath	No symptoms	1	18	2	13	3	34
	Mild	10	9	14	18	13	2
	Moderate	12	7	5	5	5	1
	Severe	1	3	3	0	2	0
Headache	No symptoms	17	10	18	29	19	29
	Mild	6	12	5	6	2	3
	Moderate	0	9	1	0	2	3
	Severe	0	5	0	1	0	1



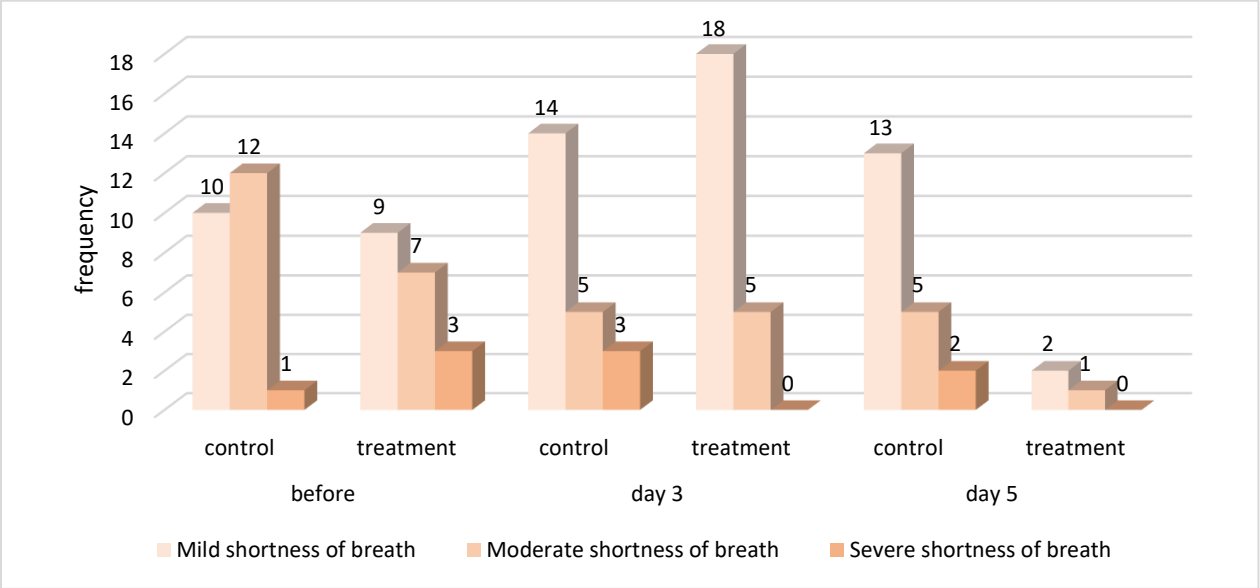
Graph 1. Frequency of cough symptoms at different assessments by group



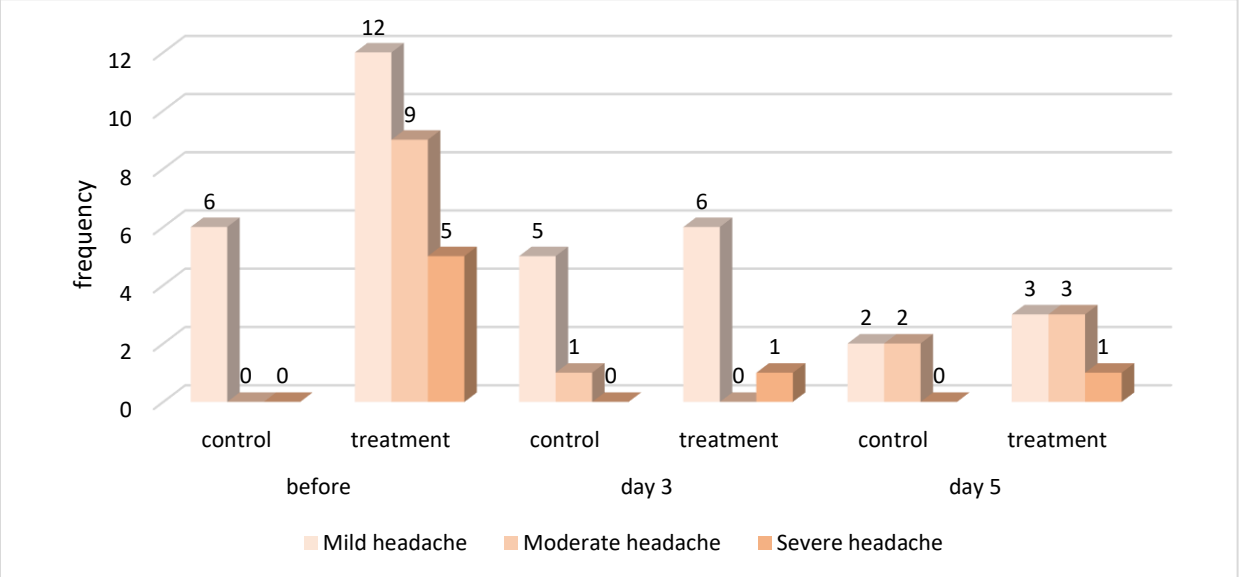
Graph 2. Frequency of sore throat symptoms at different assessments by group



Graph 3. Frequency of body pain symptoms at different assessments by group



Graph 4. Frequency of shortness of breath symptoms at different assessments by group



Graph 5. Frequency of headache symptoms at different assessments by group

4. Discussion

Despite the increasing number of people getting vaccinated against COVID-19 globally, the virus continues to spread at an alarming rate. Currently, various antiviral medications, such as hydroxychloroquine, remdesivir, lopinavir, and adjuvant medications, such as corticosteroids and ascorbic acid, are being administered orally or intravenously [14]. Since the nose is the primary entry point for the virus, investigating the drug delivery route via the lungs may be a more effective approach for treating COVID-19 [14].Vaccines administered by nasal inhalation have shown promising results and may be a more affordable alternative for boosting immunity[15]. Compared to traditional methods of drug administration, such as oral consumption or injection, the nasal route has unique advantages. It can stimulate both local and systemic immune responses, effectively suppressing the spread of the virus to others[16]. Additionally, the mouth is also a potential entry point for the virus and, various liquid solutions have been studied as potential remedies to alleviate symptoms associated with COVID-19. One such solution is nitric oxide, which has been shown to significantly reduce the viral load of COVID-19 in patients when administered as a nasal spray [17,18] . In a study conducted in the United Kingdom, the SanNOtize brand nitric oxide nasal spray was found to be an effective antiviral treatment that reduced the spread of COVID-19 and shortened the duration of symptoms [19]. Another solution, ciclesonide nasal spray, was evaluated in a multicenter, randomized, double-blind trial and was found to reduce the number of emergency department visits and hospitalizations for COVID-19-related illnesses [20]. Chlorpheniramine maleate, a nasal spray with antiviral properties, was also studied by Xu et al. and was found to exhibit strong antiviral activity against SARS-CoV-2 [21]. In another study, Torres et al. found that using Chlorpheniramine maleate nasal spray as an adjunctive treatment in COVID-19 patients led to rapid improvement in clinical symptoms [22]. A study evaluated the therapeutic efficacy of ivermectin nasal spray in treating patients with mild COVID-19. The results showed that the duration of fever, cough, shortness of breath, and loss of smell in the intervention group was significantly shorter than the control group without a significant difference in the duration of gastrointestinal symptoms [23]. Another clinical trial was conducted to study the effectiveness of povidone-iodine solution in reducing the viral load in patients infected with COVID-19. The results revealed that this solution might reduce the viral load in adults with mild to moderate COVID-19 infection. However, using this drug caused thyroid dysfunction in patients (an increase in thyroid-stimulating hormone was observed in all patients after five days of administration), and some patients experienced an unpleasant tingling sensation in the nose after using this drug [24]. Another study aimed to evaluate the effectiveness of hydrogen peroxide (H_2O_2) in the form of mouthwash and nasal spray as an adjunctive treatment for COVID-19 infection [25]. The solutions were used for seven days, and the patients were monitored every two days for eight days. On the first day, coughing was the most prevalent symptom, with 72% of the intervention group and 76.5% of the control group reporting it. This percentage gradually decreased over time. No significant difference was found between the two groups in the evaluated symptoms. Most patients (75%) in the intervention group showed decreased shortness of breath between days zero and two. Few patients reported side effects while using the solutions. In contrast, the treatment with Ivermectin had a significant effect on fever, cough, shortness of breath, and loss of smell, and like Sinudrain, no significant difference was seen in the duration of gastrointestinal symptoms. The administration of hydrogen peroxide solution for seven days, unlike Sinudrain, did not cause a significant difference between the treatment and control groups. Unlike Iodine Povidone, which can cause thyroid dysfunction and unpleasant tingling in the nose, and hydrogen peroxide, which can have side effects in a few patients, Sinudrain did not cause any secondary effects when consumed. Additionally, rapid relief with Sinudrain, similar to Chlorpheniramine maleate nasal spray and SanNOtize, may reduce the duration, course, and the severity of COVID-19 symptoms. Other advantages of this solution over other medicines include its cost-effectiveness and availability, and the natural composition of the ingredients used in this product, making it a suitable candidate to reduce the symptoms caused by COVID-19.

5. Conclusion

Patients with symptoms of acute respiratory infection were enrolled in a clinical trial for Sinudrain solution. The results of the trial revealed that the drug was more effective in resolving symptoms compared to the control group. Overall, the treatment had a significant effect on all symptoms except for fever, loss of smell, and digestive symptoms. The new 5EG variant, recognized by the WHO as a spin-off of the recombinant XBB strain of the Omicron family, is the latest variant. According to the WHO's latest analysis, the 5EG variant has increased prevalence, growth advantage, and immune escape properties, but no changes in disease severity have been reported [26].

The Sinudrain solution could potentially be effective in combating the symptoms caused by this particular strain. In conclusion, While Sinudrain's antiseptic properties (sodium chloride) may explain symptom relief, its exact antiviral mechanism requires investigation through viral load studies. Future trials should measure viral load and include placebo arms. Comparative studies with other herbal solutions (e.g., povidone-iodine) are warranted.

Ethical Considerations

Compliance with ethical guidelines

The study was conducted in accordance with the Declaration of the Vice-Chancellor of Research and Technology at Shahid Beheshti University of Medical Sciences and was subsequently approved by the Ethics Committee (IR.SBMU.RETECH.REC.1399.1209 ,01/10/2021).

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Author's contributions

Data curation, Sara Arezi, Mohammad Jalal Tabatab-aie, Hananeh Seyed Azizolah, and Najmeh Haji Ebr-ahim Tehrani; Investigation, Sara Arezi, Mohammad Jalal Tabatabaie and Hananeh Seyed Azizolah; Metho -dology, Hamid Chegini; Project administration, Koro -sh Saki and Hamid Chegini; Supervision, Korosh Saki and Hamid Chegini; Writing – original draft, Sara Arezi, Mohammad Jalal Tabatabaie and Hananeh Seye -d Azizolah; Writing – review & editing, Sara Arezi, Mohammad Jalal Tabatabaie and Hananeh Seyed Aziz -olah; Translation,Yasna Gomar.

Conflict of interest

The authors declare no conflicts of interest.

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