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Efficacy and Safety of Sea Salt-Derived Physiological Saline Nasal Spray as Add-On Therapy in Patients with Acute Upper Respiratory Infection: A Multicenter Retrospective Cohort Study

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Background: The purpose of this study was to assess the effects of seawater on nasal congestion and runny nose symptoms in adults with an acute upper respiratory infection (URI).

Material/Methods: This was a multicenter retrospective cohort trial of patients with acute URI and symptoms of nasal congestion and runny nose. The patients were assigned to 2 groups and were administered regular non-drug supportive treatment or supportive treatment with nasal irrigation with sea salt-derived physiological saline. The primary efficacy endpoint was the effective rate (percentage of patients with ≥30% symptom score reduction from baseline for nasal congestion and runny nose).

Results: In total, 144 patients were enrolled, including 72 in each group, and 143 patients completed the study. Both groups had similar demographics and vital signs. The effective rates for nasal congestion and runny nose were significantly increased in the seawater group compared with patients in the control group (87.3% vs 59.7% for nasal congestion; 85.9% vs 61.1% for runny nose; both $P<0.001$). In addition, the 2 groups showed markedly different degrees of patient symptom score improvement in sleep quality and appetite (both $P<0.01$), but not in cough and fatigue (both $P>0.05$). There were no adverse events in either group.

Conclusions: The sea salt-derived physiological saline nasal spray device satisfactorily improved nasal congestion, runny nose, sleep quality, and appetite in adults with URI, with no adverse effects.

Keywords: Clinical Trial • Nasal Lavage • Respiratory Tract Infections

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Background

Acute upper respiratory infections (URIs) are the most common diseases affecting adults, who usually have from 2 to 5 acute URIs yearly [1-5]. Acute URIs include acute infections involving the nose, sinus, pharynx, middle ear, larynx and epiglottis, airway, and bronchus. The common cold, the URI with the highest incidence, constitutes an acute, self-limiting disease affecting the upper respiratory tract, causing different levels of sneezing, nasal congestion, runny nose, sore throat, cough, mild fever, headache, and weakness [1,3-7]. Acute URIs may be caused by various pathogenic viruses [1]. Acute URIs generally requires only symptomatic treatment, with no need for antibiotics [5,8]. The usual treatment for an acute URI is supportive, and high fluid intake and rest are recommended [1,2].

Nasal irrigation is considered to alleviate the symptoms of URI by clearing mucus, decreasing congestion, and improving breathing [9]. In addition, mucus clearance could be improved through increased frequency of the ciliary beats, and infection materials could be washed away [10].

Nasal irrigation is mainly used for sinusitis and nasal diseases such as allergic rhinitis [11,12], but is used less often in acute URIs. There are only a few reports utilizing seawater or saline in children with URI and influenza [12,13]. Consequently, whether seawater effectively relieves URI symptoms in adults remains unknown. A meta-analysis of studies conducted before 2015 suggested that nasal saline irrigation might not hasten symptom improvement in adults with acute URI [14]. A previous trial showed that the use of hypertonic saline results in no nasal symptom improvement or shortened disease duration in adult URI [15].

The present trial aimed to assess the relieving effects of seawater on nasal congestion and runny nose symptoms in adults with acute URI in the context of supportive treatment.

Material and Methods

Study Design

The current trial was approved by the Medical Ethics Committee of the Jiangxi Provincial People's Hospital (No. 2017-clinical inspection 14). Informed consent was not required due to the retrospective nature of this study.

This was a multicenter retrospective cohort trial. The study complied with the Good Clinical Practices, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, and all applicable laws and regulations. The trial was carried out at the Jiangxi Provincial People's Hospital. It was registered under No. ChiCTR2000031171.

Exclusion criteria were: 1) pregnancy or breastfeeding; 2) known hypersensitivity to seawater; 3) use of alcohol or illicit drugs; 4) other respiratory diseases such as herpangina, suppurative tonsillitis, bronchitis, and chronic rhinitis; 5) present acute pathology or uncontrolled chronic ailment; 6) serious systemic diseases; 7) antiviral treatment required for influenza A or B; 8) antibiotic treatment required for acute respiratory infection; 9) drug treatment of conditions prior to enrollment; 10) participation in another clinical trial less than 3 months before enrollment; and 11) likelihood of poor compliance or unlikeliness to complete the trial, as determined by the investigators.

Treatment

Patients with acute URI underwent routine basic supportive treatment (control group) or routine basic supportive treatment and nasal irrigation with sea salt-derived physiological saline (seawater group). The routine basic supportive treatment included drinking warm or boiled water and getting good rest, without specific drugs or medication. The amount and the temperature of the drinking water and the resting time depended on the specific needs of the patients.

Sea salt-derived physiological saline (0.9%) nasal spray was provided by Jiangsu-Aipeng Medical Technology Co., Ltd, and included 5 parts: a bottle, manual pump, nozzle, sea salt-derived physiological saline, and dust cover. The clinical product registration of the device has been filed with the State Food and Drug Administration (SFDA; No. 2013-2640258). The SFDA approval of the device covers uses for nasal dryness, stuffy nose, nasal itching, runny nose, and nasal bleeding.

All patients were instructed on how to operate the device. First, the patient needed to remove the dust cover (**Figure 1A**). Second, the patient tilted their head backward, put the nozzle in the nostrils one at a time, and gently pressed the manual pump (**Figure 1B**) 4 to 8 times per nostril. Third, the patient wiped nasal secretions and excess sea salt-derived physiological saline with a paper towel (**Figure 1C**). Finally, the patient cleaned the nozzle and replaced the dust cover (**Figure 1D**). The patients used 4 to 8 sprays (0.12 mL/spray) in each nostril each time, 2 to 6 times per day, depending upon the severity of nasal congestion.

Clinical Trial Duration and Endpoints

The duration of the clinical trial was 5 days: screening and enrollment lasted for 2 days, and the treatment period was 3 days. The visual analog scale of symptom severity was used for various symptoms, including runny nose, nasal congestion, cough, sleep quality, appetite, and fatigue. A 10-cm line was marked with 0 (no symptoms at all) on the left side and 10 (worst imaginable symptoms) on the right side. The patients

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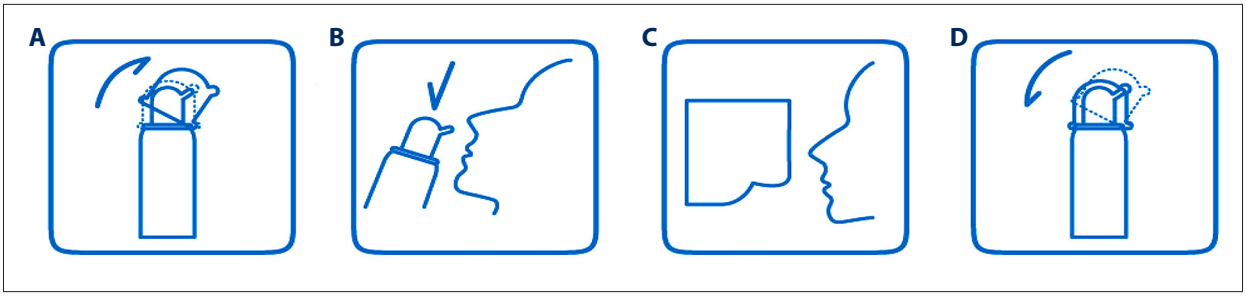

Figure 1. Instructions for sea salt-derived physiological saline nasal spray use. The spray device consisted of a bottle (up to 60 mL), a hand pump, a nozzle, a dust cover, and sea salt-derived physiological saline. Instructions: (**A**) remove the dust cover; (**B**) tilt the head backward, put the nozzle in the nostrils, and gently press the manual pump 4 to 8 times per nostril (spray distance ≥200 mm); (**C**) wipe the nasal secretions and excess sea salt-derived physiological saline with a paper towel; (d) clean the nozzle and replace the dust cover.

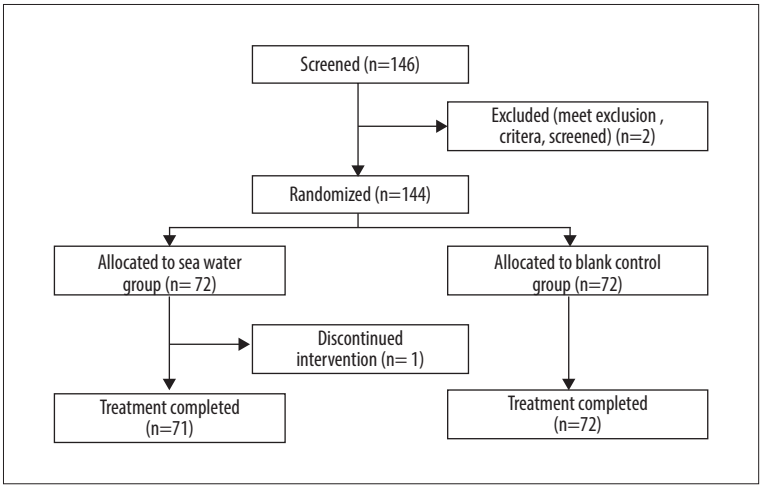

Figure 2. Study flowchart.

marked the line for each symptom accordingly and completed a diary of the use of the nasal spray.

The primary efficacy endpoint was the effective rate, defined as the percentage of patients with ≥30% symptom score reduction from baseline for nasal congestion and runny nose. The secondary efficacy endpoints were cough, sleep quality, appetite, and fatigue. Adverse events were recorded throughout the study, by the investigator or in the patient diary. The patients were advised that a slight tingling sensation might be felt in the nasal cavity after using the spray, and that the fluid flowing out of the nasal cavity can cause some discomfort. Nevertheless, they were told to note such discomforts if they occurred. Vital sign assessment and physical examinations were conducted at screening and on day 3.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and compared by the chi-square (intergroup comparisons) and McNemar's (intragroup comparisons) tests. Continuous data were described by mean±standard deviation or ranges and were analyzed by the *t* test (intergroup comparisons) and paired *t* test (intragroup comparisons). Continuous data with non-normal distribution (according to the Kolmogorov-Smirnov test) were assessed by the Wilcoxon rank-sum test. All data were assessed with SPSS version 12.0 (Chicago, IL, USA), with $P<0.05$ indicating statistical significance.

Results

Characteristics of the Patients

In total, 144 patients were examined, including 72 each in the seawater and control groups, and 143 patients completed the study (**Figure 2**). One patient in the seawater group dropped out on day 2. The groups were comparable in baseline sex, age, body temperature, heart and respiratory rates, and systolic and diastolic blood pressure levels (**Table 1**).

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Table 1. Baseline patient features and posttreatment vital signs in the 2 groups.

	Seawater group	Control group	P
Baseline			
Age (years)	40.3±13.3 (20–65)	39.2±13.1 (20–64)	0.611
Sex			0.725
Female	31	29	
Male	41	43	
Body temperature (°C)	36.6±0.3 (36.1–38.5)	36.6±0.3 (36.0–37.3)	0.437
Pulse rate (beats/min)	77±13 (58–95)	79±5 (68–90)	0.406
Respiratory rate (breaths/min)	21±11 (15–24)	19±1 (15–21)	0.209
Systolic pressure (mmHg)	122±8 (96–140)	120±9 (95–139)	0.147
Diastolic pressure (mmHg)	76±6 (60–90)	75±8 (60–92)	0.241
Posttreatment			
Body temperature (°C)	36.5±0.3 (36.0–37.0)	36.4±0.2 (36.4–37.1)	0.333
Pulse rate (beats/min)	77±9 (69–90)	77±8 (68–89)	0.290
Respiratory rate (breaths/min)	19±2 (15–22)	19±2 (15–21)	0.446
Systolic pressure (mmHg)	122±8 (96–140)	119±8 (95–139)	0.301
Diastolic pressure (mmHg)	74±5 (60–86)	75±6 (60–90)	0.403

All continuous data are shown as mean±standard deviation (range).

Efficacy

The effective rates for nasal congestion and runny nose were significantly elevated in the seawater group compared with that of the control group (87.3% vs 59.7% for nasal congestion; 85.9% vs 61.1% for runny nose; both $P<0.001$) (**Figures 3-5**). The 2 groups did not differ significantly in symptom score improvement for cough (**Figure 6**) ($P>0.05$); they differed significantly for sleep quality (**Figure 7**) and appetite (**Figure 8**) (both $P<0.01$); they did not differ significantly for fatigue (**Figure 9**) ($P>0.05$).

Safety

The 2 groups were comparable in body temperature, respiration rate, pulse rate, and systolic and diastolic blood pressure (all $P>0.05$) (**Table 1**). No intragroup differences from day 0 to day 3 were observed (all $P>0.05$). There were no device-related accidents, nasal hemorrhage, or other adverse events in either group.

Discussion

The effectiveness of nasal irrigation in adults with URI is not yet established [14,15]. Therefore, this multicenter retrospective cohort trial investigated the alleviating effects of sea salt-derived physiological saline on nasal congestion and runny nose in adult acute URI. The results indicated that the sea salt-derived physiological saline nasal spray device had satisfactory effective rates for nasal congestion, runny nose, sleep quality, and appetite in adult patients with URI. In addition, its safety profile did not differ from traditional supportive treatment.

Across the United States, acute URIs constitute 1 of the 3 most diagnosed diseases in outpatients, accounting for 10 million yearly outpatient visits [3]. Non-influenza viral URIs cost approximately $22 billion yearly [16]. Symptom alleviation is the major reason for outpatient visits in adult individuals in the first days following disease onset, with most appointments to the doctor resulting in the administration of prescribed drugs. Decongestants, either combined with antihistamines or not, alleviate congestion, cough, and other symptoms in adult patients [17]. In addition, topical (eg, oxymetazoline) and oral (eg, pseudoephedrine) nasal decongestants are moderately beneficial to adults and adolescents in decreasing nasal airway resistance [6,18]. Owing to the risk of increased blood pressure with decongestant use, patients with hypertension should be cautious while using decongestants [19,20]. H1-receptor antagonists modestly reduce rhinorrhea and sneezing in the initial 2 days after cold onset in adult patients [18]. First-generation antihistamines present adverse effects such as drowsiness, to which patients should pay attention [21]. Acetaminophen and nonsteroidal anti-inflammatory drugs could reduce discomfort

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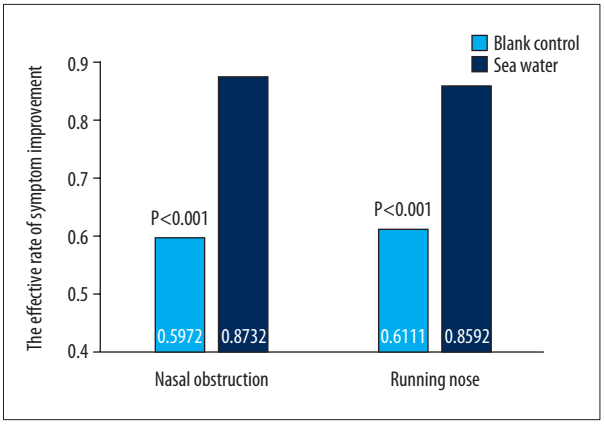

Figure 3. Effective rates of seawater in relieving nasal congestion and runny nose.

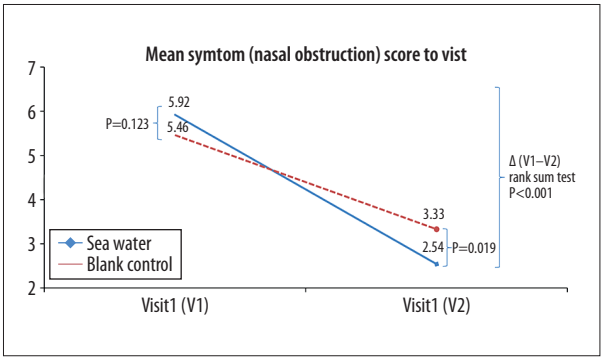

Figure 4. Mean symptom (nasal obstruction) scores before and after treatment. * Comparison between mean symptom scores by paired *t* test for independent samples; ** Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

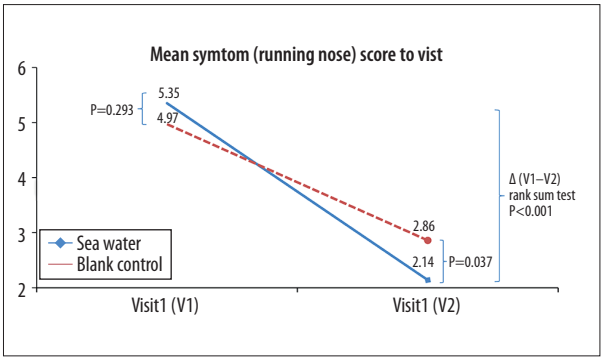

Figure 5. Mean symptom (runny nose) scores before and after treatment. * Comparison between mean symptom scores by paired *t* test for independent samples; ** Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

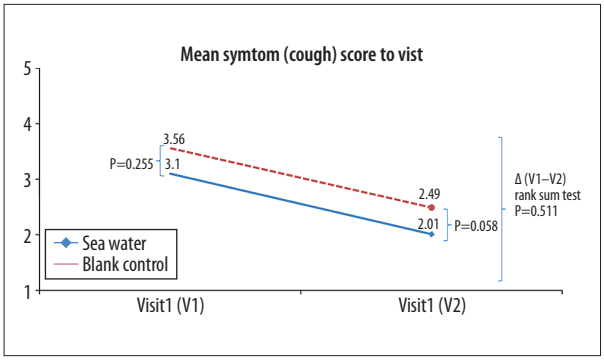

Figure 6. Mean symptom (cough) scores before and after treatment. * Comparison between mean symptom scores by paired *t* test for independent samples; ** Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

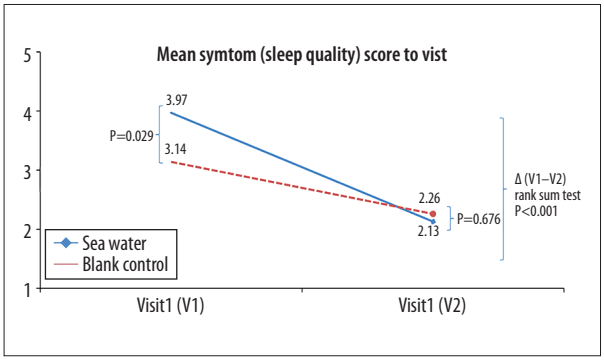

Figure 7. Mean symptom (sleep quality) scores before and after treatment. *Comparison between mean symptom scores by paired *t* test for independent samples; **Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

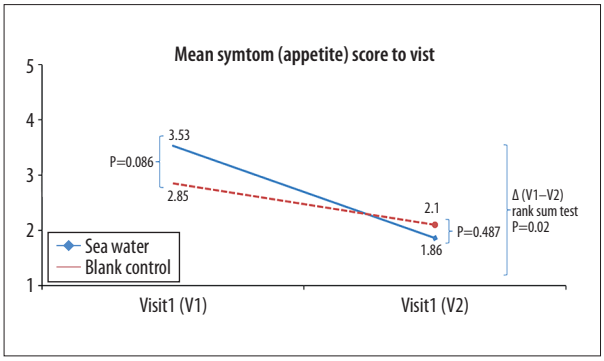

Figure 8. Mean symptom (appetite) scores before and after treatment.* Comparison between mean symptom scores by paired *t* test for independent samples; ** Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

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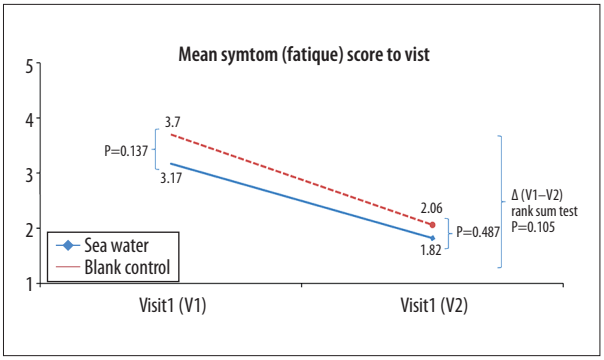

Figure 9. Mean symptom (fatigue) scores before and after treatment. * Comparison between mean symptom scores by paired *t* test for independent samples; ** Mean score variations between the 2 groups (V1-V2) assessed by the rank-sum test.

and pain but are also associated with adverse effects such as gastric irritation [22,23]. Therefore, considering the possible harm that can be caused by the available drugs, the development of novel, safe, and effective drugs or devices for relieving acute URI symptoms is needed.

Multiple reports assessing nasal irrigation have demonstrated its effectiveness in treating seasonal allergic rhinitis in adult and pediatric patients [24-26]. Seawater nasal irrigation, as utilized in the present trial, represents a simple method with high reproducibility and facile execution. Therefore, the study participants performed nasal irrigation without reserve. The current trial assessed the effects of nasal irrigation on acute URI signs in adults. We found a significant improvement on day 3 in the seawater group after administration of nasal irrigation in comparison with the control group, which was administered routine non-drug supportive treatment alone. These findings indicate that nasal seawater irrigation provides a safe and cost-effective method for treating acute URI, although the precise mechanism of the treatment remains undefined and may involve multiple parameters.

Nasal irrigation exerts several physiological effects, which might help the nasal mucosa decrease the pathological activities of inflammatory factors and other inducers of allergic rhinitis [12]. It might increase mucus displacement toward the nasopharynx [9]. The mucosal lining of the nasal cavity represents an important barrier to pathogens and comprises multiple inflammatory factors, including histamine, prostaglandins, and leukotrienes [27].

Koksal et al [13] reported relief in nasal congestion, rhinorrhea, weakness, sleep quality, diet, and cough after seawater administration in pediatric patients with a common cold. Symptom alleviation was similarly observed in nasal congestion, rhinorrhea, sleep quality, and diet in the present study. Nevertheless, no relief was observed in cough and fatigue. This discrepancy might be related to factors including patient age, work, and social responsibilities. The patients recruited in this study were adults, while Koksal et al [13] assessed individuals below 2 years of age. This suggests that the use of seawater as a nasal drop may be more suitable for young children.

The strengths of this study rely its design. This was a multicenter study, and patients with common URI were recruited, while those with chronic conditions that could influence the results were excluded. Nevertheless, this study had limitations. The current spray was designed to relieve the general symptoms of all upper respiratory infections, not focusing on any specific type. Therefore, specific upper respiratory infections were not recorded. Excluding some patients with specific conditions may have helped us observe the effect of nasal irrigation more precisely but limited the generalizability of the results. In addition, although the sample size was adequate, as per the calculation, larger studies may pinpoint the exact benefits of nasal irrigation in adults with URI. Furthermore, whether sea salt derived-physiological saline causes respiratory tract injury (even transiently) is unknown and deserves further investigation. Finally, the retrospective nature of the study carries inherent shortcomings.

Conclusions

The present findings indicated that nasal irrigation constitutes an efficient, cost-effective adjunct therapy for relieving acute URI in adults, with no adverse effects. Significant improvements were observed in mean symptom scores for nasal obstruction, runny nose, sleep quality, and appetite after irrigation.

Ethics Statement

The current trial had approval from the Medical Ethics Committee of Jiangxi Provincial People's Hospital [No. 2017-clinical inspection 14].

Conflict of interest

None.

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