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Investigating the Therapeutic Effect of Lota Carrageenan in Allergic and Non-Allergic Rhinitis

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ABSTRACT

Introduction:
Allergic and non-allergic rhinitis are chronic upper airway inflammatory diseases. Iota carrageenan is an herbal extract of red algae used as a prophylactic treatment for rhinitis in the common cold and other viral infections. This study was designed to evaluate the clinical efficacy of Iota carrageenan in the treatment of allergic and non-allergic rhinitis.

Materials and Methods:
60 patients with allergic and non-allergic rhinitis clinical symptoms were randomly divided into carrageenan and placebo (control) groups. The Standard Sino-Nasal Outcome Questionnaire 22 (SNOT-22) and Rhino Juniper Mini Conjunctivitis Quality of Life Questionnaire (Mini-RQLQ) were completed for each patient before and after receiving the drug. Smear of nasal secretions and rhinomanometry were also performed for all studied participants.

Results:
The mean score of SNOT-22 in the study group was 43.3 and 23.7 in the first and fourth weeks after therapy. The mean score of Mini RQLQ was 36.3 and 19.3 at the same time points ($P< 0.001$). SNOT-22 ($P= 0.002$) and Mini RQLQ ($P= 0.005$) scores showed a statistically significant decrease in the study group compared to the control group. The decrease in the eosinophil count and rhinomanometry results following treatment in both groups was statistically insignificant.

Conclusion:
Our findings showed a positive effect for carrageenan over placebo in the management of both non-allergic and allergic rhinitis in symptom control. However, non-allergic rhinitis patients' symptoms may improve better with this drug.

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Introduction

Rhinitis is defined by nasal congestion, rhinorrhea, sneezing, and/or posterior nasal drainage. It unfavorably affects the quality of life of many individuals and raises great challenges in diagnostic and therapeutic domains (1,2). Rhinitis is generally categorized as allergic and non-allergic. Allergic rhinitis is a heterogeneous disorder that may occur occasionally or have a constant course (3-5). Non-allergic rhinitis has inflammatory and noninflammatory etiologies. Inflammatory non-allergic rhinitis is accompanied by eosinophilia, post infections, and nasal polyps, while the noninflammatory type is associated with idiopathic non-allergic (vasomotor) rhinitis, medication-induced rhinitis, is hormone-related (e.g., pregnancy) or systemic diseases related (4,6). With paying attention to the form of the septum and inferior turbinates, clinical examination of the nasal cavity provides important information regarding the etiology and severity of rhinitis and its accompanying diseases, such as conjunctivitis, otitis, asthma, and atopic dermatitis. In children, chronic nasal obstruction can induce teeth-clenching disorders and facial malformations (7).

In the treatment of allergic rhinitis, intranasal steroids are the strongest and most frequently used drugs, which do not have significant clinical side effects, especially in adults. However, the treatment of non-allergic rhinitis may not be as effective as allergic rhinitis (8). Antihistamines, either oral or intranasal, have been more effective in allergic rhinitis (9) . Aeroallergen's test is useful for proving the presence of immunoglobulin E antibodies and distinguishing non-allergic from allergic rhinitis. Patient awareness, allergen prevention, and pharmacotherapy are the three most important treatment approaches in this respect (1). The main medications for treating rhinitis include intranasal corticosteroids, oral and intranasal antihistamines, intranasal anticholinergic agents, oral decongestants, and leukotriene receptor antagonists (10).

Carrageenan is a carbohydrate found in the cell wall of red algae that is used as gelatin, bulking agent, and stabilizer in the food industry. Based on the amount of sulfite, carrageenan is divided into three different types. Kappa carrageenan has the lowest amount, and Landa carrageenan has the highest sulfite molecules. Lota carrageenan, with antiviral properties, is approved for use in the production of pharmaceutical products. The antiviral role of carrageenan is attributed to its reaction to the positive charges on the virus's surface, which inhibits the diffusion of the virus into the cells. In addition to its antiviral and anticoagulant roles, Carrageenan can also regulate the immune system besides having anti-cancer effects (11). The Landa type with the highest anticoagulant effect has a strength of about one-fifteenth that of heparin for inhibiting thrombin (12). Moreover, carrageenan can prevent the connection of cancer cells and the basement membrane, resulting in a halt in metastasis. The anti-tumor role of carrageenan has already been proven in colon cancer (13). When in contact with human cells, carrageenan produces cytokines according to its concentration and polysaccharide structure. At high concentrations, all types of carrageenan increase the inflammatory mediators such as interleukin-6 and TNF-alpha levels. Interestingly, all types of carrageenan can provoke the expression of interleukin-10, which is a strong anti-inflammatory mediator (14). To date, the effects of this substance in the treatment and prevention of common viral infections such as colds and influenza have been investigated. This study evaluated the effect of carrageenan on treating allergic and non-allergic rhinitis (15).

Materials and Methods

Study design and subjects

All studied subjects were enrolled at the Immunology Clinic of Ghaem Hospital affiliated with Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. All adults with allergic rhinitis (AR) with a positive prick test or non-allergic rhinitis with a negative prick test were recruited. Sensitization to an allergen was considered positive if a wheal with a diameter ≥ 3 millimeters was present in skin prick testing. The AR patients had a disease with moderate and severe intensity based on the ARIA (Allergic rhinitis and Impact on Asthma)

classification system. This randomized-controlled clinical trial was designed to show the effect of carrageenan-comprising nasal spray over placebo in subjects with allergic and non-allergic rhinitis. Randomization was done following verification of inclusion and exclusion criteria. Patients were randomly assigned to study and control groups. We used the permutation blocks approach to construct a sequence for randomly assigning participants to the two groups. The sequence of randomly allocating subjects was done using https://www. sealedenvelope. com/ simple-randomiser/ v1/lists and a six-block size. Our direction in this study was to randomly select one of the blocks, and this process continued until all samples were allocated. The study group consisted of 15 males and 15 females, whereas 14 males and 16 females were assigned to the control group. The study group received carrageenan-containing nasal spray, and saline solution nasal spray was prescribed for the control group. Each nasal spray was administered twice daily into each nostril for one month. Both groups also received an antihistamine, fexofenadine (60 mg q12 hours), as the standard treatment. Past medical history was recorded, and a skin prick test, eosinophil count in nasal secretions, and rhinomanometry were performed for all patients at the study entrance.

The same tests were repeated one month after taking the carrageenan-containing nasal spray or placebo in all patients. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS. MEDICAL. REC. 1394. 775), and written informed consent was obtained from each participant and their parents before the study.

Data Analysis

Statistical analysis was performed using IBM SPSS 22.0 statistical software (La Jolla, CA, USA). Independent t-test and ANOVA were applied to compare quantitative variables between the two groups. Paired sample T-test was used to compare quantitative variables before and after treatment. The Chi-square and Fisher's exact tests were used to study the frequency in the two groups. A P value <0.05 was considered statistically significant.

Results

Nasal smear study, rhinomanometry, and clinical symptoms assessment using Snot 22 and Mini RQLQ questionnaires were performed for all patients before and after treatment. In total, 60 patients were studied: 30 cases with a mean age of 25.4 ± 11.68 yrs in the study group and another 30 subjects with a mean age of 26.3 ± 11.06 yrs in the control group (Table 1).

Table 1. Clinicopathological characteristics of the studied patients

Factor	Control (n=30)	Study (n=30)	P-value
Age (mean± SD)	26.3 ± 11.06 years	25.4 ± 11.68 years	0.8
Sex Male Female	 14 16	 15 15	 0.79
P-value is significant at 0.05.			

Clinical findings

Clinical symptoms were measured using the standard table for recording sinonasal symptoms (SNOT-22) and the Mini RQLQ questionnaire (Table 2). The symptom severity before and after treatment in the study group was 43.34±16.2 and 23.7±18.7, respectively (P< 0.001), indicating a significant reduction in the symptom severity in patients receiving the carrageenan-containing nasal spray. However, no statistically significant difference was found in the symptom severity before and after treatment in the control group (P= 0.49). The collected data also demonstrated a significant difference in the symptom severity between the two groups following treatment (P= 0.002). Response to treatment based on quality of life improvement were 36.3 ± 12.8 and 19.3 ± 15.6 before and after the treatment in the study group, respectively (P< 0.001); the same values were 37.4±19.1 and 32.4±18.4 for the control group (P= 0.31). These results

demonstrated a significant improvement in the patient's quality of life following treatment in the study group (Table 2). Moreover, subgroup analysis showed the symptom severity rate to be 28.1 and 17.7 in AR and non-AR patients, respectively (P= 0.08) (Table 3). The eosinophil count in AR and non-AR patients was 22.4% and 12.5%, respectively (P=0.1). Rhinomanometry alterations in AR and non-AR subjects were 0.27 and 0.24, respectively (P=18). No statistically significant difference was obtained between the two subgroups regarding symptom severity, eosinophil count, and rhinomanometry alterations.

Laboratory findings

A pathology examination was performed on the nasal secretion smears. The percentage of eosinophils before and after treatment in the study group were 22.1±28.8 and 18.4±20.0, respectively (P= 0.5). The same values were 23.4±31.9 and 19.1±28.4 in the control group, respectively (P= 0.2). The eosinophil count in the nasal smear of both groups showed a decrease following treatment. The rhinomanometry alterations before and after treatment were 0.3±0.8 and 0.26±0.6 in the study group (P< 0.001) and 0.32 ± 0.08 and 0.29 ± 0.07 in the control group (P=0.19), respectively. Although the response to the carrageenan-containing nasal spray was better than the placebo, this difference was statistically insignificant (P= 0.2). Patients with non-allergic rhinitis responded better to treatment with carrageenan-containing nasal spray (Table 2 and Table 3).

However, the quality of life in AR patients improved more than in non-AR subjects (P= 0.2).

Table 2. Comparison of the studied parameters between the two groups before and after treatment

Variables	Study Group		Control Group		P-value
	Before	After	Before	After	
SNOT22 (mean ± SD)	43.34 ± 16.2	23.7 ± 18.7	45.3 ± 20.9	40.8 ± 20.7	0.002
Nasal Eosinophil count (mean ± SD)	22.1 ± 28.8	18.4 ± 20	23.4 ± 31.9	19.1 ± 28.4	0.1
Rhinomanometry (mean ± SD)	0.3 ± 0.8	0.26 ± 0.6	0.32 ± 0.08	0.29 ± 0.07	0.2
Mini RQLQ (mean ± SD)	36.3 ± 12.8	19.3 ± 15.6	37.4 ± 19.1	32.4 ± 18.4	0.005
The P-value is significant at the 0.05 level.					

Table 3. Comparison of response to the prescribed herbal spray between allergic and non-allergic rhinitis patients

	Allergic Rhinitis	Non-Allergic Rhinitis	P-value
SNOT22 (mean)	28.1	17.7	0.08
Nasal Eosinophil count (Percent)	21.4	12.5	0.1
Rhinomanometry (ml/s)	0.27	0.24	0.18
Mini RQLQ (mean)	23.2	16.3	0.03
The P-value is significant at 0.05			

Discussion

The importance of this chronic respiratory disease is due to its high prevalence, considerable effects on the quality of life and performance, and its association with other diseases (16). Herein, we investigated the medicinal effects of Utah Carrageenan, known as Koldamaris nasal spray in Iran, in treating allergic and non-allergic rhinitis. Several studies have reported its application in treating and preventing colds due to its proven anti-inflammatory and anti-viral effects. However, its effect in treating allergic or non-allergic rhinitis has not been examined (15,17,18). Therefore, in this study, we investigated the effect of the mentioned drug on allergic and non-allergic rhinitis patients to assess its anti-inflammatory properties better.

One of the most common and most effective treatments used for rhinitis is intranasal steroids with few and insignificant side effects; however, their long-term impact, especially in children in their growing age, is still a matter of concern (19). Steroid uptake can increase blood sugar levels in diabetic individuals. Therefore, their usage may cause noncompliance (20). Notably, most

drugs used to treat non-allergic rhinitis have also demonstrated effects on allergic rhinitis patients (14). This study assessed patients with allergic and non-allergic rhinitis for their clinical symptoms with the standard SNOT-22 and Mini RQLQ questionnaires. According to the statistical analysis, the treatment response was statistically significant in both types. Interestingly, the obtained scores in the control group also decreased, possibly due to either the placebo effect, the seasonal changes in the symptoms, or the proven weak effect of sodium chloride spray in some cases of rhinitis, mainly non-allergic (21). However, according to the statistical analysis, the improvement of patients' symptoms in the study group (carrageenan spray) was significantly higher than in the control group (sodium chloride nasal spray). Considering the improvement in life quality based on the Mini RQLQ questionnaire, a significant improvement was achieved: a milder response in the control group compared to the study group. Statistical comparisons using an independent t-test revealed that the investigated drug positively affected symptom improvement in allergic and non-allergic rhinitis patients compared to placebo, the difference being statistically significant. In the study by Ludwig et al. on 211 patients affected with a cold, the patient's symptoms were monitored for 21 days and after seven days of using carrageenan extract. These changes were compared with the rate of changes in symptoms in the control group, which was treated with normal saline spray. In the affected adults of the study group, symptoms improved 2.1 days earlier on average. An otolaryngologist examined these patients, and co-morbidities and other otolaryngological problems were initially ruled out in them. The patients were examined regarding symptoms and the number of viruses in the secretions, which were higher in the control group (17). The carrageenan antiviral and anti-inflammatory effects have been proven by several studies (15). This study used carrageenan to treat patients with allergic and non-allergic rhinitis. Our results show that the clinical response measured with standard questionnaires was higher in the study group than in the control group. However, given laboratory tests, the results regarding the nasal smear and the eosinophil count were contradictory yet statistically insignificant. In the rhinomanometry test, although the improvement of patients in the study group was better than the controls, the difference was not statistically significant. During our study, three patients with allergic rhinitis experienced a relative exacerbation of symptoms after taking the drug, which did not cause them to withdraw from the study. In the skin test performed with carrageenan spray, two of these patients had a positive skin test, which suggests that this condition may have been due to an allergic reaction to the drug.

In another study, cold symptoms improved significantly and the number of viruses in the secretions declined following treatment with Carrageenan. In addition, the amount of pro-inflammatory cytokines such as FGF-2, Fractalkine, GRO, G-CSF IL8, IL-1α, IP-10, and IFN-α2 in the nasal secretions of patients reduced after taking carrageenan (15). The anti-inflammatory effects of carrageenan spray can justify improving rhinitis symptoms in affected patients. Since the pathology, etiology, and treatment of allergic and non-allergic rhinitis differ, in the next step, according to the skin test of the patients, the effect of carrageenan spray was measured in allergic or non-allergic patients through the covariance test after controlling the confounding variables. A comparison of SNOT-22 scores showed that patients with non-allergic rhinitis responded better to this drug. In this study, nasal smears were performed, and in patients with allergic and non-allergic rhinitis, a mean percentage of 32.8 and 10.25 cells were eosinophils. After treatment, the mean percentage of eosinophils in the non-allergic rhinitis subgroup reduced to 5.5%, whereas it reached 22.8% in the allergic rhinitis subgroup. On the other hand, the decrease in the percentage of eosinophils in the control group was higher than in the study group, so in our study, the positive effect of carrageenan in reducing the percentage of eosinophils was not proven. Improvement of clinical symptoms in the non-allergic rhinitis subgroup after carrageenan treatment was more than in the allergic rhinitis subgroup;

in addition, in the non-allergic rhinitis subgroup, the percentage of eosinophils was not very high, which may be due to neutrophilic inflammation. Furthermore, in some patients with allergic rhinitis, an allergic reaction to the drug itself was seen, which can result in increased eosinophilia in the study group after receiving the drug. In addition, based on the effect of the rhinomanometry test regarding the improvement of physical nasal obstruction, the response of patients in the non-allergic rhinitis subgroup was better than the allergic rhinitis cases. However, a great difference was observed in both groups compared to the placebo. Although rhinomanometry test results were more consistent than the results of nasal smear, the changes in the number of symptoms stated by the patients (measured by questionnaires) were not noteworthy. It means that the two laboratory methods performed do not fully express the clinical results achieved from the response to the carrageenan drug. Improvement of patients' symptoms depends on various factors, such as the percentage of eosinophil cells and the air pressure passing through the nose caused by obstruction.

Conclusion

Considering the better effect of carrageenan on non-allergic rhinitis patients in this study, this drug can be recommended as an alternative treatment for non-allergic rhinitis, especially in children. In the case of allergic rhinitis, this drug is effective in improving clinical symptoms, although not as good as non-allergic rhinitis. Given the herbal root of the drug and the possibility of an allergic reaction to the drug itself, it is better to perform a skin test with the drug before treatment administration, and in case of a positive skin test result, it should not be prescribed. Eventually, carrageenan can be a suitable alternative for patients with steroid phobia or those with an unfavorable response to intranasal steroids.

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