Background: Rhinitis is an extremely common medical problem characterized by nasal congestion, clear rhinorrhea, sneezing, and itching. Hyaluronate is an endogenous compound that has an important role in mucociliary clearance by the epithelial surface of the nasal passages and in mucosal surface healing and repair. The objective of this work was to determine the effects of intranasal administration of sodium hyaluronate on nasal cytology in patients with allergic and nonallergic rhinitis.

Methods: In a single-center, randomized, blinded trial, 78 patients received intranasal mometasone and oral desloratadine plus either intranasal sodium hyaluronate or saline for 1 month. Nasal cytology was performed and the change from baseline in the numbers of neutrophils, eosinophils, mast cells, lymphocytes, and infective species was determined. Other outcomes included changes in symptoms and the endoscopic appearance of the nasal mucosa, and tolerability.

Results: Patients receiving sodium hyaluronate experienced a significant decrease in the median neutrophil count seen on nasal cytology compared with controls ($p = 0.001$). Sodium hyaluronate was associated with significant improvements in sneezing, rhinorrhea, and nasal congestion, and on exudate seen on endoscopy at 1 month compared with baseline. Intranasal sodium hyaluronate received better tolerability scores than saline over the 1-month treatment period.

Conclusion: The addition of sodium hyaluronate to intranasal corticosteroid and systemic antihistamine reduced the neutrophil count seen on nasal cytology in patients with allergic and nonallergic rhinitis and improved several clinical and endoscopic parameters while being well tolerated. These data provide encouraging evidence of the efficacy of sodium hyaluronate in the treatment of this common disease.

Key Words: allergic rhinitis; eosinophils; intranasal corticosteroids; nasal cytology; neutrophils; nonallergic rhinitis; rhinological therapies; sodium hyaluronate; vasomotor rhinitis; Yabro®

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Rhinitis is a condition characterized by the presence of nasal congestion, clear rhinorrhea, sneezing, and itching. Allergic rhinitis is an immunoglobulin E (IgE)-mediated inflammatory condition associated with a response to environmental allergens. It is traditionally classified as seasonal or perennial, depending on whether the causative allergen is a cyclic pollen or present year round, such as dust mites. The most common form of nonallergic rhinitis is vasomotor rhinitis. Nonallergic rhinitis is characterized by the absence of systemic allergic sensitization (such as negative skin test and/or lack of serum-specific IgE) to the allergens implicated in allergic rhinitis. Patients with vasomotor rhinitis generally suffer more from nasal congestion and clear rhinorrhea than from itching and sneezing, and exhibit sensitivity to irritants and changes in the weather. Importantly, some patients may present with or develop rhinitis that exhibits characteristics of both allergic and nonallergic rhinitis, known as “mixed rhinitis.”
Allergic rhinitis affects 20 to 40 million Americans; estimated prevalence rates are between 10% and 30%. While the true incidence of nonallergic rhinitis is more difficult to establish, it is thought that 50 million Europeans and 19 million Americans experience the condition, with vasomotor rhinitis being the most common subtype.

Hyaluron (also known as hyaluronic acid or hyaluronate) is a large nonsulfated glycosaminoglycan that is an important component of extracellular matrices, such as those in respiratory epithelial cells and gland serous cells of the nasal and tracheobronchial mucosa. Hyaluron has an important role in the function of mucociliary clearance by the epithelial surface, in the processes involved in wound healing and repair of mucosal surfaces, and in the viscoelasticity of the structures responsible for speech. Furthermore, hyaluron promotes phagocytosis of Streptococcus pyogenes in vitro and in vivo by interfering with the processes involved in wound healing and repair of mucosal surfaces, and in the viscoelasticity of the structures responsible for speech.

This work reports the results of a randomized controlled study comparing the effects of intranasal sodium hyaluronate with saline on nasal cytology in patients with allergic and nonallergic rhinitis.

Patients and methods

Study design

This randomized, controlled, double-blinded study was performed between March 2011 and May 2012 in accordance with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol and amendments were approved by the local institutional review board and all patients provided informed consent prior to entry into the study.

Study population

Patients affected by allergic and nonallergic vasomotor rhinitis attending the outpatient Rhinology Clinic of the Otolaryngology Unit of the University of Bari were enrolled in this study. Patients were assessed at the first clinic visit, at which time a clinical history, skin test for allergens, nasal endoscopy, and nasal cytology were performed, and the degree of nasal obstruction was assessed.

The history of patients was carefully taken to determine the presence of a family history of atopy, asthma, and aspirin allergy. We also determined the patient history of asthma, aspirin allergy, headache and/or facial pain, nasal obstruction, type of rhinorrhea (serous, mucous, purulent, or purulent-hematic), itch, sneezing, daytime or nighttime cough, halitosis, postnasal drip, and fever.

The patient rated the degree of nasal obstruction from 0 to 10 using a 100-mm visual analogue scale (VAS) where 0 = nose free from obstruction and 10 = nose completely obstructed.

Allergic sensitization was assessed by the presence of a positive skin prick test carried out and read in accordance with approved methods. The panel of allergens used included: house dust mite (Dermatophagoides farinae and D. pteronyssinus); cat; dog; grass mix; Compositae mix; Parietaria judaica; birch, hazel, and olive trees; Alternaria tenuis; Cladosporium; and Aspergilli mix. The concentration of allergen extracts was 100 index of reactivity (IR)/mL (Stallergenes, Milan, Italy). Individuals with equivocal skin tests were further investigated by a CAP-RAST assay (Phadia, Uppsala, Sweden).

Endoscopic examination was performed with a flexible fiber optics endoscope (ENT 2000; Vision Sciences, Orangeburg, NY), with a diameter of 3.4 mm. Patients were rated according the following objective criteria: (1) presence of intranasal anatomic alterations (septal deviation, cartilaginous spurs, concha bullosa, intranasal tumors); (2) mucosal appearance (hyperemia, edema, atrophy, areas of de-epithelialization); and (3) type of secretions (serous, mucous, pus, hematic, exudate clotted scabs).

Nasal cytology was performed by anterior rhinoscopy using a nasal speculum and good lighting. Scrapings of the nasal mucosa were collected from the middle portion of the inferior turbinate, using a Rhino-Probe™ (Arlington Scientific, Inc. Springville, UT, USA) nasal cytology curette.

Samples were placed on a glass slide, fixed by air drying and then stained by the May-Grunwald Giemsa method (Carlo Erba®, Milan, Italy). The slide was observed under a Nikon E600 light microscope (Nikon, Canada) equipped with a digital camera (Nikon “Coolpix 3:34”, Nikon, Tokyo, Japan) for the acquisition of microscopic images. For the rhinocytogram analysis, 50 microscopic fields were read at a magnification of ×1000 to assess the presence of normal and abnormal cellular elements, along with any microscopic features (spots, special inclusions, etc.) important for diagnosis. Cell counts and bacterial and fungal analysis were carried out by a semiquantitative grading.

In particular, bacterial and fungal spore assessment was determined as follows: grade 0 (not visible); grade 1+ (occasional groups); grade 2+ (moderate number); grade 3+ (easily visible); and grade 4+ (many cover the entire field of view).

Patients were subdivided on the basis of the skin prick test and nasal cytology into subjects with allergic or nonallergic rhinitis. Cellular forms were further subdivided based on their cytotype as follows: nonallergic rhinitis with neutrophils (NARNE; neutrophils > 50% with absent spores and bacteria); nonallergic rhinitis with eosinophils (NARES; eosinophils > 20%); nonallergic rhinitis with mast cells (NARMA; mast cells > 10%); and nonallergic rhinitis with eosinophils and mast cells (NARESMA; eosinophils > 20% and mast cells > 10%).

Patients that had received medical treatment for rhinitis in the 2 weeks prior to enrolment were excluded from the study.
Randomization, blinding, and treatment

Patients were randomized into 2 treatment groups and treated for 30 days. Randomization was designed to take into account patient’s age, sex, and type of rhinopathy, and was performed by Stata software (StataCorp LP, College Station, TX). Patients and the investigators were blinded to treatment group allocation. Medical personnel who were not part of the investigational team administered the study drugs.

Patients in the investigational arm (group 1) were treated with mometasone furoate nasal spray 50 μg/spray (2 sprays into each nostril once daily), oral desloratadine 5 mg once daily and sodium hyaluronate (Yabro®, IBSA, Lodi, Italy) 9 mg twice a day aerosolized in 3 mL sodium chloride 0.9% using the Fluirespira® nasal douche device (Zambon, Bresso (Mi), Italy) administered 30 minutes after the mometasone.

Patients in the control arm (group 2) were treated with mometasone furoate nasal spray 50 μg/spray (2 sprays in each nostril once daily), oral desloratadine 5 mg once daily, and sodium chloride 6 mL twice a day aerosolized using the Fluirespira® nasal douche device administered 30 minutes after the mometasone.

Outcomes

Outcome parameters were measured at the first assessment (baseline) and after 1 month of treatment. Cytologic outcomes included neutrophils, eosinophils, mast cells, lymphocytes, bacteria spores, and infectious stains/biofilms. Clinical outcomes included cough, asthma, rhinorrhea, postnasal drip, halitosis, itch, sneezing, and nasal congestion. Endoscopic outcomes included edema, hyperemia, desquamation, exudate, and nasal hyperactivity. At the end of the study, all patients were asked to evaluate the tolerability of the treatment under study using a questionnaire in which 1 = sufficient, 2 = good, and 3 = excellent.

Statistical analysis

Continuous baseline characteristics are presented as a median and interquartile range (IQR), or a mean and standard deviation (SD), where appropriate. For proportions, absolute and relative frequencies are reported. To test differences at baseline between the 2 groups of treatment, the Wilcoxon Mann-Whitney test or t test was used for continuous and ordinal variables, respectively, and Fisher’s exact test was used for proportions.

In order to evaluate the effect of treatment on prespecified outcomes we used the Wilcoxon test or t test for quantitative and ordinal variables, respectively, and Fisher’s exact test for binary variables.

To measure the effect of treatment on outcomes, we calculated relative risks (RRs) and 95% confidence intervals (CI). Risk ratios indicate the relative probability of an improvement in the outcome associated with the active treatment compared with control.

In order to explore the relationship between some patterns of variables (nominal), we used Cramer’s V index. All significance tests were 2-tailed at the 0.05 significance level. All the analyses were conducted using Stata 11.

Results

Patient characteristics

Seventy-eight patients were enrolled in the study. The baseline demographic and clinical characteristics of each patient group are shown in Table 1. The age of patients ranged between 21 and 63 years and the patient groups were well matched for age, gender, and diagnosis at baseline. Approximately a quarter of patients in each group had NARES and a further 23% had allergic rhinitis to pollen (Table 1). Approximately 20% of patients in each group were diagnosed with allergic rhinitis to house dust mites and pollen, and 15% had NARESMA.

Cytological outcomes

A significant improvement in median nasal neutrophil cytology scores was seen in patients receiving sodium hyaluronate compared with control subjects at 1 month. The median neutrophil cytology score decreased from 98 at baseline to 41 at 1 month in patients receiving sodium hyaluronate compared with 98 vs 89 in control subjects (p = 0.001) (Table 2, Fig. 1A and B). The RR of an improvement in neutrophils in patients receiving sodium hyaluronate compared with control subjects was 2.33 (95% CI, 1.55–3.52). Other cytology scores did not reach statistical significance in either treatment group (Table 2).

Clinical outcomes

The addition of sodium hyaluronate to mometasone furoate and desloratadine significantly improved sneezing, rhinorrhea, and nasal obstruction at 1 month compared with baseline (Tables 2 and 3). The number of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sodium hyaluronate (n = 39)</th>
<th>Control (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, range</td>
<td>21–63</td>
<td>22–61</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>23 (59)</td>
<td>21 (54)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NARNE</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>NARMA</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>NARES</td>
<td>9 (23)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>NARESMA</td>
<td>6 (15)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>AR (M)</td>
<td>4 (10)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>AR (P)</td>
<td>9 (23)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>AR (M + P)</td>
<td>7 (18)</td>
<td>8 (21)</td>
</tr>
</tbody>
</table>

AR = allergic rhinitis; M = house dust mite; NARES = nonallergic rhinitis with eosinophils; NARESMA = nonallergic rhinitis with eosinophils and mast cells; NARMA = nonallergic rhinitis with mast cells; NARNE = nonallergic rhinitis with neutrophils; P = pollen.
TABLE 2. Improvements seen in clinical, endoscopic and cytological outcomes at 1 month compared with baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sodium hyaluronate (n = 39)*</th>
<th>Control (n = 39)*</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Cytological scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>98 (79, 205)</td>
<td>41 (24, 74)</td>
<td>98 (65, 207)</td>
<td>89 (39, 102)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>9 (5, 18)</td>
<td>3 (0, 5)</td>
<td>9 (5, 27)</td>
<td>5 (3, 7)</td>
</tr>
<tr>
<td>Mast cells</td>
<td>0 (0, 8)</td>
<td>0 (0, 2)</td>
<td>3 (0, 7)</td>
<td>0 (0, 4)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>0 (0, 5)</td>
<td>0 (0, 0)</td>
<td>0 (0, 3)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0 (0, 2)</td>
<td>0 (0, 1)</td>
<td>0 (0, 2)</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>Spores</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Biofilm</td>
<td>0 (0, 4)</td>
<td>0 (0, 0)</td>
<td>0 (0, 4)</td>
<td>0 (0, 2)</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1 (1, 2)</td>
<td>1 (0, 2)</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>Nasal obstructionb</td>
<td>7 (6, 8)</td>
<td>4 (2, 5)</td>
<td>7 (6, 8)</td>
<td>5 (4, 6)</td>
</tr>
<tr>
<td>Endoscopic outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exudate</td>
<td>2 (1, 2)</td>
<td>1 (0, 2)</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
</tr>
</tbody>
</table>

*Values are median (IQR).
bAssessed using a visual analogue scale of 1–10.
CI = confidence interval; IQR = interquartile range.

experiencing improvements in sneezing at 1 month was significantly greater in patients receiving sodium hyaluronate compared with control subjects (17 vs 4; \( p = 0.002 \)) (Table 3).

The degree of nasal obstruction, as expressed as the median of a VAS, decreased from 7 to 4 in patients receiving sodium hyaluronate and from 7 to 5 in control subjects (\( p = 0.048 \)) (Table 2). A significantly greater decrease in rhinorrhea was seen in sodium hyaluronate recipients, compared with control subjects. While median rhinorrhea scores for each group were 1; importantly, a reduction in the IQRs, as shown in square brackets, was observed (1 [IQR 1, 2] vs 1 [IQR 0, 2]) (\( p = 0.017 \); Table 2).

A significantly greater likelihood of improvement in rhinorrhea (RR, 3.8; 95% CI, 1.58–9.16), and sneezing (RR, 4.25; 95% CI, 1.57–11.49) was seen in patients receiving sodium hyaluronate compared with control subjects was (Tables 2 and 3).

No other significant changes from baseline in symptoms were reported.

Endoscopic outcomes

A significant improvement in exudate was seen in sodium hyaluronate recipients compared to those in the control group at 1 month (Table 2). The median exudate score seen on endoscopy reduced from 2 to 1 in patients receiving sodium hyaluronate but remained stable in control subjects (1 vs 1) (\( p = 0.000 \); Table 2). Again, IQRs for this parameter were significantly reduced (Table 2). There was a significantly greater chance of an improvement in exudate in patients receiving sodium hyaluronate compared with control subjects (RR, 3.83; 95% CI, 1.76–8.37).

No other significant changes from baseline in endoscopic outcomes were observed at 1 month compared to baseline.

Tolerability

When asked to make a judgment concerning the tolerability of treatment, significantly more patients preferred the active treatment compared with control. The median score awarded to sodium hyaluronate was 2 (IQR 1, 3) compared with a median score of 1 (IQR 1, 2) for control (\( p = 0.0001 \)).

Discussion

Our study shows that the addition of intranasal sodium hyaluronate 9 mg twice a day to mometasone furoate and desloratadine for 1 month significantly reduced the number of neutrophils seen on nasal cytology and improved several clinical and endoscopic parameters in patients with allergic and nonallergic rhinitis.

Alterations in the cellularity seen in nasal disorders are thought to underpin the physiological and clinical effects of this heterogeneous group of diseases. Rearrangements of the respiratory mucosa comprising a reduction in the ciliated cell component and increases in muciparous cells leads to an increase in the production of mucous, which stagnates in endonasal sinuses and favors bacterial replication. Alterations in the cellularity seen in nasal disorders are thought to underpin the physiological and clinical effects of this heterogeneous group of diseases. Rearrangements of the respiratory mucosa comprising a reduction in the ciliated cell component and increases in muciparous cells leads to an increase in the production of mucous, which stagnates in endonasal sinuses and favors bacterial replication.21 Mucociliary transport is reduced and allows recurrent inflammatory episodes that impede the reconstruction of the
Sodium hyaluronate in allergic-nonallergic rhinitis

**FIGURE 1.** (A) Important cytology signs of nasal immune-mediated inflammation, with ciliated cell decrease and clear alterations in the ciliary apparatus. C = ciliated cell (nasal cytology in T0). (B) Significant reduction of immunoinflammatory cells. Ciliated cells well shown with intact ciliary apparatus. C = ciliated cell (nasal cytology in T1 in patients treated with Yabro®). May-Grunwald Giemsa staining, magnification ×1000. E = eosinophils; N = neutrophils.

normal ratio of the various cell types in the respiratory tract epithelium. Prolonged or delayed mucociliary clearance itself may increase the propensity toward infection and predispose the individual to the development of rhinosinusitis. Destruction of the respiratory mucosa reduces its ability to function as a barrier and allows greater exposure of the irritant trigeminal receptor, located immediately beneath the basal membrane, to chemical, physical, or atmospheric stimuli, resulting in exaggerated reactivity of these patients to various stimuli.

Nonallergic rhinitis is associated with increased expression of cellular elements (neutrophils, eosinophils, mast cells, lymphocytes, plasma cells) and their mediators (eosinophil cationic protein, major basic protein, histamine, leukotrienes, tryptase, elastase). While the mechanisms linking cellularity and clinical expression are well known in allergic rhinitis, they are less well understood in nonallergic rhinitis.

Four main types of nonallergic rhinitis have been described based on the presence of inflammatory cell infiltrates: NARES; NARMA; NARNE; and NARESMA. We have previously demonstrated differences in clinical and functional features in patients presenting with NARES, NARMA, and NARNE, and have shown that NARESMA represents a particularly severe form of nonallergic rhinitis.

Hyaluron is an important regulator of inflammatory processes and is broken down under the influence of free radicals and enzymes during inflammation. The resulting low molecular weight fragments play a role in tissue damage signaling and immune cell mobilization, while the high molecular weight form suppresses immune cell function. Hyaluron is believed to play a role in vascular leakage and edema formation in the larynx, to regulate levels of substances, such as endothelin-1, that affect vasomotor tone and serous and mucous gland secretion in the nasal mucosa, and to induce mucous hypersecretion in airway epithelium.

Hyaluron, due to its peculiar physicochemical characteristics, has been proven to have several biologic functions in the tissues of animals and humans, such as a dose-related inhibiting effect on the migration and chemotaxis of polymorphonuclear leucocytes. The exogenous application of sodium hyaluronate might be an important therapeutic regimen to restore the natural barrier against polymorphonuclear leucocyte migration, and could therefore be helpful for interrupting the inflammatory cascade. Hyaluron appears to inhibit migration, chemotaxis, and aggregation of polymorphonuclear leucocytes and monocytes in airway inflammation, and reduce bronchial hyperreactivity in asthmatics.

In our study sodium hyaluronate was associated with a significant decrease in the number of neutrophils in nasal cytology from 98 to 41 compared with a decrease from 98 to 89 seen in control subjects (p = 0.001). Moreover, the RR of a decrease in neutrophil count was 2.35 (95% CI, 1.55–3.52). A decrease in median eosinophil cytology score was seen in both groups, as would be expected with the use of topical corticosteroid, but this decrease was not significant in either treatment group. Sodium hyaluronate did not significantly alter the numbers of mast cells or infective species. While we must be cautious in drawing conclusions from this study due to its exploratory design and small number of patients, it may be that sodium hyaluronate may be more effective in NARNE than in other forms of the disease. This finding is similar to that of another exploratory study in children treated with recurrent upper respiratory tract infections, in which sodium hyaluronate produced favorable effects on neutrophils, but not eosinophils or mast cells (Macchi A. personal communication). However, further studies are required to confirm these data.

Current treatment options for vasomotor rhinitis include nasal corticosteroids, sodium cromoglycate or ipratropium bromide. While the effect of these agents on clinical endpoints has been well studied in rhinitis, their effects on...
TABLE 3. Improvements seen in clinical and endoscopic outcomes at 1 month compared with baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sodium hyaluronate (n = 39)*</th>
<th>Control (n = 39)*</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3 (7.7)</td>
<td>2 (5.1)</td>
<td>1.50 (0.26–8.49)</td>
<td>1.0</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (5.1)</td>
<td>4 (10.3)</td>
<td>0.50 (0.1–2.57)</td>
<td>0.675</td>
</tr>
<tr>
<td>Postnasal drip</td>
<td>4 (10.3)</td>
<td>2 (5.1)</td>
<td>2.0 (0.39–10.29)</td>
<td>0.675</td>
</tr>
<tr>
<td>Halitosis</td>
<td>3 (7.7)</td>
<td>1 (2.6)</td>
<td>3.0 (0.33–27.6)</td>
<td>0.615</td>
</tr>
<tr>
<td>Itching</td>
<td>9 (23.1)</td>
<td>10 (25.6)</td>
<td>0.9 (0.41–1.97)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sneezing</td>
<td>17 (43.6)</td>
<td>4 (10.3)</td>
<td>4.25 (1.57–11.49)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Endoscopic outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>14 (35.9)</td>
<td>7 (17.9)</td>
<td>2.0 (0.91–4.41)</td>
<td>0.125</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>3 (7.7)</td>
<td>0</td>
<td>–</td>
<td>0.24</td>
</tr>
<tr>
<td>De-epithelialization</td>
<td>2 (5.1)</td>
<td>1 (2.6)</td>
<td>2.0 (0.19–21.16)</td>
<td>1.0</td>
</tr>
<tr>
<td>Nasal hyperactivity</td>
<td>5 (12.8)</td>
<td>3 (7.7)</td>
<td>1.67 (0.43–6.5)</td>
<td>0.711</td>
</tr>
</tbody>
</table>

*aValues are numbers of patients (%). CI = confidence interval.

nasal cytology have not. Nasal administration of corticosteroids has been consistently shown to reduce levels of eosinophils and basophils in the nasal mucosa in studies in allergic rhinitis, but the effect on neutrophils has not been reported. Intranasal sodium cromoglycate produced a significant reduction from baseline in nasal eosinophil levels in 1 study, but ipratropium did not produce any changes in nasal cytology in a study in patients with perennial allergic rhinitis. The significant reduction in neutrophil count in the nasal cytology of patients with allergic and nonallergic rhinitis in the present study suggests that sodium hyaluronate may have advantages over current therapies for vasomotor rhinitis by altering the number of inflammatory cells in the nasal mucosa of these patients, thus reducing symptoms at the source of inflammation.

The effects of currently used treatments for vasomotor rhinitis on symptoms vary in randomized controlled trials in patients with nonallergic rhinitis. Nasal budesonide improves the symptom of nasal obstruction in patients with nonallergic rhinitis but does not appear to improve any other symptoms. Ipratropium bromide administered intranasally consistently reduces nose blowing frequency and rhinorrhea, but the symptoms of nasal congestion—sneezing and itch—appear to respond less well. In 1 comparative study, nasal budesonide produced significantly greater improvements in the symptoms of nasal secretion and sneezing than ipratropium, although in a second study the treatments appeared similar. Last, sodium cromoglycate improved the symptoms of rhinitis, reducing sneezing and congestion scores and itch in 2 randomized controlled trials. The evidence for symptomatic relief in patients with allergic rhinitis is far more unequivocal, with nasal corticosteroids and sodium cromoglycate improving multiple symptomatic endpoints in a large number of well-designed studies. Furthermore, ipratropium bromide produced a significant reduction in rhinorrhea and postnasal drip in 1 randomized controlled study. Endoscopic outcomes are less well reported and no improvements in these have been seen with the currently used agents in randomized controlled studies.

In the present study, sodium hyaluronate was associated with improvements in symptoms associated with sneezing, rhinorrhea, and nasal congestion in our patients with vasomotor rhinitis, but did not appear to affect cough, asthma symptoms, postnasal drip, halitosis, or itch. On endoscopy, sodium hyaluronate was associated with a significant improvement in exudate, a trend toward improvement in edema and hyperemia, and no improvement in de-epithelialization and nasal hyperactivity. These endoscopic improvements support the expected changes that should occur through cytological remodeling observed with a decrease in neutrophils and, therefore, in inflammatory mediators in the nasal passages. While the improvements in clinical and endoscopic outcomes in the active treatment arm were modest compared with controls, this may be due to the low numbers of patients presenting with symptoms and signs at baseline, and a larger treatment effect may be anticipated in a patient group showing more overt signs of and/or more severe disease.

Sodium hyaluronate aerosolized in saline and administered intranasally using the Fluirespira nasal douche device was well tolerated and no safety signals were detected. Indeed, when patients were asked about the tolerability of the products used in this study, significantly more patients preferred the active treatment group compared with control, suggesting good symptomatic relief from nasal symptoms.
Conclusion

This analysis of the effects of the addition of sodium hyaluronate to intranasal corticosteroid and systemic antihistamine showed a reduction in neutrophil count on nasal cytology in patients with allergic and nonallergic rhinitis. Furthermore, improvements in clinical and endoscopic disease parameters were also seen. This study provides encouraging data with which to continue development of this product in the treatment of this common disease.

Acknowledgments

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References