Effect of sodium hyaluronate added to topical corticosteroids in chronic rhinosinusitis with nasal polyposis

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ABSTRACT

Background: *Available medical treatments for chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP) comprise systemic and topical therapies. Although topical corticosteroids are effective in the treatment of CRS, they are not completely devoid of adverse effects. Thus, care has to be taken when long-term treatments are prescribed. There is recent evidence that sodium hyaluronate (SH), the major component of many extracellular matrices, promotes tissue healing, including activation and moderation of the inflammatory responses, cell proliferation, migration, and angiogenesis.*

Objective: *The aim of the study was to evaluate clinical outcomes and quality of life in two groups of patients with CRSwNP treated with topical corticosteroids alone or in combination with 9 mg of high-molecular-weight SH.*

Methods: *The impact of treatments was determined by using nasal endoscopy and validated quality of life questionnaires (Short Form-36, 22-item Sino-Nasal Outcome Test, visual analog scale [VAS]). Eighty subjects who had CRS with grade IV nasal polyposis: 40 diagnosed with allergic rhinitis (AR) and 40 with non–allergic-eosinophilic rhinitis (NARES) based on skin-prick test and nasal cytology results, were divided in two groups. Group I comprised 40 subjects (20 AR and 20 NARES), who received mometasone furoate plus SH; group II comprised 40 subjects (20 AR and 20 NARES), who received mometasone furoate plus saline solution alone. All the patients were followed up for 3 months.*

Results: *At baseline, no statistically significant differences were observed between the groups and the VAS score showed a moderate-to-severe degree of disease. After treatments, Lund and Kennedy, Short Form-36, 22-item Sino-Nasal Outcome Test, and VAS scores were statistically significant in both groups but slightly in favor of the group I and in the subjects with allergic CRSwNP.*

Conclusion: *Analysis of our data indicated that an SH supplement to standard corticosteroid seems to play an important role in improving the severity of symptoms, the endoscopic appearance, and discomfort associated with CRSwNP. This effect seems to be strongest in patients with allergic CRSwNP.*

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Chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP) affects 0.5–4% of the world population[1–3] and is associated with reduction of quality of life (QoL).[4] The available medical treatments for CRSwNP comprise systemic and topical therapies,[5–8] but, for patients with medically resistant CRSwNP, the surgical approach represents the treatment of choice.[5,9] However, it is well known that both medical and surgical therapeutic strategies have high rates of recurrence as the result of severe inflammatory reactions during the mucosal healing period.[10] Recently, there is mounting evidence that sodium hyaluronate (SH), the major component of many extracellular matrices, including those in respiratory epithelial cells and gland serous cells of the nasal and trachea-bronchial mucosa, serves important biologic roles beyond its generally accepted function as a structural component of interstitial and connective tissues.[1]

Because of its biologic properties, SH has several clinical applications, such as esthetic surgery, dermatology, orthopedics, and ophthalmology.[11] Despite such a wide use, only a few studies assessed the effects of SH on chronic or recurrent upper respiratory tract infections.[1,3,4,12–14] Most of them provided evidence that SH is beneficial in improving clinical and laboratory outcomes in affected children and adults.[1,3,4,12–14] In this regard, SH has been shown to promote wound healing, repair mucosal surfaces, and cell motility.[4,12,15] Particularly, results of a previous research indicated that topical application of SH significantly improves the healing process of the nasal mucosa and prevents extensive crust formation, and eventually leads to the recovery of smell parameters and cooling sensation.[14] Results of a prospective randomized controlled trial indicated that a new absorbable SH hydrogel, similar to a nasal dressing or packing after functional endoscopic sinus surgery, promotes the postoperative reepithelization process and reduces the presence of synechia, edema, crust, and mild mucopurulent drainage.[16]

Furthermore, SH, in association with intranasal corticosteroid and systemic antihistamine, reduces the neutrophil count shown on nasal cytology in patients with allergic rhinitis (AR) and non-AR and improves several clinical and endoscopic parameters.[13] Although evidence on the effectiveness of SH on postoperative care after functional endoscopic sinus surgery is currently available,[1] there remains a dearth of evidence that evaluated its actual impact as enhancer of intranasal corticosteroid on the CRSwNP and QoL of affected patients. The aim of the study was to evaluate clinical and QoL outcomes in two groups of patients with CRSwNP treated with intranasal corticosteroids alone or in combination with 9 mg of high-molecular-weight SH. In addition, we evaluated the effect of SH as adjuvant therapy to intranasal corticosteroid on CRSwNP with AR or with non-AR with eosinophils (NARES), with particular regard to the QoL.

METHODS

This double-blind study was carried out from October 2013 to April 2015 at the Ear Nose and Throat (ENT) section of the University of Naples, "Federico II." The patients were sequentially enrolled in the study until reaching the planned sample size of 80 patients (mean [standard deviation] age, 56.3 ± 5.4 years) with CRSwNP. To exclude sex-related interference reported in the literature, which revealed that women have more severe disease than do men,[17] we recruited 40 men and 40 women; whereas, to evaluate the efficacy of SH in both subjects with allergy and subjects without allergy, we recruited 40 subjects with positive skin-prick test results and 40 with negative skin-prick test results and eosinophilic infiltration at rhinocytogram.

The diagnosis of CRSwNP was based on the European Position Paper on Rhinosinusitis and Nasal Polyps diagnostic criteria.[9] and confirmed by nasal endoscopy and computed tomography scans with axial, coronal, and sagittal images. Nasal endoscopy with a 4-mm, 30°, rigid endoscope (Storz, Tuttlingen, Germany) was performed by an experienced otolaryngologist (E.C.) blinded to patients' clinical and

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therapeutic data, before and after treatment, without decongestant or local anesthesia and was scored as previously described by Lund and Kennedy[18] (score range, 0–20). The presence of residual polyps, edema, discharge, scarring, and crusting of both nasal cavities was scored from 0 to 2 as follows: absence of polyps (0), the presence of polyps confined to the middle meatus (1), presence of polyps beyond the middle meatus (2); no discharge (0), clear and thin discharge (1), thick and purulent discharge (2); no edema or scarring or crusting (0), mild (1), and severe (2).[18]

Computed tomographies performed only at baseline were scored for both sinonasal sides as previously described by Lund and Mackay[19] (score range, 0–24). The Lund-Mackay scoring system quantifies the severity of image opacification, no (0), partial (1), or complete opacification (2), in the maxillary, ethmoidal, sphenoidal, osteomeatal complex, and frontal sinuses.[19]

To characterize the allergic status, a skin-prick test and nasal cytology were performed. For the nasal cytology, scraping of the nasal mucosa was collected from the middle portion of the inferior turbinate through anterior rhinoscopy by using a Nasal Scraping cytology curette (IR Medical, Lugo, Italy). Samples were placed on a glass slide, fixed by air-drying, stained according to the May-Grünwald-Giemsa method, and then observed by optical microscopy.[4,13] For the rhinocytogram analysis, 50 microscopic fields were read at a magnification of ×1000 to assess the presence of normal and abnormal cellular elements or other pathologic microscopic features. The cell count was carried out by a semiquantitative grading system, as proposed by Meltzer and Jalowayski.[20] We performed the nasal cytological assessment evaluating the presence and the number of eosinophils.

In brief, we enrolled 40 subjects with positive skin-prick test results and 40 with negative skin-prick test results and eosinophilic infiltration at rhinocytogram >20%. Patients with systemic diseases, acetylsalicylic acid sensitivity, cystic fibrosis, or primitive ciliary dyskinesia, or with a history of interventions were excluded from the study as well as subjects with other forms of non-AR: non-AR infiltrated by mast cells, by eosinophils and mast cells, and by neutrophils. Subjects who were being treated with antibiotics, steroids, antihistamines, and local vasoconstrictive decongestants 3 months before were also excluded.

All the participants gave their informed consent to participate in the study, which was fully approved by the board of medical ethics of the University of Naples, "Federico II." Recruited patients were alternately assigned to two intervention groups and given the treatment. The investigational arm (group I) comprised 40 subjects (20 men and 20 women; 20 with AR and 20 with NARES), and the control arm (group II) comprised 40 subjects (20 men and 20 women; 20 with AR and 20 with NARES). Group I received 200 μg of mometasone furoate nasal spray once a day for 3 months and 9 mg (3 mL) of high-molecular-weight SH (Yabro; IBSA, Lugano, Switzerland) plus saline solution (2 mL of sodium chloride 0.9%) administered twice a day for 15 consecutive days per month for 3 consecutive months by using a nebulizer ampoule for nasal douche. This device produces particles of >10 μm and acts only on the upper airways over a time of 60 to 90 seconds for each application.[1] Group II received 200 μg of mometasone furoate nasal spray and saline solution (5 mL of sodium chloride 0.9%) alone, administered by using a nebulizer ampoule for nasal douche according to the same protocol as group I. All the patients were followed up for 3 months.

To assess therapeutic outcomes and QoL, both groups were asked to answer three questionnaires. The first was the Italian Short Form-36 (SF-36) questionnaire.[1] This questionnaire, which measures patients' general health status, contains 36 questions that refer to eight health concepts grouped into subgroups (physical functioning, physical role functioning, bodily pain, general health, vitality, social role functioning, emotional role functioning, and mental health). Each question was asked independently. The second was the 22-item Sino-Nasal Outcome Test (SNOT-22), which is a validated patient self-reported measure,[21] which encompasses all major symptoms included in the diagnostic criteria set in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 for CRS.[9] Furthermore, to evaluate the severity of symptoms, all the subjects filled out the self-reported visual analog scale (VAS) questionnaire, which included questions on nasal obstruction and on nasal discharge. In brief, it consists of a continuous scale made of a 10-cm horizontal line anchored by two verbal descriptors, one for each symptom extreme (0, not troublesome; 10 cm, most troublesome imaginable). Based on the average severity of the VAS scores, the degree of severity of the disease was classified into three categories: mild, moderate, and severe (mild, VAS score = 0–3; moderate, VAS score = 4–7; and severe, VAS score = 8–10). A VAS of >5 indicated poor QoL.[9]

QoL tools, as well as nasal endoscopy, was administered at baseline before treatments (T0) and 3 months after therapies (T1). Continuous baseline characteristics were described as mean and standard deviation. Differences between the groups were tested with the Student's *t*-test. A p value of <0.05 was considered statistically significant.

RESULTS

At baseline, no statistically significant differences were observed between the groups in the clinical, endoscopic, imaging, and QoL tools, and the VAS score showed a moderate-to-severe degree of disease (Table 1). In particular, at T0, all the diagnostic tools showed a greater degree of severity in CRSwNP with NARES than in AR (Table 2). After treatments, the Lund-Kennedy, SF-36, SNOT-22, and VAS scores were statistically significant ($p < 0.05$) in both investigational and control groups, but a more significant improvement in clinical and instrumental parameters ($p < 0.05$) was observed in favor of group I (Table 3). In the same way, a more significant improvement ($p < 0.05$) was observed in favor of subjects with AR than in subjects with NARES in both the investigational and control groups (Table 4). No patients reported adverse reactions or complications.

DISCUSSION

Oral and intranasal corticosteroids are the most commonly used medications for CRS.[9] According to the current state of knowledge, topical corticosteroids are used in upper airway diseases with different inflammatory mechanisms, such as CRSwNP and CRS without nasal polyposis.[22] Unquestionable advantages of topical corticoste-

Table 1 **Baseline**

Group	Age mean ± SD	Score mean ± SD					
		LK	LM	SF-36	SNOT-22	VASo	VASd
I	56.9 ± 5.6	8.7 ± 1.6	15.5 ± 5.4	56.9 ± 2.9	49.4 ± 3.7	8.5 ± 1.0	8.5 ± 1.0
II	56.8 ± 4.4	8.6 ± 1.9	16.2 ± 4.2	57.4 ± 4.8	49.0 ± 3.6	8.5 ± 1.1	8.3 ± 1.2
p Value	0.8	0.9423	0.5793	0.6033	0.6791	0.9717	0.3739

SD = Standard deviation; LK = Lund-Kennedy; LM = Lund-Mackay; SF-36 = Short Form 36; SNOT-22 = 22-item Sino-Nasal Outcome Test; VASo = visual analog scale, nasal obstruction; VASd = visual analog scale, nasal discharge.

Table 2 **Degree of severity between AR and NARES at T0**

T0	Score mean ± SD					
	LK	LM	SF-36	SNOT-22	VASo	VASd
AR	8.3 ± 1.8	15.4 ± 4.1	59.0 ± 2.3	47.8 ± 3.2	8.2 ± 1.1	8.1 ± 1.2
NARES	9.6 ± 1.5	18.6 ± 3.5	53.8 ± 4.2	50.8 ± 3.1	9.0 ± 0.9	8.9 ± 0.8
p Value	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

CRSwNP = Chronic rhinosinusitis with nasal polyposis; NARES = non–allergic-eosinophilic rhinitis; AR = allergic rhinitis; SD = standard deviation; LK = Lund-Kennedy; LM = Lund-Mackay; SF-36 = Short Form 36; SNOT-22 = 22-item Sino-Nasal Outcome Test; VASo = visual analog scale, nasal obstruction; VASd = visual analog scale, nasal discharge.

Table 3 **Results after treatment between group I and II**

	Score mean ± SD				
	LK	SF-36	SNOT-22	VASo	VASd
Group I					
T0	8.7 ± 1.6	56.9 ± 2.9	49.4 ± 3.7	8.5 ± 1.0	8.5 ± 1.0
T1	5.1 ± 1.6	63.6 ± 2.0	44.9 ± 3.7	5.8 ± 1.1	5.6 ± 1.0
p Value	<0.05	<0.05	<0.05	<0.05	<0.05
Group II					
T0	8.6 ± 1.9	57.4 ± 4.8	49.0 ± 3.6	8.5 ± 1.1	8.3 ± 1.2
T1	6.4 ± 2.1	60.5 ± 5.4	47.4 ± 3.8	7.2 ± 1.0	7.3 ± 1.1
p Value	<0.05	<0.05	<0.05	<0.05	<0.05
T1 results between group I and group II					
T1 group I	5.1 ± 1.6	63.6 ± 2.0	44.9 ± 3.7	5.8 ± 1.1	5.6 ± 1.0
T1 group II	6.4 ± 2.1	60.5 ± 5.4	47.4 ± 3.8	7.2 ± 1.0	7.3 ± 1.1
p Value	<0.05	<0.05	<0.05	<0.05	<0.05

LK = Lund-Kennedy; SF-36 = Short Form 36; SNOT-22 = 22-item Sino-Nasal Outcome Test; VAS = visual analog scale; VASo = visual analog scale, nasal obstruction; VASd = visual analog scale, nasal discharge.

Table 4 **Results after treatment between AR and NARES**

	AR	NARES	*p* Value
Group I, mean (SD)			
LK	4.4 ± 1.2	6.7 ± 1.3	<0.05
SF-36	64.3 ± 1.4	60.3 ± 2.7	<0.05
SNOT-22	43.7 ± 2.9	45.2 ± 3.8	<0.05
VASo	5.5 ± 1.0	6.3 ± 1.1	<0.05
VASd	5.6 ± 1.0	5.3 ± 1.0	<0.05
Group II, mean (SD)			
LK	5.4 ± 1.7	8.3 ± 1.4	<0.05
SF-36	62.4 ± 3.4	57.2 ± 4.9	<0.05
SNOT-22	45.9 ± 3.7	48.4 ± 2.7	<0.05
VASo	7.1 ± 1.0	7.7 ± 0.9	<0.05
VASd	6.8 ± 1.1	8.0 ± 0.9	<0.05

AR = Allergic rhinitis; NARES = non–allergic-eosinophilic rhinitis; SD = standard deviation; LK = Lund-Kennedy; SF-36 = Short Form 36; SNOT-22 = 22-item Sino-Nasal Outcome Test; VASo = visual analog scale, nasal obstruction; VASd = visual analog scale, nasal discharge.

roids are their strong anti-inflammatory local action, with little impact on general health, and few adverse effects. In particular, their anti-inflammatory effect can reduce mucosal edema and decrease the size of nasal polyps.[22] The main mechanism of action of corticosteroids is the binding to the intracellular corticosteroid receptors and their impact on nuclear cytoplasmic transcriptional factors. Corticosteroids suppress gene expression of factors responsible for generating and supporting inflammatory processes, proinflammatory cytokines and chemokine production, and adhesive molecules expression. It seems that corticosteroids also have additional mechanisms of action, which do not involve intracellular receptors and do lead to inhibition of early and late phase of allergic reaction.[22]

Topical nasal corticosteroids are of proven efficacy for treating CRSwNP; however, they may be responsible for several adverse effects, among which the most common are epistaxis, dry nose, nasal burning, and nasal irritation.[9,23] These conditions are commonly tolerated by the patient, but the prolonged use of topical corticosteroids may compromise not only the patient's QoL but also the compliance to therapy. Thus, although many studies have investigated the use of different topical agents to improve symptoms related to CRSwNP,[9] there is still an unmet medical need for an effective therapy that can be administered for a long time without adverse effects.

Recently, SH treatment has been shown to stimulate the mucociliary clearance, thereby improving wound healing and repairing of mucosal surfaces.[1,3,4,12,14,15] Additional evidence has also reported the effectiveness of 9 mg of nebulized high-molecular-weight SH in the treatment of sinonasal clinical, endoscopic, and psychologic parameters in patients undergoing functional endoscopic sinus surgery for sinonasal remodeling.[1,3,4,12,14,15] Furthermore, SH, in association with intranasal corticosteroid and systemic antihistamine, reduces the neutrophil count shown on nasal cytology in patients with AR and non-AR, and improves several clinical and endoscopic parameters.[13]

In our study we evaluated the effect of SH supplement to standard intranasal corticosteroid in the treatment of CRSwNP with AR and NARES, not only in terms of clinical outcomes but also in terms of QoL. Indeed, we strongly believe that patients' perspective on treatment outcomes is a crucial element for improving high-quality care. For these reasons, in this study, the impact of treatments was determined by using endoscopic parameters and validated QoL questionnaires such as SF-36, SNOT-22, and VAS. At baseline, no statistically

significant differences were observed between groups I and II in the clinical, endoscopic, imaging, and QoL tools, and the VAS score showed a moderate-to-severe degree of disease (Table 1). In particular, at T0, all diagnostic tools showed a greater degree of severity in CRSwNP with NARES than in AR (Table 2). After treatments, the Lund-Kennedy, SF-36, SNOT-22, and VAS scores were statistically significant ($p < 0.05$) in both investigational and control groups, but a more significant improvement in clinical and instrumental parameters ($p < 0.05$) was observed in favor of group I (Table 3). This is not surprising because the control arm was not treated with placebo but with topical corticosteroids and saline solution that *per se* are therapeutic options. However, these results require additional studies to evaluate the use of different therapeutic protocols in which the corticosteroids in association with SH could be used for shorter periods and/or at lower doses than that used in the present study.

In the same way, a more significant improvement ($p < 0.05$) was observed in favor of subjects with AR than in the subjects with NARES, in both investigational and control groups (Table 4). This finding is in accordance with previous studies in which, although both patients with AR and those with non-AR had good steroid response, the patients with non–allergic phenotypes had less improvement than the patients with AR.[24] Our findings demonstrated that both therapeutic protocols (topical corticosteroids plus SH and saline solution, and topical corticosteroids and saline solution) are effective in the treatment of CRSwNP, but an SH supplement to standard corticosteroids seems to enhance their efficacy with the perspective of reducing the corticosteroid dosage, the duration of topical therapy, and, as a consequence, the onset of the most common drug-related events, such as epistaxis, dry nose, nasal burning, and irritation. It remains to understand whether the therapeutic enhancement operated by SH can prolong the well-being and the therapy-free periods. Hence, this could be a future research project.

CONCLUSION

Analysis of our data indicated that SH supplement to standard corticosteroid seems to play an important role in improving the severity of symptoms and the endoscopic appearance and discomfort associated with CRSwNP. This effect seems to be strongest in patients with AR associated with CRSwNP. In addition, the supplement of SH may significantly enhance the QoL, both in terms of the general health status (SF-36) and in terms of the specific sinonasal status (SNOT-22).

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