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Pathological and cytological changes of the nasal mucosa in acute rhinosinusitis: the role of hyaluronic acid as supportive therapy

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the reparative role of hyaluronic acid in acute rhinosinusitis (ARS).

PATIENTS AND METHODS: 48 patients affected by ARS were submitted to nasal endoscopy, nasal cytology, mucociliary transport evaluation (MCTt) and visual analogue scale questionnaire (VAS) at T0, after 14-18 days (T1) and after 30-35 days (T2). The patients were randomized into two groups, A and B, and received Levofloxacin and Prednisone. Moreover, using a nebulizer ampoule for nasal douche, Group A received high molecular weight Sodium Hyaluronate (3%) plus saline solution (NaCl 0.9%) twice a day for 30 days; Group B received saline solution twice a day for 30 days.

RESULTS: At T0 only the VAS score showed differences regarding nasal discharge and post-nasal drip. At T1, in Group A MCTt and the number of bacteria were significantly lower than in Group B. The VAS score showed improvement in Group A. At T2 in Group A, MCTt and number of neutrophils were significantly lower than in Group B. The VAS score showed statistically significant differences between the two groups regarding nasal discharge.

CONCLUSIONS: In ARS patients sodium hyaluronate plus saline solution significantly improved symptoms, MCT time and reduced neutrophil count on nasal cytology.

Key Words
Rhinosinusitis, Nasal cytology, Mucociliary transport, Hyaluronic acid, Visual analogue scale questionnaire.

Introduction

Acute rhinosinusitis (ARS) is a highly common condition whose incidence is steadily increasing. Its incidence varies among different studies from 6% to 15%, but its real impact is probably higher because it represents one of the major causes of primary care consultation. Therefore, ARS presents a considerable socio-economic burden and may be related to a negative impact on quality of life, especially for the recurring form[1,2].

In most cases, ARS is sustained by a viral aetiology (rhinoviruses, coronaviruses) and, generally, bacterial infection occurs only secondarily. The main bacterial pathogens identified in ARS are *Streptococcus pneumoniae, Haemophilus influenza* and *Moraxella catarrhalis*. In a minority of cases, *Streptococcus pyogenes, Staphylococcus aureus*, Gram-negative bacilli, and oral anaerobes may also be identified[3-5].

According to EPOS criteria, ARS is defined as a simultaneous inflammation of the mucosa of both the nose and paranasal sinuses: the obstruction of the sinus ostia caused by edema and congestion of the rhinosinusal mucosa and the alteration of mucociliary transport induced by impairment of the cilia, determine stagnation of secretions and bacterial proliferation. Signs and symptoms characteristic of ARS are nasal blockage, congestion or stuffiness, nasal discharge or postnasal drip, often mucopurulent, facial pain or pressure, headache, and reduction/loss of smell (for <4 weeks)[2].

The goal of therapy is to reduce the severity and duration of symptoms and prevent complications. In addition to antibiotic and corticosteroid therapy, adjunctive therapies such as antihistamines, intranasal corticosteroids, decongestants, saline irrigation, mucolytic and phytotherapeutic agents have been investigated[6-14]. To our knowledge, of all these substances, the most widely used as adjuvant treatment is still the saline solution[7,8].

Recently, studies have evaluated the role of hyaluronic acid in the inflammation of the nasal mucosa[15-17]. There are two forms of hyaluronic acid, based on molecular weight. High molecular weight hyaluronic acid (>103 kDa) shows higher viscosity, longer resident time and higher biocompatibility than the lower one (<103 kDa)[15]. The physiological

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role of high molecular weight hyaluronic acid can suppress immune system function and limit inflammatory response[16,17]. During an inflammatory process, the free radicals and enzymes, produced during this status, lead to a fragmentation of hyaluronic acid into low molecular weight molecules that display proinflammatory effects[18]. Recently, high molecular weight hyaluronic acid has been introduced into clinical practice for the management of sinus and nasal pathologies. In fact, some studies have demonstrated that it plays an anti-inflammatory and reparative role in the treatment of chronic rhinosinusitis, minimizing symptoms and preventing exacerbations[19,20]. Moreover, it was employed in patients undergoing functional endoscopic sinus surgery for rhinosinusal remodelling[21,22].

The aim of this study was to compare the adjuvant therapeutic value of high molecular weight hyaluronic acid in a group of adult patients suffering from ARS under treatment with antibiotics, systemic steroid treatment and irrigation with saline solution as local therapy. The therapeutic effect of hyaluronic acid was evaluated by analyzing nasal cytological properties and mucous ciliary clearance.

Patients and Methods

From December 2014 to April 2015, in the Department of Sense Organs of Sapienza University in Rome, 48 consecutive adult patients with acute bacterial rhinosinusitis symptoms, according to the above-reported guidelines[2], were prospectively enrolled in the study. Ethics approval has been obtained by our IRB of the Sapienza University.

All enrolled patients signed a written informed consent prior to entering the study and were investigated at first time evaluation (T0), after 14-18 days (T1) and after 30-35 days (T2).

All patients underwent to:

- Clinical records collection and ENT examination with nasal endoscopy (2.7 mm 0-degree rigid endoscope);
- CT scan of nasal and sinusal structures (axial, coronal and sagittal projections) performed at T0 time in order to confirm the diagnosis of ARS;
- Nasal cytology: a scraping of the nasal mucosa on the middle third of the inferior turbinate was performed. After sampling, the material was laid on a microscope slide, fixed for air dry and stained by the May-Grunwald-Giemsa method. The smear was observed under a common light microscope equipped with 1000 x objective. For analyzing the rhino cytogram, we performed with a reading for fields (not less than 50), in order to observe the cellular elements that composed the nasal mucosa (eosinophils, mast cells, neutrophils, lymphocytes, bacteria, spores, biofilms and so on). To calculate the percentage of each cellular element, semi-quantitative grading counts of each cell type, according to the previously published studies, were performed (grade 1+: occasional groups, grade 2+: moderate number, grade 3+: easily visible, grade 4+: elevated number)[23-26]. This model of grading for nasal cytology that we used[26] is well represented in Table I.
- Nasal MCT-time was determined by applying some charcoal powder to the head of the inferior turbinate using a cotton stick. The subsequent appearance of blackish colouring in the oro-pharynx (normal values= 12 min ± 3)[27-30] was evaluated by direct pharyngoscopy.
- Visual Analog Scale (VAS): a questionnaire was issued for subjective assessment of symptoms such as nasal obstruction, nasal discharge, post-nasal drip, facial pain (0=absent; 1=mild; 2=moderate; 3=severe) and olfactory perception (0=normal; 1=decreased; 2=absent)[31,33].

Patients were enrolled with a randomized selection into Group A and Group B. All patients received antibiotic and systemic steroid therapy (Levofloxacin, 500 mg for 10 days, and Prednisone, 50 mg for 8 days, 25 mg for 4 days and 12, 5 mg for 4 days). Moreover, Group A received high molecular weight (800.000-1.000.000 Daltons) sodium hyaluronate (3%) plus saline solution (3 mL sodium chloride-NaCl- 0.9%) twice a day for 30 days using a nebulizer ampoule for nasal douche (Rinowash, Air Liquide Medical System Spa, Bovezzo, Brescia, Italy). Group B received saline solution (6 mL sodium chloride-NaCl-0.9%) twice a day for 30 days using a nebulizer ampoule for nasal douche.

All the patients enrolled completed all the evaluations and no episodes of drug intolerance occurred.

Statistical analysis was performed by comparing the data of Group A and Group B at T0, T1 and T2. The Chi-square test was used for categorical variables; while the non-parametric Wilcoxon Mann-Whitney test was used for continuous variables. Continuous variables were presented as median and interquartile range (IQR). All data were analyzed using Stata SE 10.1 System.

Table I. Description and semiquantitative grading for Nasal Citology reporting.

	Description	Grading*
Epithelial ciliated cells	Normal	N
	Abnormal	A (CCP/MN)
Mucinous cells	None	0
	Occasional	1+
	Moderate number	2
	Large number	3+
	Covering the entire field	4+
Neutrophils and Eosinophils	None	0
	Occasional	½+
	Few scattered cells, small clumps	1+
	Moderate number, large clumps	2+
	Large clumps not covering the field	3+
	Clumps covering entire field	4+
Basophils (Mast cells)	None	0
	Occasional	½+
	Few scattered cells, small clumps	1+
	Moderate number, large clumps	2+
	Large clumps not covering the field	3+
	Upt to 25 per an X100 field	4+
Eosinophil/Mast cell degranulation	None observed	0
	Occasional granules	1+
	Moderate number of granules	2+
	Many granules easily seen	3+
	Massive degranulation, entire field	4+
Bacteria and spores	None observed	0
	Occasional clumps	1+
	Moderate number	2+
	Many cells easily seen	3+
	Bacteria/spores over the entire field	4+

*CCP: ciliocytophtoria; MN: multinucleation.

Results

Both groups were composed of 24 patients:

- Group A, 12 males and 12 females, mean age of 44 years (38-50 IQR);
- Group B, 14 males and 10 females, mean age of 43 years (35-55 IQR).

There were no statistical differences between the two groups regarding demographic data (Table II).

CT scans showed rhinosinusitis and congestion involving the ostio-meatal complex in 100% of patients, ethmoidal, ethmoido-maxillar and fronto-ethmoidal rhinosinusitis in 15%, 65% and 20% of cases respectively in Group A and in 25%, 45% and 30% respectively in Group B.

At the beginning of treatment (T0), there were no statistical differences between the two groups regarding cytological and MCTt data, but the self-assessment questionnaire (VAS) score showed statistically significant differences between the two groups regarding nasal discharge (p=0.010) and post-nasal drip (p=0.02) (Table III). This result represented an unexpected finding at this moment of study (T0), considering that patients were randomized into the two different groups and did not begin any adjuvant therapies. So, it was a not relevant result at this moment of examination for the aim of the study.

After 14-18 days' treatment (T1), MCTt was significantly lower in Group A than in Group B:

Table II. Demographic data.

	Group A (n=24)	Group B (n=24)	p
Male, n (%)	12 (50.0%)	14 (58.3%)	0.562
Age (years), median (IQR)	44 (38-50)	43 (35-55)	0.975

Table III. Baseline characteristics of patients (T0).

	Group A (n=24)	Group B (n=24)	p
MCTt, median (IQR)	20 (20-25)	20 (20-25)	0.853
Cytology			
Neutrophils, median (IQR)	3 (2-3)	2 (1-3)	0.252
Eosinophils, median (IQR)	0 (0-1)	0 (0-0)	0.089
Mast-cells, median (IQR)	0 (0-0)	0 (0-0)	0.686
Bacteria, median (IQR)	2 (1-2)	1.5 (1-2.5)	0.947
Biofilm, n (%)	8 (33.3%)	8 (33.3%)	1.000
Mycetes, n (%)	3 (12.5%)	2 (8.3%)	0.637
VAS			
Smell 0-2	2 (1-2)	1.5 (1-2)	0.388
Obstruction 0-3	2 (1.5-2)	1.5 (1-2)	0.142
Discharge 0-3	2 (2-3)	1 (1-2)	0.010
Post-nasal drip 0-3	1 (0-2)	0 (0-1)	0.022
Facial pain	1 (1-2)	1 (1-2)	0.274

Table IV. Comparing data after 14-18 days' treatment (T1).

	Group A (n=24)	Group B (n=24)	p
MCTt, median (IQR)	15 (12.5-15)	20 (15-20)	0.003
Cytology			
Neutrophils, median (IQR)	1 (1-1)	1 (0-1)	0.282
Eosinophils, median (IQR)	0 (0-0)	0 (0-0)	0.416
Mast-cells, median (IQR)	0 (0-0)	0 (0-0)	1.000
Bacteria, median (IQR)	1 (0-1)	1 (1-1.5)	0.019
Biofilm, n (%)	6 (25.0%)	3 (12.5%)	0.267
Mycetes, n (%)	2 (8.3%)	1 (4.2%)	0.551
VAS			
Smell 0-2	0 (0-1)	1 (1-1)	0.018
Obstruction 0-3	0 (0-0.5)	1 (1-1)	<0.001
Discharge 0-3	0.5 (0-1)	1 (1-2)	0.006
Post-nasal drip 0-3	0 (0-0)	0 (0-0)	0.714
Facial pain	0 (0-1)	0 (0-1)	0.700

the median value was 15 minutes (IQR: 12.5-15) in Group A and 20 minutes (IQR: 15-20) in Group B (p=0.003) (Table IV).

Cytological evaluation yielded a lower number of bacteria in Group A (Figure 1). Although the median distribution was the same in both groups, there was a statistically significant difference (p=0.019). There were no statistical differences between the two groups regarding other cytological evaluations, even those regarding biofilm and mycetes distribution (Figure 4) (Table IV).

The VAS score showed statistically significant differences between the two groups, in particular for smell (p=0.018), nasal obstruction (p<0.001) and nasal discharge (p=0.006) that had a lower incidence in group A (Table IV).

After 30 days' treatment (T2), MCTt was significantly lower in Group A than in Group B: the median value was 15 minutes in both groups but there was a different distribution of values (IQR: 10-15 in Group A, IQR: 15-15 in Group B) (p=0.021) (Table V).

At T2 cytological evaluation, we found a lower number of neutrophils in Group A (p<0.001) (Figures 2, 3) There were no statistical differences between the two groups regarding other cytological evaluations (Table V).

The VAS score showed a statistically significant difference between the two groups for nasal discharge alone that had a lower prevalence in Group A (p=0.040, same median, different distribution) (Table V).

Discussion

During ARS, the inflammatory response of the nasal mucosa results in edema, mucous production and fluid extravasation. In addition to antibiotic and corticosteroid therapy, adjunctive

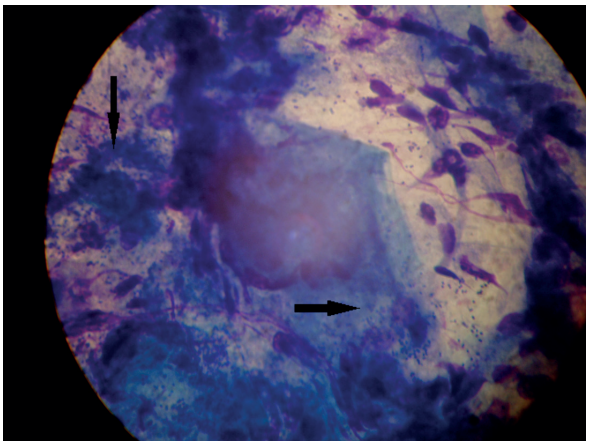

Figure 1. Bacterial biofilm *(arrows)* (May-Grumwald-Giemsa, 1000X).

therapies have been investigated to reduce the severity and duration of symptoms and prevent complications. Decongestant, nasal irrigation with saline and intranasal corticosteroids may be used as a support therapy to reduce mucosal edema, improve mucociliary clearance and facilitate aeration and drainage during acute episodes. Even if there are not enough studies to support the action of these drugs when used in association with antibiotic and corticosteroid therapy, they may provide additional benefits by alleviating symptoms[6-12]. Antihistaminic therapy is often used but, according to a Cochrane review, should be used for symptomatic relief of acute sinusitis only in patients with a history of allergy[13]. During recent years, phytotherapeutic agents and herbal compounds have also been introduced but further studies and meta-analysis are needed for understanding their real effectiveness in the

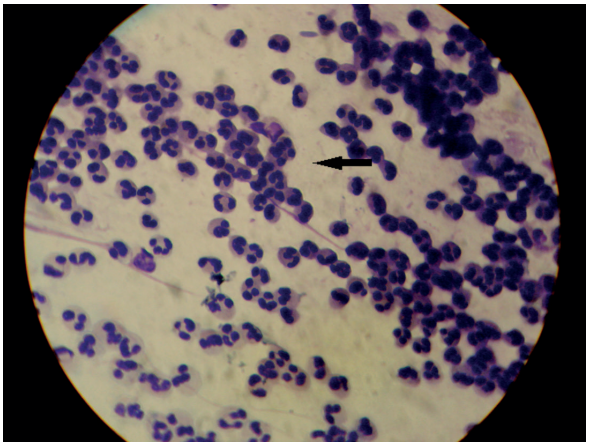

Figure 2. Acute Rhinosinusitis: clear evidence of large distribution of neutrophils *(arrow)* (May-Grumwald-Giemsa, 1000X).

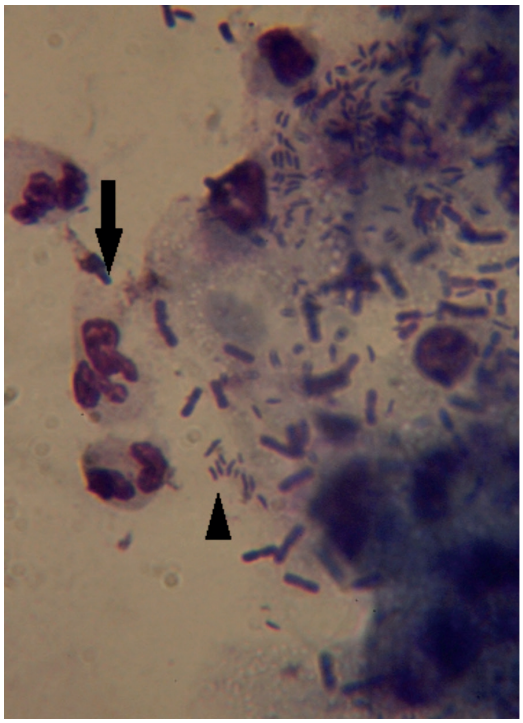

Figure 3. Neutrophils and Bacteria (*arrow* and *arrow head*) (May-Grumwald-Giemsa, 1000X).

treatment of ARS[2,14]. In accordance with the above-reported data, the substance that is still widely used as an adjuvant therapy in ARS patients is the saline solution[7,8]. However, throughout the last few years, several studies have documented the effectiveness of hyaluronic acid in the prevention of exacerbations of chronic rhinosinusitis and in post-operative tissue repair after rhinosinusal surgery[20-22].

Hyaluronic acid is a large non-sulphated glycosaminoglycan with a high molecular weight and is the main component of many organs and tissues, such as connective tissue, skin, and synovial fluid. The extracellular matrices of the respiratory epithelial cells and gland serous cells in the mucosa of upper airways and tracheobronchial tracts is made up of a three-dimensional plot of hyaluronic acid, chondroitin sulphate and heparin sulphate. This structure is essential for ciliary clearance and for the regulation of enzymatic activity, which are essential for maintaining the homeostasis on the apical surface[34,35]. The presence of tissue damage or inflammation activates the coordinated action of platelet cells, neutrophils, and monocytes that, in turn, triggers the development of a network made up of signals responsible for automatization and consolidation

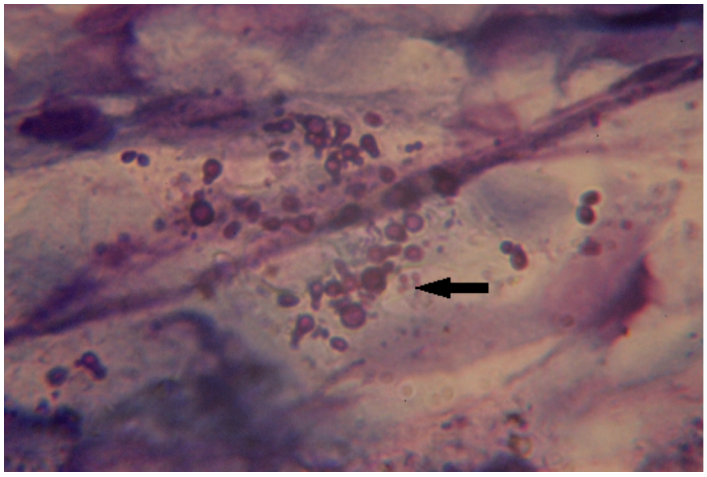

Figure 4. Fungal spores *(arrow)* (May-Grumwald-Giemsa 1000X).

of tissue response. The free radicals and enzymes, produced during inflammatory status, lead to a fragmentation of hyaluronic acid into low molecular weight molecules that act as proinflammatory mediators, promoting and supporting the immune response[18]. Therefore, the high molecular weight of hyaluronic acid molecules suppresses the immune system function and limits the inflammatory response, thus promoting tissue proliferation and tissue remodelling, and modulating cell migration and chemotaxis, angiogenesis and inflammatory responses[16,17].

In our study, we added sodium hyaluronate (3%) plus saline solution (3 mL-NaCl- 0.9%) using a nebulizer ampoule for nasal douche to antibiotic and steroid therapy and to investigate its effect in all enrolled patients after 14 (T1) and 30 (T2) days' treatment. All patients underwent MCT time evaluation, nasal cytology performed by scraping of the nasal mucosa on the middle third of the inferior turbinate. They also filled out a VAS questionnaire for subjective assessment of nasal obstruction, nasal discharge, post-nasal drip, facial pain and olfactory perception[31-33]. Regarding cytological evaluation, there were no statistical differences between the two groups at first evaluation (T0); after 14 days therapy (T1), a lower number of bacteria were observed in Group A; after 1 month (T2) there was a significant decrease in the number of neutrophils ($p<0.001$). In addition, we observed a moderate improvement of clinical parameters and of MCTt at T1 and T2 in Group A. These data showed that in Group A recovery of the physiological function of the nasal mucosa was faster, as demonstrated by normal MCT-time values at T2. The use of hyaluronic acid as supporting therapy in ARS allowed a faster recovery of mucociliary clearance, modulation of inflammatory responses and tissue

Table V. Comparing data after 30 days' treatment (T2).

	Group A (n=24)	Group B (n=24)	*p*
MCTt, median (IQR)	15 (10-15)	15 (15-15)	0.021
Cytology			
Neutrophils, median (IQR)	0 (0-1)	1 (0.5-1)	<0.001
Eosinophils, median (IQR)	0 (0-0)	0 (0-0)	0.686
Mast-cells, median (IQR)	0 (0-0)	0 (0-0)	0.530
Bacteria, median (IQR)	0 (0-0)	0 (0-1)	0.059
Biofilm, n (%)	2 (8.3%)	0 (0%)	0.149
Mycetes, n (%)	0 (0%)	1 (4.2%)	0.312
VAS			
Smell 0-2	0 (0-0)	0 (0-0)	1.000
Obstruction 0-3	0 (0-0)	0 (0-1)	0.335
Discharge 0-3	0 (0-0)	0 (0-1)	0.040
Post-nasal drip 0-3	0 (0-0)	0 (0-0.5)	0.125
Facial pain	0 (0-0)	0 (0-0)	0.388

proliferation and remodelling. According to other studies, the inflammatory modulation effect manifests as a reduction in the bacterial count after 14 days and in the neutrophil count after one month of treatment. It is also confirmed by the subjective improvement of some symptoms, after just 14 days of therapy[22], such as nasal obstruction, smell and nasal discharge in Group A. After 30 days of therapy (T2) results showed a persistent improvement of nasal discharge. This is an important data that suggests the possibility of increasing patient compliance by using adjunctive therapy.

Conclusions

Our study demonstrated the effectiveness of hyaluronic acid as a support therapy to systemic antibiotic and corticosteroid treatment in patients with acute rhinosinusitis. Treatment with sodium hyaluronate (3%) plus saline solution brought about a significant improvement in global assessment of subjective symptoms, normalization of MCT time and reduction of neutrophil count on nasal cytology. ARS represents a considerable socio-economic burden and may also have a negative impact on the quality of life, especially in the recurring forms. Therefore, sodium hyaluronate could play an important role in the treatment of acute rhinosinusitis by favouring tissue repair, restoring mucosal function and reducing the severity and duration of symptoms.

Conflict of interest

None of the authors have any conflict of interest, including specific financial interests, relationships.

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