Hyaluronan in the Treatment of Chronic Rhinosinusitis with Nasal Polyposis

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Abstract Chronic rhinosinusitis (CRS) is a common condition and affects the quality of life of approximately 16 % of adults in US and 10.9 % in Europe. Hyaluronan (HA) is a nonsulphate glycosaminoglycan found in the extracellular matrix of connective tissues, and plays an important role in the healing process and repair of mucosal surfaces. We aim to evaluate the effect of HA on nasal symptoms and endoscopic appearance in patients with CRS and nasal polyps (NP) who have not undergone sinus surgery. Eighty patients older than 18 years old were randomized to receive either open-label nebulized saline solution (NS) or intranasal corticosteroid spray (ICS) 200 µg bid or nebulized sodium hyaluronate (NHA, YABRO[®]) or both ICS and NHA. Results were collected at 1 month, 3 months and 3 months after treatment. Significant improvements in nasal symptoms scores, endoscopic appearance scores, radiologic scores, rhinomanometry and saccharine clearance test were observed in the NHA, ICS and ICS + NHA groups after 1 month and 3 months of

treatment compared with baseline (all $p \leq 0.005$). The use of oral steroids was significantly reduced after 3 months of therapy in the same groups versus baseline (all $p < 0.05$). The incidence of adverse events at 3 months was similar between the 4 groups (all $p > 0.05$). Throat irritation, nasal burning and drug-related epistaxis were not reported in the group NHA. HA, as a nebulized nasal douche preparation, improved nasal symptoms and endoscopic appearances in patients with CRS and NP who have not undergone sinus surgery.

Keywords Hyaluronan · Hyaluronic · Chronic rhinosinusitis · Nasal polyposis · Glycoaminoglycans · Randomized · YABRO[®] · Rhinomanometry

Introduction

Rhinosinusitis is characterized by mucosal inflammation of the nasal cavity and paranasal sinuses, and is associated with nasal congestion or obstruction, facial pain and olfactory disturbance [1]. Chronic Rhinosinusitis (CRS) is defined as rhinosinusitis that persists longer than 12 weeks. The aetiology of CRS is multifactorial and comprises a cycle of pathophysiological, anatomical, and constitutive factors. Diagnosis of CRS is primarily based on symptoms that are confirmed by endoscopy and computed tomography [1].

Nasal polyps (NP) are associated with a more severe subset of CRS and result when the oedematous lining blocks the nasal cavity to a significant degree [1]. More than 80 % of polyps occur due to eosinophilic inflammation. NPs are characterized by subepithelial caps of eosinophils covering pseudocysts filled with albumin [2]. NP are usually seen in adults in the aged 20–60 years and

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its presence in children is usually associated with cystic fibrosis [3]. Its incidence is 4 % in general population and 7–15 % in asthmatics [4]. The association of NP, asthma and aspirin-exacerbated respiratory disease is called Samter's triad [5].

Guidelines for the diagnosis and treatment of rhinosinusitis differ in terms of diagnosis of CRS and therapy; oral and intranasal corticosteroids are the standard therapy for CRS and NP [6–10]. Glycosaminoglycans (GAGs) also known as mucopolysaccharides, are long unbranched chains of disaccharide units that are repeated in the determined order by alternating an aminosaccharide (containing an amino group instead of a simple-OH group) to a monosaccharide usually acid (containing one or more carboxyl groups and/or sulphates and thus negative charges). Hyaluronan (HA), also known as hyaluronate or hyaluronic acid, is a nonsulphate glycosaminoglycan formed by a chain of dimers each constituted by a D-glucuronic acid molecule and a D-N-acetylglucosamine [11]. HA is one of the main constituents of all connective matrices and many organic liquids, and is widely distributed in the body. HA is found in human respiratory epithelial cells and serous cells in submucosal glands, and accounts for approximately 80 % of uronic acids in human nasal secretions [12]. Additionally, HA exerts an important function on mucociliary clearance on the epithelial surface. To ensure effective mucociliary clearance it is important that ciliary activity remains at an adequate level, in vivo, ciliary activity is regulated by HA and adenosine triphosphate [13]. An experiment has shown that following exposure to an enzyme system that breaks down high molecular HA to generate superoxides, the ciliary activity of human respiratory epithelial cells increase [13]. Reactive oxygen species strongly induce the depolarization of HA into fragments of small size and able stimulate ciliary to beat. It has been demonstrated that HA plays an important role in the processes of wound healing and repair of mucosal surfaces; the presence of mucosal ulcers increase the expression of HA receptors, which provides a ligand for cell adhesion. HA binds to and interacts with the hyaluronic acid-mediated motility [14]. Patients with chronic bronchitis and recurrent exacerbations treated with HA have seen reduce the number of exacerbations, with less need for antibiotic therapies to control recurrent episodes [15]. This study investigates the effect of HA, administered as a nebulizer, in patients with CRS and NP who have not undergone sinus surgery.

Materials and Methods

Between September 2011 and April 2012, 80 patients aged ≥ 18 years with CRS with NP who had not undergone sinus

surgery from the Department of Otorhinolaryngology of the University Hospital “San Giovanni di Dio e Ruggi d’Aragona” in Salerno, Italy were enrolled in this randomized study. This study aimed to evaluate the therapeutic benefits of nasal douches with nebulized HA in the treatment of CRS with NP in patients who have not undergone sinus surgery. The primary outcome was the assessment of nasal related-symptoms and nasal endoscopic appearance. Secondary outcome measures were nasal radiologic examination, rhinomanometry, saccharine clearance test, the use of oral steroids, and the incidence of adverse events (AEs).

Patients and Selection Criteria

Written consent was obtained from all patients and the study was approved by the ethics committee. The treatment period was 3 months. Subjects were included in the study if they were aged ≥ 18 years and had CRS with NP. Pregnant or breast-feeding subjects and subjects with diseases that might interfere with study treatments were excluded from the study. We defined CRS on the duration of 12 weeks with the presence of at least two of the following nasal symptoms: inflammation of the nose and paranasal sinuses, nasal obstruction, postnasal drip, sneezing, cough, olfactory disturbance, facial pain, snoring, nasal dryness in accordance with current clinical guidelines.

Treatment

Patients were randomly assigned to 4 treatment groups of 20 subjects, drug was administered on an open-label basis.

1. Nebulized saline (NS): aerosol therapy (NEBULA[®], Air Liquide Medical Systems Italy) with 5 mL of saline bid.
2. Intranasal corticosteroid spray (ICS): mometasone furoate nasal sprays (MFNS) 200 μ g bid.
3. Nebulized sodium hyaluronate (NHA): aerosol therapy (NEBULA[®], Air Liquide Medical Systems Italy) with 3 mL sodium hyaluronate 9 mg (YABRO[®], IBSA, Switzerland) and 2 mL saline bid.
4. Intranasal corticosteroid sprays (ICS) + nebulized sodium hyaluronate (NHA) (YABRO[®], IBSA, Switzerland).

Examination

No subjects received any investigational drug therapy for 4 months before study start. All patients were assessed before therapy and returned for visits at 1 month and 3 months following treatment initiation and 3 months following treatment cessation. At each clinic visit, the

assessment of symptoms such as nasal obstruction, nasal discharge, postnasal drip, sneezing, cough, olfactory disturbance, facial pain, snoring, nasal dryness was recorded by the patient and guardian using a validated 10 cm visual analogue scale (VAS) [16]. The 10-cm VAS we used consisted of a statistically validated questionnaire that the patient filled out, answering the question “how troublesome are your symptoms of rhinosinusitis?” is used. The answers range from 0 (not troublesome) to 10 (worst thinkable troublesome), the scores range from 0 to 3 (absent, mild, moderate, severe disease) [16]. We used the VAS for the diagnosis of CRS with NP. Endoscopic investigations were performed in a sitting position by a

flexible endoscope (2.7 mm, Storz, Germany). Nasal decongestants and local anaesthesia were not used. Nasal endoscopy was scored by two otorhinolaryngologists using modified post-operative criteria of endoscopic appearance originally described by Lund et al. which includes the examination of deviation of nasal septum, turbinate hypertrophy, hyperemia, discharge, polyps [16]. Axial and coronal computed tomography (CT) scans of nose and paranasal sinuses were performed, using the multi-slice CT method, and were blindly scored by two otorhinolaryngologists using well-defined radiological staging. Radiological staging was performed as described by Lund et al. [17]. Specifically, for paranasal sinuses (maxillary,

Table 1 Baseline characteristics of the study population

	NS (n = 20)	ICS (n = 20)	NHA (n = 20)	ICS + NHA (n = 20)
Age (mean $\pm$ SD)	38.6 $\pm$ 13.06	38.4 $\pm$ 12.70	38.75 $\pm$ 13.08	38.85 $\pm$ 13.31
Gender (M/F)	11/9	10/10	12/8	12/8
Skin prick tests, % of positive patients	40	45	40	45
Smoking (%)	55	40	45	50
Time by the initial diagnosis (years) (Mean $\pm$ SD)	5.7 $\pm$ 5.19	4.45 $\pm$ 2.46	4.7 $\pm$ 2.72	4.65 $\pm$ 2.92

ICS intranasal corticosteroid spray, NS nebulized saline, NHA nebulized sodium hyaluronate

* Differences compared to before therapy: $p < 0.01$ (student's t-test)

† Differences compared to saline only therapy: $p < 0.01$ (student's t-test)

Fig. 1 Mean total nasal symptoms scores during the overall treatment and follow-up periods of the trial

Fig. 2 Mean endoscopic appearance scores during the overall treatment and follow-up periods of the trial

ethmoid anterior and posterior, sphenoid and frontal) the following score has been assigned (per side): 0 = no opacification; 1 = partial opacification; 2 = total opacification. For the osteomeatal complex (per side): 0 = not occluded; 1 = occluded.

The active anterior rhinomanometry was assessed by a Rhinotest MP500 (EVG Electronic Vertriebs GmbH, Germany). The examination was performed inserting a small probe in one nostril and asking the patient to breathe through the other nostril in a soft mask applied on the face. The total resistance (Pa/cc³/sec) to 150 Pascal was recorded. Mucociliary clearance was assessed by performing a saccharine test where a fragment of saccharin was placed 1 cm behind the anterior margin of the inferior turbinate and the patient instructed to sit with his head inclined forward by 10 degrees. Mucociliary transport time under endoscopic control was investigated [18].

Statistical Analysis

Statistical analysis was performed with SPSS 21.0 software (SPSS Inc., Chicago, IL). Data of the four groups in the

clinical trial are presented as mean $\pm$ SD and percentages. Comparisons between the treatment groups and between each parameter within the groups were analyzed by unpaired Student's t test. All hypothesis tests were set with an alpha level of 0.05.

Results

A total of 80 patients with CRS and NP were enrolled in this single-centre, randomized study. Baseline data of patients are summarized in Table 1. There were no significant differences between the treatment groups.

Significant improvements in nasal symptoms scores, endoscopic appearance scores, radiologic scores, rhinomanometry and saccharine clearance test were observed in the NHA, ICS and ICS + NHA groups after 1 month of treatment, these effects were also seen after 3 months of treatment (Figs. 1, 2, 3, 4, and 5). Improvements in scores were partially reversed 3 months after the treatment but still remained significant relative to baseline. As shown in Figs. 1, 2, 3, 4, and 5, either at 1 month of therapy, 3 months of therapy and at 3 months after ending of

Fig. 3 Mean radiological scores during the overall treatment and follow-up periods of the trial

treatment in NHA, ICS and ICS + NHA groups all scores show a significant improvement compared to NS group ($p < 0.01$). Evidence of this improvement was visible in CT scans images (Fig. 6). The treatment ICS + NHA appeared to be the most effective therapy, reaching a statistically significant improvement in the control of nasal symptoms at both 3 months of therapy (4.04 vs. 20.20 at baseline; $p < 0.01$) and at 3 months after therapy cessation (11.72; $p < 0.01$).

At 3 months, nasal symptoms scores were reduced from 19.40 at baseline to 6.60 in the ICS group ($p < 0.01$), and in the NHA group from 19.80 to 10.80 ($p < 0.01$). These improvements were maintained 3 months after therapy ($p < 0.01$ for both). Endoscopic appearance scores at 3 months were: ICS 9.33 versus 23.15 ($p < 0.01$ vs. baseline); NHA 13.75 versus 23.05 ($p < 0.01$ vs. baseline); ICS + NHA 6.60 versus 23.15 ($p < 0.01$ vs. baseline).

A significant reduction in the use of oral steroids was seen at 3 months in the NHA, ICS and ICS + NHA groups (all $p < 0.05$ versus baseline) (Table 2). The incidence of adverse events at 3 months was similar between the 4 groups (all $p > 0.05$) (Table 3). There were no reports of throat irritation, nasal burning and drug-related epistaxis in the group NHA.

Discussion

This was a single-centre, randomized trial that investigated the effects of nebulized HA, administered by aerosol therapy with nasal washes, in patients with CRS with NP who have not undergone sinus surgery. HA, used alone or in combination with corticosteroids improved nasal symptoms in patients with CRS with NP. Rhinosinusitis is a common condition that represents a continuous challenge for physicians in both diagnosis and appropriate treatment strategy. In addition to nasal symptoms, for an accurate diagnosis, we performed nasal endoscopy as a primary screening setting differential diagnosis of CRS without NP, CRS with NP and allergic fungal rhinosinusitis. We have also performed secondary screening CT scans, rhinomanometry, and a saccharine clearance test. Furthermore, in agreement with the British Society for Allergy and Clinical Immunology, we performed a prick skin test on all patients because an association between CRS and allergy in more than 60 % of cases has been reported in the literature [1]. In our sample of 80 patients the incidence of allergy was 42 %. Many physicians suggest the use of systemic antibiotics (macrolides) for long-term treatment [19], although their effectiveness has not been scientifically established

* Differences compared to before therapy: $p < 0.05$ (student's t-test)

Fig. 4 Mean rhinomanometry scores during the overall treatment period and at the 3-month follow-up period

for long-term use, the efficacy of long-term (more than 3 months) intranasal corticosteroid (mometasone furoate) has been reported in the literature [20].

Considering the pathogenesis of CRS with NP and controversies surrounding its management, our group decided to introduce a therapy molecule that is already on the market but never used for the treatment of CRS with NP. The molecule considered is sodium hyaluronate 9 mg, in its new formulation administrable by aerosol (YABRO®). The nebulization permits integration in the mucosa of the entire respiratory tract, performing the regulation functions of hydration and mucociliary clearance useful for inflammatory or allergic reactions [21].

As previously mentioned, HA is widely distributed in the body, it is one of the main constituents of all connective matrices. Its main characteristic is hydrophilicity associated with the high viscosity that determines action of lubrication and may act as a barrier against the spread in the body of toxins, foreign bodies and micro-organisms. Many studies have confirmed the physiological role of HA in the upper airway. It is able to stimulate the mucociliary clearance through which removes the secretions on the epithelial surface [13], regulates the activity of enzymes needed for the homeostasis of the respiratory mucosa involved in allergic bronchoconstriction which prevents

bacterial colonization of the upper airways. The ability of HA to reduce the infectious exacerbation of bacterial infections has been demonstrated in a randomized controlled trial study on patients with chronic bronchitis [22].

HA plays an important role in the healing process and repair of mucosal surfaces to be considered for the treatment of patients undergoing surgery [23]. In view of the pharmacological properties of sodium hyaluronate and controversies in the literature about the standard therapy for CRS with NP, we administered a long-term treatment with nebulized sodium hyaluronate 9 mg, alone or in combination with corticosteroids.

Analyzing the results obtained at 1 month of therapy, at 3 months of therapy and after 3 months after therapy, we have found an inefficacy of nasal douches with nebulized saline with both at 1 month and 3 months of therapy, while significant improvements in evaluation scores were observed after 1 and 3 months of treatment with NHA, ICS and NHA + ICS. It was observed that the combination of NHA + ICS treatment resulted in statistically significant improvements after 3 months of therapy compared with the ICS only group. We then re-evaluated patients 3 months after cessation of therapy, in order to evaluate the stability of the results obtained, which has proved sufficiently stable even the difference between NHA + ICS compared with

Fig. 5 Mean times for the saccharine clearance tests before, during and after the treatment period

ICS only was no longer significant. It is important to note that HA, even administered alone, showed sustained results after cessation of therapy, compared with that seen with ICS and ICS + NHA groups. The use of NHA long-term (3 months) was not associated with AEs such as throat irritation, nose or nasal discharge; moreover it was observed that the combination of ICS with NHA significantly reduced the incidence of adverse effects associated with the topical use of corticosteroids. The addition of NHA to standard therapy with ICS for 3 months, also reduced the use of systemic corticosteroids.

The improvements in nasal symptoms seen in our study with HA are comparable with other studies using HA for the treatment of CRS with NP. There have been two recent randomized studies that have evaluated the effects of absorbable HA nasal packing in patients with rhinosinusitis with or without NP who have undergone sinus surgery. Franklin et al. [24] conducted a prospective, randomized, controlled study that investigated the effect of absorbable HA nasal packing on postoperative discomfort and mucosal healing in 35 patients with rhinosinusitis without NP following sinus surgery. Improvements in endoscopic appearances were reported with the absorbable HA nasal packing. The other study was conducted by Berlucchi et al. [25] in 66 patients with CRS with or without NP. A lower proportion of nasal lesions were observed in the absorbable HA nasal packing compared with control.

An animal study investigated the effect of two new HA hydrogels in a rabbit maxillary sinus model. Both gels significantly prevented neo-ostium stenosis and promoted wound healing [26].

Another study evaluated the efficacy of intranasal injection of HA gel into inferior nasal concha and under mucous membrane in three patients with empty nose syndrome. The injections improved patient symptoms [22].

More recently, a randomized study examined the effects of an absorbable nasal dressing of HA in combination with carboxymethylcellulose (CMC) in 39 patients with CRS and in 14 patients with CRS with NP [27]. This study concluded that there were no long-term differences between the HA/CMC and control group after 8 weeks. The authors stated that further studies investigating HA/CMC versus other absorbable nasal packing were required. Despite the fact that HA was used in the studies as an absorbable nasal dressing preparations and not nasal douches with nebulized solution, these studies confirm the therapeutic benefit of HA in the treatment of CRS with NP.

The fact that this study was conducted at a single centre and the small number of sub-samples analysed (NSD, ICS, SHND and ICS + SHND) does not allow for definitive conclusions on the efficacy of HA in the treatment of CRS with NP to be drawn. The confirmation of the findings presented in this study would require further trials with a

Fig. 6 CT scans of a patient in the NHA treatment group with chronic polypoid pansinusitis (about 30 years) showing obstruction and erosion of ostia: **a** CT scan at the baseline; **b** CT scan at 3 months after the end of the therapy. Marked reduction of the mucosa hypertrophy is visible

Table 2 Use of oral steroids at 3 months of therapy

	NS	ICS	NHA	ICS + NHA
No. of patients users	8/20	6/20	6/20	4/20
Total number of days of use (mean $\pm$ SD)	58 (7.25 $\pm$ 3.24)	30 (5.00 $\pm$ 0.00)	36 (6.00 $\pm$ 1.10)	22 (5.50 $\pm$ 1.00)

ICS intranasal corticosteroid spray, NS nebulized saline, NHA nebulized sodium hyaluronate

Table 3 Incidence of adverse events at 3 months of therapy

	NS (%)	ICS (%)	NHA (%)	ICS + NHA (%)
Headache	15	10	10	5
Throat irritation	0	5	0	0
Upper respiratory infection	15	15	10	5
Epistaxis	5	10	0	5
Nasal burning	0	5	0	5

Epistaxis was defined as a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge to flecks of blood in the mucus

ICS intranasal corticosteroid spray, NS nebulized saline, NHA nebulized sodium hyaluronate

larger number of patients and a multicentre, double-blind design.

Conclusion

Sodium hyaluronate 9 mg, administered by nasal douches with nebulized preparation, improved nasal symptoms in patients with CRS and NP who have not undergone sinus surgery from first month of therapy. The combination with

a steroid nasal spray results in a significant synergism in the disease control and a reduction adverse effects associated with the topical use of corticosteroids. Further studies evaluating the effects of HA as a nasal douche preparation in combination with standard therapy need to be conducted.

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References

- Scadding GK, Durham SR, Mirakian R et al (2008) BSACI guidelines for the management of rhinosinusitis and nasal polypsis. *Clin Exp Allergy* 38(2):260–275
- Bachert C, Gevaert P, Holtappels G et al (2000) Nasal polyposis: from cytokines to growth. *Am J Rhinol* 14(5):279–290
- Lurie MH (1959) Cystic fibrosis of the pancreas and nasal mucosa. *Ann Otol Rhinol Laryngol* 68(2):478–486
- Larsen K (1996) The clinical relationship of nasal polyps to asthma. *Allergy Asthma Proc* 17(5):243–249
- Roediger FC, Goldberg AN (2008) Evaluation and treatment of recurrent nasal polyposis, in revision sinus surgery. Springer, Berlin Heidelberg, pp 143–152
- Fokkens W, Lund V, Mullol J et al (2007) European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 20:1–136
- Meltzer EO, Hamilos DL (2011) Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc* 86(5):427–443
- Meltzer EO, Hamilos DL, Hadley JA et al (2006) Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol* 118(5 Suppl):S17–S61
- Scadding GK, Durham SR, Mirakian R et al (2008) BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 38(1):19–42
- Slavin RG, Spector SL, Bernstein IL et al (2005) The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol* 116(6 Suppl):S13–S47
- Weissmann B, Meyer K (1954) The structure of hyalobiuronic acid and of hyaluronic acid from umbilical cord 1,2. *J Am Chem Soc* 76(7):1753–1757
- Laurent TC, Fraser JR (1992) Hyaluronan. *FASEB J* 6(7):2397–2404
- Manzanares D, Monzon ME, Savani RC et al (2007) Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. *Am J Respir Cell Mol Biol* 37(2):160–168
- Forteza R, Lieb T, Aoki T et al (2001) Hyaluronan serves a novel role in airway mucosal host defense. *FASEB J* 15(12):2179–2186
- Souza-Fernandes AB, Pelosi P, Rocco PR (2006) Bench-to-bedside review: the role of glycosaminoglycans in respiratory disease. *Crit Care* 10(6):237
- Lund VJ, Holmstrom M, Scadding GK (1991) Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. *J Laryngol Otol* 105(10):832–835
- Lund VJ, Kennedy DW (1995) Quantification for staging sinusitis. The staging and therapy group. *Ann Otol Rhinol Laryngol Suppl* 167:17–21
- Klingbeil P, Wiersbitzky S, Bruns R et al (1990) The saccharin test in the pediatric broncho-function of the respiratory tract in children. *Kindererztl Prax* 58:205–210
- Ragab SM, Lund VJ, Scadding G (2004) Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope* 114(5):923–930
- Stjarne P, Blomgren K, Caye-Thomasen P et al (2006) The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 126(6):606–612
- Passali D, Damiani V, Passali FM et al (2005) Atomized nasal douche vs nasal lavage in acute viral rhinitis. *Arch Otolaryngol Head Neck Surg* 131(9):788–790
- Modrzynski M (2011) Hyaluronic acid gel in the treatment of empty nose syndrome. *Am J Rhinol Allergy* 25(2):103–106
- Soldati D, Rahm F, Pasche P (1999) Mucosal wound healing after nasal surgery. A controlled clinical trial on the efficacy of hyaluronic acid containing cream. *Drugs Exp Clin Res* 25(6):253–261
- Franklin JH, Wright ED (2007) Randomized, controlled, study of absorbable nasal packing on outcomes of surgical treatment of rhinosinusitis with polyposis. *Am J Rhinol* 21(2):214–217
- Berlucchi M, Castelnuovo P, Vincenzi A et al (2009) Endoscopic outcomes of resorbable nasal packing after functional endoscopic sinus surgery: a multicenter prospective randomized controlled study. *Eur Arch Otorhinolaryngol* 266(6):839–845
- Chen Q, Sun G, Wang Y et al (2012) The evaluation of two new hyaluronan hydrogels as nasal dressing in the rabbit maxillary sinus. *Am J Rhinol Allergy* 26(2):152–156
- Woodworth BA, Chandra RK, Hoy MJ et al (2010) Randomized controlled trial of hyaluronic acid/carboxymethylcellulose dressing after endoscopic sinus surgery. *ORL J Otorhinolaryngol Relat Spec* 72(2):101–105