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Effect of sodium hyaluronate on mucociliary clearance after functional endoscopic sinus surgery

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KEY WORDS

Sodium hyaluronate, mucociliary clearance, functional endoscopic sinus surgery (FESS), nasal polyposis, intranasal therapy, Yabro®

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SUMMARY

Background: To determine the effect of intranasal sodium hyaluronate on mucociliary clearance time following functional endoscopic sinus surgery in patients with nasal polyposis. **Study Design:** Randomized, controlled, blinded study. **Methods:** Thirty-six patients with grade II nasal polyposis undergoing functional endoscopic sinus surgery received intranasal sodium hyaluronate 9mg twice daily or saline for 30 days commencing on the second day after surgery. Ciliary mucous transport time was assessed using charcoal powder and saccharin administered during rhinoscopy. Other outcomes included changes in symptoms, endoscopic appearance of the nasal mucosa, and tolerability. **Results:** Patients receiving sodium hyaluronate had a significantly faster mucociliary clearance time at 1 month compared with controls (14.3 ± 2.5 vs. 23.6 ± 3.3 minutes; $p = 0.000$). Furthermore, sodium hyaluronate recipients experienced a lower incidence of rhinorrhea, less nasal obstruction and a lower incidence of exudate on endoscopy than control subjects at 1 month (all $p < 0.05$). Sodium hyaluronate was well tolerated in patients following functional endoscopic sinus surgery. **Conclusion:** The use of intranasal sodium hyaluronate in patients undergoing functional endoscopic sinus surgery for nasal polyposis augmented the improvement in mucociliary clearance observed following this procedure and improved several clinical and endoscopic parameters. These data provide encouraging evidence of the beneficial effects of sodium hyaluronate in the care of patients undergoing functional endoscopic sinus surgery with which to continue the development of the product for this indication.

Introduction

Nasal polyps are tumor-like hyperplastic swellings of the nasal mucosa originating most commonly from the ethmoid or middle meatus regions of the nasal mucosa and are understood to result from long-term inflammation (1). Polyposis is usually associated with symptoms such as nasal obstruction, congestion, facial pressure, and anosmia, and significantly reduces quality of life (2).

The prevalence of nasal polyps ranges between 1-4% (3), is twice as common in men than women (4), and has a peak incidence at age 50 to 59 years (1).

Surgery is the treatment of choice in patients with marked mechanical obstruction of the airways or chronic disease that does not respond to maximal medical therapy (5).

Functional endoscopic sinus surgery (FESS) has become a widely used treatment for nasal polyposis with the aim to restore the physiological function of the nose and allow

infected sinuses to drain (4). While this procedure has a lower rate of recurrence compared with simple polypectomy (6), the optimum choice of surgical technique for nasal polyposis remains controversial (4).

A number of studies have investigated the use of topical agents to improve intranasal symptoms, prevent complications and aid healing following FESS (7-9).

Hyaluron (also known as hyaluronic acid or hyaluronate) is a large non-sulphated 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 from the epithelial surface (10), in the processes involved in wound healing and repair of mucosal surfaces (11), and in the viscoelasticity of the structures responsible for speech (12-14). Furthermore, hyaluron promotes phagocytosis of *Streptococcus pyogenes* *in vitro* and *in vivo* by interfering with mechanisms of recognition (15,16). Hyaluron has been shown to augment wound healing following nasal surgery (17) and reduce the number of exacerbations in patients with chronic bronchitis (18). Sodium hyaluronate has also been assessed for its use as an anti-adhesive and/or augmentative agent in vocal cord surgery for the treatment of vocal fold atrophy, sulcus vocalis, and post-surgery scarring (19).

This paper reports the results of a randomized controlled study comparing the effects of sodium hyaluronate versus saline on mucociliary clearance in patients undergoing FESS to treat nasal polyps.

Materials and methods

Study design

This randomized, controlled, blinded study was performed between January 2012 and June 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 review board, "Comitato Etico dell'Azienda Ospedaliera Policlinico Consorziale di Bari", and all patients provided informed consent prior to entry into the study.

Study population

Patients affected by grade II nasal polyposis according to International Conference criteria (20) undergoing FESS

at the Otolaryngology Unit of the University of Bari were enrolled in the study. Before surgery, patients' clinical history was carefully assessed to determine the presence of a family history of atopy, the presence of asthma, allergy to seasonal or perennial inhalants, and allergy to aspirin or non-steroidal anti-inflammatory drugs. The number of previous interventions for nasal polyps and the type of intervention was also recorded.

Patients affected by grade I nasal polyposis, cystic fibrosis, primitive ciliary dyskinesia and choanal atresia were excluded from the study.

Randomization and treatment

All patients underwent FESS as described by Stammberger (21). In all patients the nose was not packed at the end of the procedure after careful hemostasis with bipolar coagulation and the inferior turbinates were not treated.

After surgery patients were randomized into two treatment groups and treated for 30 days starting on the second day after surgery.

The investigational arm was treated with sodium hyaluronate (Yabro[®], IBSA) 9mg nebulized in 3mL sodium chloride 0.9% twice a day. The control arm was treated with 5mL sodium chloride 0.9% twice a day. Treatment was administered using the Fluirespira[®] nasal douche device (Zambon, Italy) into each nostril.

Outcomes and assessments

Patients were assessed 30 days after surgery, at which time nasal endoscopy and investigation of ciliary mucous transport time were performed.

Endoscopic examination was performed with a flexible fibroscope ENT 2000 - Vision Sciences[®] (USA), with a diameter of 3.4mm. Patients did not receive local anesthetic or nasal decongestant.

Ciliary mucous transport time was assessed using the mixture formed from charcoal powder and 3% saccharin (22). In a patient sitting and undergoing rhinoscopy, approximately 10mg of the above powder was placed in the nasal cavity at the head of the inferior turbinate using Nasal Scraping[®] (IR-Medical, Italy) and the time at which the powder appeared on the posterior wall of the oropharynx, immediately below the margin of the soft palate, was recorded.

Clinical outcomes included the degree of nasal obstruction, burning, dryness of the mucosa, and the presence or absence of rhinorrhea. Nasal obstruction was expressed on

a visual analogue scale as a score from 0 to 10 where 0 = nose free from obstruction and 10 = nose completely obstructed.

At 30 days after surgery, all patients were also asked to evaluate the tolerability of the post-operative topic treatment: 1 = fair, 2 = good, 3 = excellent.

Statistical analysis

Continuous baseline characteristics are presented as median and interquartile ranges (IQRs) or mean and standard deviation, where appropriate. For proportions, absolute and relative frequencies are reported. To test baseline differences between the two treatment groups, the Wilcoxon-Mann-Whitney test was used for continuous and ordinal variables, and Fisher's exact test for proportions.

In order to evaluate the effect of treatment on pre-specified outcomes we used the Wilcoxon test for quantitative and ordinal variables, and Fisher's exact test for binary variables.

To measure the effect of treatment on outcomes, we calculated relative risks and 95% confidence intervals (CIs).

Risk ratios (RRs) indicate the relative increase of the probability of outcome success associated with the active treatment arm.

All significance tests were two-tailed at the 0.05 level. All analyses were conducted using Stata 11.

Results

Patient characteristics

Thirty-six patients were enrolled in the study. The baseline demographic and clinical characteristics of each group are shown in table 1. Patient groups were well matched at baseline and no significant between-group differences were seen.

Functional outcomes

After one month of treatment, patients receiving sodium hyaluronate had a significantly faster mucous ciliary

Table 1 - Patient baseline demographic and clinical characteristics

	Sodium hyaluronate (n = 19)	Control (n = 17)	P value
Age, mean \pm SD - years	47 \pm 14	47 \pm 14	0.775
Male sex - no. (%)	8 (42.1)	8 (47.1)	1.0
Familiar atopy - no. (%)	7 (36.8)	7 (41.2)	1.0
Allergy - no. (%)			1.0
None	12 (63.2)	12 (70.6)	
DM	2 (10.5)	1 (5.9)	
P	2 (10.5)	2 (11.8)	
DM+ P	3 (15.8)	2 (11.8)	
Asthma - no. (%)	4 (21.1)	4 (23.5)	1.0
Aspirin allergy - no. (%)	2 (10.5)	2 (11.8)	1.0
Previous surgery - no. (%)			1.0
None	13 (68.4)	13 (76.5)	
FESS	1 (5.3)	0	
Traditional	4 (21.1)	4 (23.5)	
Recurrence - median (IQR)	0 (0, 1)	0 (0, 0)	0.601

DM = dust mites; FESS = functional endoscopic sinus surgery; IQR = interquartile range; P = pollen; SD = standard deviation.

transport time than those in the control arm. The mean time of mucous ciliary clearance was 14.3 ± 2.5 minutes in sodium hyaluronate recipients compared with 23.6 ± 3.3 minutes in those receiving saline ($p = 0.000$) [table 2]. The relative risk of patients receiving sodium hyaluronate experiencing a faster time of mucous ciliary clearance was 4.25 (table 2).

Clinical outcomes

Patients treated with sodium hyaluronate experienced a significantly lower incidence of rhinorrhea and less nasal obstruction than saline recipients 1 month after surgery (table 2). Four (21%) patients receiving sodium hyaluronate and 10 (59%) control subjects experienced rhinorrhea at 1 month ($p = 0.039$). After 1 months' treatment, the median nasal obstruction score was 2 (IQR 0,2) in patients receiving sodium hyaluronate and 3 (IQR 2,4) in control subjects (RR 1.92; 95% CI 1.04, 3.54; $p = 0.023$).

No other significant differences in clinical endpoints were observed.

Endoscopic outcomes

A significantly lower incidence of exudate was seen in sodium hyaluronate recipients at 1 month compared with control. The median endoscopic rating scale was 0 (IQR 0,1) in patients receiving sodium hyaluronate and 4 (IQR 1,4) in control subjects at 1 month after surgery (RR 9.84; 95% CI 1.41,68.47; $p = 0.000$) [table 2].

Tolerability

Sodium hyaluronate was significantly better tolerated than saline in patients undergoing FESS. When asked to make a judgment concerning the tolerability of treatment, the median score for the active treatment group was 3 (IQR 2,3) compared with 2 for the control group (IQR 1,2) [$p = 0.000$].

Discussion

The present study shows that the administration of nebulized sodium hyaluronate for one month after FESS to treat nasal polyps is associated with lower mucociliary clearance time, and improved clinical and endoscopic endpoints. To the best of our knowledge, this is the first report of a pharmacological agent enhancing the recovery of mucociliary clearance time following FESS in a controlled study.

While postoperative care following FESS is accepted as being important to prevent recurrences (3), it varies widely between centers and its effect on outcomes is poorly documented (7-9). Cote and Wright showed that triamcinolone-impregnated nasal packing significantly improved sinonasal cavity findings at 6 months compared with saline-soaked packing (23). Dissolvable carboxymethyl cellulose foam with (24) or without (25) triamcinolone has been shown to reduce postoperative bleeding and scar formation and improve endoscopic findings and symp-

Table 2 – Functional, clinical, and endoscopic outcomes at 1 month compared with baseline.

Outcome	Sodium hyaluronate (n = 19)	Control (n = 17)	Relative risk (95% CI)	P value
Clinical outcomes, no. (%) unless stated otherwise				
Burning	2 (10.5)	6 (35.3)	1.38 (0.94,2.03)	0.114
Dryness	1 (5.3)	5 (29.4)	1.34 (0.97,1.86)	0.081
Nasal obstruction ^a	2 (0,2)	3 (2,4)	1.68 (0.96,2.92)	0.023
Rhinorrhea	4 (21.1)	10 (58.8)	1.92 (1.04,3.54)	0.039
Endoscopic outcome, median (IQR)				
Exudate	0 (0,1)	4 (1,4)	9.84 (1.41,68.47)	0.000
Functional outcome, mean \pm SD				
tTCM	14.3 \pm 2.5	23.6 \pm 3.3	4.25 (1.80,10.01)	0.000

CI = confidence intervals; IQR = interquartile range; SD = standard deviation; tTCM = time to mucous ciliary clearance. a. Median (IQR) score expressed on a visual analogue scale.

toms. In a 5-year study in 109 patients undergoing FESS, 77 of whom had polyposis, Rowe-Jones et al. showed that postoperative administration of fluticasone propionate nasal spray significantly improved symptoms, endoscopic scores, and total nasal volumes, and significantly reduced rescue steroid use compared with placebo (26). Interestingly, patients receiving placebo exhibited greater improvements in nasal mucociliary clearance times than those receiving the corticosteroid (26).

The mucociliary system is the primary nonspecific mechanism that protects the respiratory tract from invasion of inhaled particles and specifically targets particles with a diameter of between 8 and 10 microns (27,28). Once inside the nasal cavity, these particles are deposited onto the nasal sinus cavity mucosa and undergo mucociliary clearance to the back of the nasopharynx and thence to the oropharynx from where they are excreted via the gastrointestinal tract (29). The presence of cytokines and inflammatory mediators in the mucosa neutralizes infective species (30).

In the present study, sodium hyaluronate was associated with significant improvements in mucociliary clearance time compared with saline, suggesting augmentation of the restoration of mucociliary activity after FESS. Sodium hyaluronate also reduced the incidence of rhinorrhea and nasal obstruction, and reduced the appearance of exudate on endoscopy. These results support those of a pilot study in which sodium hyaluronate nasal washes following FESS for rhinosinusal remodeling was associated with improvements in nasal obstruction, the appearance of nasal mucosa and ciliary motility (31).

Conflicting results have been seen when hyaluronic acid packing is used following FESS. In a randomized, controlled study in 66 patients undergoing FESS, hyaluronic acid pack (Merogel[®]) significantly improved synechiae, re-epithelialization and granulation tissue formation compared with standard nasal packing (32). However, no significant benefits, in terms of synechiae, edema or infections, were observed with Merogel[®] in an earlier study (33).

Hyaluron is broken down under the influence of free radicals and enzymes during inflammation into active low molecular weight fragments, which increase ciliary beat frequency. This action is mediated by an increase in calcium ion concentration and by the interaction between the hyaluronic acid fragments and the receptor for hyaluronic acid-mediated motility and receptor of origin nantais present on cilia (10).

Hyaluron appears to play a primary role in the process of

healing and repair of damaged mucosal surfaces. Increased expression of hyaluron has been measured in mucosal ulcers and acts as a ligand for cell adhesion through epithelial CD44 receptors (34). Hyaluron is the first substance to reach and settle in de-epithelialized areas, to which keratinocytes subsequently migrate, under the regulation of CD44 receptors. Moreover, since both CD44 receptors and hyaluron are strongly expressed in the granulation tissue that is being formed, it is possible that the receptors act as ligands for hyaluron in the cellular jambs of the developing cellular granulation tissue, such as macrophages and fibroblasts (10).

This effect has been seen in clinical practice in a study in which a cream containing hyaluronic acid was administered intranasally following nasal surgery (17). Patients receiving the cream experienced significantly faster improvements in respiration, a lower incidence of extensive crust formation and better organoleptic parameters of smell and cooling sensation compared with the control group.

Sodium hyaluronate aerosolized in saline and administered intranasally using the Fluirespira[®] nasal douche device was well tolerated by patients who have undergone FESS.

In conclusion, this study of the effects of intranasal administration of sodium hyaluronate in patient with nasal polyposis undergoing FESS showed improvements in mucociliary clearance time, clinical endpoints and the appearance of the nasal mucosa on endoscopy and provides encouraging data with which to continue the development of sodium hyaluronate in this setting.

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