



ORIGINAL ARTICLE

Nebulized hyaluronic acid and xylitol based solution after turbinate radiofrequency ablation. A triple blind randomized multicentric clinical trial



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Received 21 July 2024; accepted 10 November 2024

KEYWORDS

Turbinate;
Radiofrequency;
Hyaluronic;
Xylitol;
Rhinomanometry

Abstract

Objective: This prospective, triple blind randomized clinical trial aims to specifically evaluate the effect of Aluneb® (hyaluronic acid plus xylitol) in the postoperative treatment of inferior turbinate radiofrequency in adults compared to nebulized isotonic saline.

Methods: Adults undergoing radiofrequency turbinate ablation were included. Treatment group received Aluneb® (hyaluronic acid plus xylitol) while the control group received nebulized isotonic saline for two months after treatment. Participants were studied the week before surgery (visit 0), and at 7, 15, 30 and 60 days after surgery. At all visits, participants underwent physical examination, rhinomanometry, SNOT-22, and visual analogue scale (VAS) of symptoms.

Results: 34 participants were recruited. Crusts (endoscopy) were less in the Aluneb® hyaluronic acid plus xylitol group. Nasal crusting, epistaxis and nasal obstruction VAS were statistically significant lower. VAS for Rhinorrhea, halitosis, cacosmia and pain and nasal resistance obtained lower self-reported values in the hyaluronic acid plus xylitol group, but these differences were not statistically significant.

Conclusions: Hyaluronic acid plus xylitol demonstrated promise in improving postoperative outcomes, future studies with larger sample sizes and different surgical techniques are encouraged.

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<https://doi.org/10.1016/j.otorri.2025.512218>

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PALABRAS CLAVE

Cornete;
Radiofrecuencia;
Hialurónico;
Xilitol;
Rinomanometría

Solución Nebulizada de Ácido Hialurónico y Xilitol después de la Ablación por Radiofrecuencia de los Cornetes. Un Ensayo Clínico Multicéntrico Aleatorizado y Triple Ciego

Resumen

Objetivo: Este ensayo clínico prospectivo, triple ciego y aleatorizado tiene como objetivo evaluar específicamente el efecto de Aluneb® (ácido hialurónico y xilitol) en el tratamiento postoperatorio de la radiofrecuencia de los cornetes inferiores en adultos en comparación con solución salina isotónica nebulizada.

Métodos: Se incluyeron adultos sometidos a ablación por radiofrecuencia de los cornetes. El grupo de tratamiento recibió Aluneb® (ácido hialurónico y xilitol) mientras que el grupo de control recibió solución salina isotónica nebulizada durante dos meses después del tratamiento. Los participantes fueron estudiados la semana antes de la cirugía (visita 0) y a los 7, 15, 30 y 60 días después de la cirugía. En todas las visitas, los participantes se sometieron a un examen físico, rinomanometría, SNOT-22 y una escala visual analógica (EVA) de los síntomas.

Resultados: Se reclutaron 34 participantes. Las costras (endoscopia) fueron menores en el grupo de Aluneb® (ácido hialurónico y xilitol). La costra nasal, la epistaxis y la obstrucción nasal en la EVA fueron significativamente menores. Las EVA para rinorrea, halitosis, cacosmia, dolor y resistencia nasal obtuvieron valores autoinformados más bajos en el grupo de Aluneb, pero estas diferencias no fueron estadísticamente significativas.

Conclusiones: Aluneb® (ácido hialurónico y xilitol) demostró ser prometedor en la mejora de los resultados postoperatorios. Se recomienda la realización de estudios futuros con tamaños de muestra más grandes y diferentes técnicas quirúrgicas.

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Introduction

Nasal Respiratory Insufficiency (NRI) is a common condition, with a 30%–40% prevalence in the general population.¹ The main structure that influences nasal airflow resistance is the inferior turbinate. In fact, studies performing selective decongestion of the inferior turbinate mucosa have shown a 2/3 decrease in nasal resistance.² Nasal turbinates possess a cavernous vascular system surrounded by elastic and muscular tissue that allows them to change size according to congestion or decongestion.³

Certain nasal pathologies cause hypertrophy of this tissue, which leads to NRI and nasal obstruction. Initial treatment of rhinitis consists of medical therapy, mainly with intranasal corticosteroids and antihistamines.⁴ In unresponsive patients, clinical guidelines describe several surgical options on the inferior turbinates, such as radiofrequency, cryosurgery, external fracture, microdebrider-assisted turbinoplasty, excision and submucosal resection or partial turbinectomy.⁵

Although inferior turbinate surgery has been extensively studied and its safety has been well established, it has a high incidence of minor complications, with scabs being the most frequent.⁶ Until now, the most common postoperative treatment is saline lavage. However, in recent years, therapeutic alternatives have emerged with the aim of improving the time and quality of postoperative recovery.

One of the most studied therapeutic alternatives is the nebulized solution of hyaluronic acid. Several authors

have demonstrated improvements related to its use during the postoperative period in terms of quality of life, mucociliary clearance, nasal obstruction, rhinorrhea and nasal dryness.^{7–9} However, most of the scientific evidence comes from studies performed in patients undergoing endoscopic nasal surgery for chronic rhinosinusitis, a surgery with similar intranasal complications, including scabs and nasal secretions, that are usually more severe than turbinate surgery.

Another effective alternative is nasal xylitol, which has a grade A recommendation in the clinical guidelines of the European Rhinological Society (EPOS guidelines).¹⁰ Xylitol has shown potential in treating recurrent respiratory infections when used in nasal lavage¹¹ as well as preventing post-surgical crusting and post-surgical nasal mucosal superinfection following septoplasty and endoscopic sinus surgery.¹²

Aluneb isotónico® is a medical device authorized for postoperative treatment after nasal surgery containing sodium hyaluronate 0.1%, xylitol 5%, potassium phosphate monobasic 0.05%, and potassium phosphate dibasic 0.03%. In Spain and Italy, it is available over the counter and has a very high safety profile according to previous clinical studies with the product.¹³ It is authorized for use in both children and adults. It is applied with the intranasal mucosal atomization device (MAD™) nasal irrigation system that allows nebulization in particles of 30–100 microns in diameter.

This randomized clinical trial aims to specifically evaluate the effect of Aluneb® hyaluronic acid plus xylitol in

the postoperative treatment of inferior turbinate radiofrequency in adults compared to nebulized isotonic saline.

Materials and methods

Study design and setting

A randomized, controlled, triple-blind (researcher, patient, stitician), prospective and randomized clinical trial was conducted. Blinding was interrupted only after completion of the statistical analysis.

Participants were consecutively selected from two Spanish third referral hospitals (Hospital Complex of Santiago de Compostela and Marques de Valdecilla Hospital).

Inclusion criteria included patients > 18 years of age undergoing radiofrequency turbinate ablation. Radiofrequency ablation was considered following the consensus document of the Spanish Society of Otorhinolaryngology and the Spanish Society of Allergology and Immunology.⁵ According to this document, surgery is offered to patients with hypertrophic rhinitis resistant to 3 months of maximum dose of intranasal corticosteroid spray. In addition, a Nasal Obstruction Symptom Evaluation (NOSE) questionnaire greater than 10, an improvement in the nasal decongestion test¹⁴ and the presence of inferior turbinate hypertrophy > III in the Camacho classification¹⁵ were required.

Exclusion criteria included patients with contraindication for the use of Aluneb[®] hyaluronic acid plus xilitol according to the package leaflet (not with ultrasound devices; pregnancy or breastfeeding; allergy to any of the components). Other exclusion criteria were the existence of contraindication for the use of nasal decongestants, the presence of other causes of nasal obstruction, including adenoid hypertrophy (Cassano III-IV)¹⁶ and obstructive septal deviation (Mariño II),¹⁷ and the existence of other concomitant surgeries (septoplasty, adenoidectomy, endoscopic sinus surgery) that could alter the variables under study.

Sample size calculation and aleatorization

Required sample size was calculated for independent means comparison. A maximum alpha error of 0.05 and 0.80 power was assumed. Bilateral comparison, minimal difference to be detected in nasal endoscopy examination and estimated sigma of 1. The estimated sample size was 34 participants, 17 per group.

The randomization followed consisted of a simple balanced randomization (1:1) system utilizing the Mersenne's Twister before the selection process. Participants were included sequentially.

Intervention

All participants were submitted to inferior turbinate radiofrequency ablation. Inferior turbinate radiofrequency was carried out using Celon radiofrequency (Olympus, Japan) in both centers.

Treatment group received Aluneb isotónico[®] (Sakura Italy, Srl) while the control group received nebulized isotonic saline (same formulation as Aluneb Isotónico but without

the active ingredients Hyaluronic acid and Xylitol). Both groups used the MAD atomizer device to nebulize either the treatment or the saline. Neither the patients nor the physician were aware which treatment they were assigned to. To ensure this blinding, the treatment and saline were prepared and labeled in the same manner, making indistinguishable from one to another. The sealed randomization codes for each patient were kept in the investigation site file and in the pharmacovigilance/Health Products Surveillance department of Laboratorios Cinfa, S.A (products supplier). At no point the medical product provider knew the identity of the study participants.

Both groups were instructed to apply the treatment/saline starting the day after the surgical intervention for one month, one vial per nostril both morning and evening. Subsequently, they would apply the product in the same manner for two months, with an interval of 15 days of break and another of treatment.

Outcome variables

Participants were studied the week before surgery (visit 0), and at 7, 15, 30 and 60 days after surgery (visit 1,2,3 and 4 respectively). At all visits, participants underwent physical examination, rhinomanometry, SNOT-22, and visual analogue scale (VAS) of symptoms.

The main outcome was nasal crusts and nasal symptoms assessed through VAS scores. The secondary outcomes were quality of life (SNOT-22), nasal resistance, and safety.

Physical examination

A direct examination by nasofibroscope was performed in all patients, in both Hospitals using Olympus CV 170 digital/distal chip (Olympus, Japan). Videos of each nostril at each visit were recorded and blind examination was performed by a researcher blinded to the treatment group and the time elapsed after surgery. Recordings ensured a minimum length of 10 s with visualization of the entire nostril, the head of the inferior turbinate and the nasal floor so that they could be assessed. In each video crusts were scored as follows: 0: no crust; 1: non-obstructive crust attached to the inferior turbinate; 2: obstructive crusts < 50% of the space between inferior turbinate and nasal septum or nasal floor; 3: >50% of the space between inferior turbinate and nasal septum or nasal floor; 4: obstructive crust in contact with the nasal septum or floor.

SNOT-22 and VAS

The SNOT-22 Spanish version was used.¹⁹ This questionnaire includes 22 items that can be scored from 0 to 5. The sum of the 22 items were included in the results.

Participants filled in a VAS score ranging from 0 (minimum) to 10 (maximum) for 6 symptoms: nasal crusting, rhinorrhea, halitosis, epistaxis, pain and cacosmia. Overall quality of life was also assessed using VAS score with 10 being better and 0 being worse.

Rhinomanometry

The recommendations of the international Rhinomanometry Standardization Committee were followed.¹⁵ Rhinomanometry was performed after 30 min of acclimatization, in a room where humidity was constant and temperature was controlled with a thermostat. Airflow and nasal resistance values were registered using a 4-phase rhinomanometer (Rhinosys, Otopront. Hohenstein-Germany and NR6, Optomic. Madrid-Spain) as recommended by the RIGA consensus.¹⁸

Both devices were calibrated and offered similar values. The resistance limit was set at 30 Pa/mL s⁻¹.

Statistical analysis

The trial is reported following the Consolidated Standards of Reporting Trials statement (CONSORT).²⁰

Statistical analysis was performed by a blinded investigator with Stata 15.1 for Mac (StataCorp, Texas-USA). The significance level was established at $P < .05$ for each statistical test performed in this study. Normal distribution of the quantitative variables were assessed with Shapiro-Wilk test. Comparison between groups and a dichotomous variable was performed with Chi square test. Comparison of continuous quantitative variables with Student's t -test or Mann-Whitney U test variant. Comparison of discrete quantitative variables were performed with Mann-Whitney U test.

Comparison between quantitative variables were performed with the Spearman correlation test.

Results

Participants were recruited between October 2020 to June 2023. 3 participants were lost after the randomization; 2 due to COVID infection (1 in the hyaluronic acid plus xylitol group, 1 in the saline group), and 1 did not attend the postoperative revision (hyaluronic acid plus xylitol group). These patients were excluded and replaced with new participants.

Sample

Thirty-four participants were recruited, 17 per group. There were 19 males and 15 females and the overall mean age was 37.36 years. 30 were from Santiago de Compostela Hospital Complex, and 4 from Marques de Valdecilla Hospital.

Both groups were comparable in all assessed variables before treatment (Table 1), there were neither differences according to the Hospital group.

Blind endoscopic scabs

Crusts assessed by blinded endoscopy are summarized in Table 2. Both groups showed increased crusting after surgery, but less in the hyaluronic acid plus xylitol group, being this difference statistically significant at 2 weeks and 1 month. At 2 months, hyaluronic acid plus xylitol group had less scabbing compared to baseline values, while the saline group still had increased crusting, being this difference statistically significant.

Nasal resistance

Nasal resistance is summarized in Table 3, which shows that it was consistently higher in the saline group, although this difference was only statistically significant at 2 weeks. Both groups decreased nasal resistance compared to preoperative values from the first week. At one and two months the difference is slightly better, almost reaching significance ($P = .05$ and $.07$) in the hyaluronic acid plus xylitol group, but below the limit value of 0.30 Pa/mm³ s⁻¹, the normal limit.

Nasal symptoms

All subjective symptoms assessed by VAS are summarized in Table 4. Nasal crusting increased in the first week and progressively decreased in both groups. However, the hyaluronic acid plus xylitol group decreased faster, being this difference statistically significant at 2 weeks, 1 and 2 months.

Epistaxis was also lower in the hyaluronic acid plus xylitol group in the first week, second week and 1 month. Epistaxis was compared to crusting, with Spearman's correlation analysis demonstrating a statistically significant correlation between the two variables (correlation coefficient: 0.50; $P < .001$).

Self-reported nasal obstruction was consistently higher in the saline group, but this difference was only statistically significant at 2 weeks and 2 months. There is a weak but statistically significant correlation (correlation coefficient = 0.28; $P = .002$) between self-reported crusting and nasal obstruction.

Rhinorrea, halitosis, cacosmia and pain obtained lower self-reported values in the hyaluronic acid plus xylitol group compared to saline, but these differences were not statistically significant, only rhinorrhea 1 month and halitosis 1 month.

Discussion

This study has identified better outcomes of hyaluronic plus xylitol nasal nebulization compared to nasal nebulization of saline alone in patients undergoing exclusively turbinate radiofrequency ablation.

There are no other studies conducted exclusively in patients undergoing radiofrequency turbinate ablation. There is one previous RCT by Baptista et al.,²¹ using hyaluronic plus xylitol nasal rinse on septoplasty plus turbinate surgery. There are no other studies exclusively on turbinate surgery patients, so we will compare our results with Baptista et al. RCT as a surrogate.

The primary endpoints were nasal crusts and nasal symptoms. Reduction of crusting is of utmost importance, as we have identified that scabs are closely related to other variables such as epistaxis and self-reported nasal obstruction. In addition, avoiding crusts improves patient satisfaction and quality of life, at the time it reduces postoperative office visits and economic costs. In our study, we found increased crusting during the first 2 weeks as usual, but these scabs were higher in the saline group. Then both groups decreased, but this decrease was greater in the experimental group ($P < .05$). It is remarkable that both groups had

Table 1 Pre-treatment comparison between groups. Bold and asterisk if the difference is statistically significant ($P < .05$). Data as mean (standard deviation).

Pretreatment comparison of both samples			
Variable	Hyaluronic and xilitol group (n = 17)	Saline group (n = 17)	Statistics and P value
Sex (male/female)	58.82/41.18	52.94/47.06	chi2 = 0.12; $P = .730$
Age (year)	37.10 (2.24)	37.62 (3.22)	t = -0.132; $P = .8962$
SNOT-22 (0–110)	44.29 (2.64)	47.76 (3.48)	t = -0.79; $P = .433$
VAS scab (0–10)	1.82 (1.70)	1.76 (1.92)	z = 0.27; $P = .791$
rhinorrhea (VAS 0–10)	5.18 (2.19)	5.12 (3.00)	z = 0.16; $P = .875$
halitosis (VAS 0–10)	3.65 (2.37)	2.06 (1.85)	z = 1.91; $P = .056$
obstruction (VAS 0–10)	8.06 (1.71)	8.29 (1.36)	z = -0.32; $P = .750$
epistaxis (VAS 0–10)	0.94 (1.30)	0.59 (1.12)	z = 1.19; $P = .236$
pain (VAS 0–10)	1.00 (1.32)	1.47 (2.12)	z = -0.37; $P = .714$
cacosmia (VAS 0–10)	1.24 (1.71)	1.47 (1.94)	z = -0.29; $P = .770$
QoL (VAS 0–10)	6.29 (2.26)	6.11 (1.83)	z = 0.61; $P = .540$
Turbinate size (2–8)	5.47 (1.62)	4.94 (2.59)	z = 0.58; $P = .564$
Scab (endoscopy) (0–4)	0.18 (0.39)	0.19 (0.41)	z = 0.01; $P = 1.000$
Nasal resistance (Pa/mm ³ s ⁻¹)	1.48 (0.46)	1.45 (0.52)	t = 0.04; $P = .967$

Table 2 Values 0–4. 0: no crusting/1: no obstructive crusting/2: crust < 50% of the space between inferior turbinate and septum or floor/3: crust > 50% of the space between inferior turbinate and septum or floor/4: complete occlusion of the nasal fossa.

Scabs (blinded endoscopy)			
Variable	Aluneb (n = 17)	Saline (n = 17)	Statistics and P value
Scabs (preop) (0–4)	0.18 (0.39)	0.19 (0.41)	z = 0.01; $P = 1.000$
Scabs 1 week (0–4)	0.82 (0.85)	1.12 (0.88)	z = -1.07; $P = .291$
Scabs 2 weeks (0–4)	1.03 (0.62)	1.76 (1.13)	z = -2.03; $P = .043^*$
Scabs 1 Month (0–4)	0.50 (0.31)	1.29 (0.61)	z = -3.795; $P < .001^*$
Scabs 2 months (0–4)	0.09 (0.20)	0.35 (0.39)	z = -2.27; $P = .023^*$

Table 3 Nasal resistance in rhinomanometry. Bold and asterisk if $P < .05$. Data as mean (standard deviation).

Nasal resistance (Pa/mm ³ s ⁻¹)			
Variable	Hyaluronic and xilitol (n = 17)	Saline (n = 17)	Statistics and P value
Resistance Preop	1.48 (0.46)	1.45 (0.52)	t = 0.04; $P = .967$
Resistance 1 week	0.87 (0.11)	1.18 (0.18)	t = -1.45; $P = .157$
Resistance 2 weeks	0.45 (0.06)	0.75 (0.11)	t = -2.29; $P = .029^*$
Resistance 1 month	0.36 (0.05)	0.55 (0.08)	t = -2.00; $P = .054$
Resistance 2 months	0.27 (0.03)	0.36 (0.04)	t = -1.91; $P = .065$

scabs before surgery, as all the included patients had severe rhinitis. However, after two months of follow-up, the experimental group had less scabbing than before surgery.

The mechanism by which Aluneb[®] hyaluronic acid plus xilitol may have decreased nasal scabs has been widely discussed and reported in literature. Hyaluronic acid improves mucosal healing, moisturizes the area, and increases mucociliary clearance,⁸ while xylitol acts as a bacteriostatic agent.

Regarding the secondary endpoint, SNOT-22 experienced an overall decrease in the SNOT-22 in both groups, being lower (4–7 points) at all the postoperative visits in the

experimental group, although this difference was not statistically significant. It is also noteworthy that, despite the improvement, neither group reached the normal SNOT-22 value (12 points). Of note is the high baseline SNOT-22 over 40 points in both groups, which is defined as a high value by the EPOS guidelines. This initial value is notably higher than Baptista et al.²¹ cohorts (29 and 25), but does not differ from other allergic rhinitis cohorts reported in other studies.²²

Regarding nasal symptoms assessed through visual analogue scales, there were statistically significant better results for crusts, epistaxis, nasal obstruction and rhinorrhea. Also better results were observed for cacosmia and

Table 4 Visual analogue scale (VAS). Bold and asterisk if $P < .05$. Data as mean (standard deviation). All the variables range from 0 to 10.

Variable	Hyaluronic and xilitol (n = 17)	Saline (n = 17)	Statistics and P value
Nasal scabs (VAS)			
Scab preop	1.82 (1.70)	1.76 (1.92)	$z = 0.27; P = .791$
Scab 1 week	5.29 (2.95)	6.76 (2.31)	$z = -1.34; P = .181$
Scab 2 weeks	4.53 (1.66)	6.35 (2.55)	$z = -2.45; P = .014^*$
Scab 1 Month	2.29 (2.08)	4.24 (1.64)	$z = -3.46; P < .001^*$
Scab 2 months	1.12 (2.29)	1.41(1.06)	$z = -2.20; P = .028^*$
Epistaxis (VAS)			
Epistaxis (preop)	0.94 (1.30)	0.59 (1.12)	$z = 1.19; P = .236$
Epistaxis 1 week	1.71 (1.72)	3.59 (3.02)	$z = -2.13; P = .033^*$
Epistaxis 2 weeks	0.94 (2.01)	1.82 (2.07)	$z = -2.04; P = .041^*$
Epistaxis 1 Month	0.47 (1.18)	0.76 (0.75)	$z = -2.03; P = .043^*$
Epistaxis 2 months	0.24 (0.44)	0.29 (0.47)	$z = -0.38; P = .702$
Nasal obstruction (VAS)			
Obstruction (preop)	8.06 (1.71)	8.29 (1.36)	$z = -0.32; P = .750$
Obstruction 1 week	7.65 (2.37)	8.18 (1.88)	$z = -0.60; P = .592$
Obstruction 2 weeks	3.47 (2.60)	5.35 (2.12)	$z = -2.50; P = .012^*$
Obstruction 1 Month	2.29 (2.47)	4 (2.78)	$z = -1.78; P = .075$
Obstruction 2 months	1.59 (1.87)	3.59 (2.03)	$z = -2.69; P = .007^*$
Rhinorrhea (VAS)			
Rhinorrhea (preop)	5.18 (2.19)	5.12 (3.00)	$z = 0.16; P = .875$
Rhinorrhea 1 week	5.12 (2.09)	6.29 (2.37)	$z = -1.51; P = .132$
Rhinorrhea 2 weeks	4.71 (2.89)	5.29 (2.08)	$z = -0.54; P = .590$
Rhinorrhea 1 Month	2.18 (2.13)	4.06 (1.85)	$z = -2.55; P = .011^*$
Rhinorrhea 2 months	2.12 (2.09)	3.06 (2.33)	$z = -1.14; P = .255$
Halitosis (VAS)			
Halitosis (preop)	3.65 (2.37)	2.06 (1.85)	$z = 1.91; P = .056$
Halitosis 1 week	4.23 (2.31)	4.53 (1.91)	$z = -0.28; P = .780$
Halitosis 2 weeks	3.59 (1.37)	4.12 (2.37)	$z = -0.74; P = .461$
Halitosis 1 Month	1.94 (1.95)	2.88 (1.27)	$z = -2.50; P = .013^*$
Halitosis 2 months	2.06 (1.98)	2.59 (1.42)	$z = -1.25; P = .211$
Cacosmia (VAS)			
Cacosmia (preop)	1.24 (1.71)	1.47 (1.94)	$z = -0.29; P = .770$
Cacosmia 1 week	2.12 (1.90)	2.41 (1.94)	$z = -0.85; P = .396$
Cacosmia 2 weeks	3.35 (2.52)	4.00 (3.26)	$z = -0.65; P = .518$
Cacosmia 1 Month	1.24 (2.08)	2.53 (2.70)	$z = -1.87; P = .061$
Cacosmia 2 months	0.88 (1.93)	0.76 (1.68)	$z = 0.14; P = .890$
Pain (VAS)			
Pain (preop)	1.00 (1.32)	1.47 (2.12)	$z = -0.37; P = .714$
Pain 1 week	1.88 (2.09)	2.94 (2.44)	$z = -1.67; P = .094$
Pain 2 weeks	1.06 (1.30)	2.06 (1.78)	$z = -1.81; P = .071$
Pain 1 Month	1.59 (1.80)	1.29 (1.57)	$z = 0.64; P = .520$
Pain 2 months	1.00 (0.87)	1.47 (1.70)	$z = -0.69; P = .492$
QoL (VAS)			
QoL (preop)	6.29 (2.26)	6.12 (1.83)	$z = 0.61; P = .540$
QoL 1 week	5.24 (1.44)	4.82 (1.78)	$z = 0.64; P = .526$
QoL 2 weeks	6.65 (1.46)	5.94 (1.75)	$z = 1.19; P = .234$
QoL 1 Month	7.24 (1.82)	6.06 (1.92)	$z = 1.54; P = .124$
QoL 2 months	8.24 (1.30)	7.41 (1.87)	$z = 1.44; P = .151$
SNOT-22			
SNOT-22 (preop)	44.29 (10.90)	47.76 (14.33)	$z = -0.59; P = .557$
SNOT-22 1 week	39.00 (11.16)	42.18 (13.22)	$z = -0.64; P = .524$
SNOT-22 2 weeks	24.82 (6.93)	28.94 (11.91)	$z = -0.79; P = .427$
SNOT-22 1 Month	20.65 (6.59)	25.82 (9.73)	$z = -1.33; P = .184$
SNOT-22 2 months	17.65 (6.23)	23.35 (10.15)	$z = -1.73; P = .084$

pain but not being statistically significant. The effect on epistaxis was the most remarkable. The experimental group decreased the epistaxis VAS from the first week after the intervention. Interestingly, there was a significant correlation between crusts and epistaxis, independently of the treatment group since, as mentioned, less scabs, could probably have decreased epistaxis.

However, epistaxis can also be attributed to infection. Both xylitol and hyaluronic acid can exert bactericidal and anti-adhesive effects. Hyaluronic acid can exert in vitro anti-infective and anti-biofilm effects by preventing bacterial adhesion.²³ On the other hand, Xylitol is a natural five-carbon sugar alcohol that is commonly used as a sweetener agent and has recently shown potential in treatment of recurrent respiratory infections when used in nasal washes thanks to its innate bactericidal and anti-adhesive effects. Lysozyme, lactoferrin, and β -defensins on the surface of the respiratory tract constitute a part of the local defense system. These have stronger antibacterial activity at low salt concentrations and xylitol is an osmolyte that has a low transepithelial permeability which can reduce the salt concentration to enhance the ability of the airway surface of the nasal mucosa to clear respiratory pathogens.¹¹

Finally, the last secondary endpoint was nasal resistance assessed by rhinomanometry. Nasal resistance was lower in the hyaluronic acid plus xilitol group, but these differences were not statistically significant and probably a larger sample size would have been necessary to detect differences, as this study was underpowered for this variable.

The strengths of this study are, first, the triple blind design. Second, the scab examinations were blinded to the symptoms referred by patients. And third, we could identify differences despite the small sample size.

However, this study may have some limitations and confounding factors that are important to emphasize.

First, surgery was performed by different surgeons. Despite the device being the same, different surgeons may deliver different amounts of energy to the inferior turbinate, which may affect the amount of scar tissue.

Second, sample was expected to be recruited in 6 months. However, we experienced difficulties in including participants, as most people, although willing to collaborate, could not attend all follow-up visits or were afraid to cooperate given the COVID-19 pandemic. Therefore, the recruiting process was extended to 32 months.

The third concern is the atomizer device, which may exert itself a positive effect on recovery. Moffa et al.²⁴ compared different nasal administration devices using a color-based method to determine which device was most effective in topical medication delivery. MAD atomizer provided a more effective way to deliver local drugs deeper and higher in the nasal cavity. In our case, both groups used the MAD atomizer, so the difference cannot be attributed to the method of drug delivery.

Fourth, treatment of the saline group, that was the comparator in our study, may be of concern. Saline nasal rinses are recommended in the EPOS guidelines,¹⁰ yet, the quantity is not defined in this guideline. EPOS guidelines state that, up to date, there is not enough evidence to affirm that large-volume rinses are better than low-volume. Being strict, the saline group should not be considered as placebo, since they were receiving the standard of care. In fact, Bap-

tista et al. reported an improvement also in the saline group using MAD nebulizer, which supports that it should indeed not be considered placebo.

Fifth, allergic rhinitis may act as a confounding factor since allergic rhinitis itself improves after hyaluronic acid nebulization.²⁵ In our cohort, allergies were not systematically assessed. It is possible that the prevalence of allergies differed between the experimental and control groups. In such a scenario, given that hyaluronic acid plus xilitol nasal washes also improves allergic rhinitis, participants may have experienced relief from their nasal symptoms not only due to improved surgical healing but also due to the alleviation of allergic rhinitis.

Conclusions

hyaluronic acid plus xilitol demonstrated a significant reduction in nasal crusts, linked to other variables like epistaxis and self-reported nasal obstruction. The VAS scores for epistaxis, nasal obstruction, and rhinorrhea were also significantly improved in the hyaluronic acid plus xilitol group. Nasal resistance was lower in the hyaluronic acid plus xilitol group, although statistical significance was not reached, likely due to the study's limited power for this variable. Hyaluronic acid plus xilitol demonstrated promise in improving postoperative outcomes, future studies with larger sample sizes and different surgical techniques are encouraged.

CRedit authorship contribution statement

CCH (design, sample assessment, writing); AGLL (design, writing); BMA (design, sample assessment, writing); MRI (design, sample assessment, writing); DLD (design, sample assessment, writing); JMS (design, writing); SSG (design, sample assessment, critical review of the manuscript); IA (design, sample assessment, critical review of the manuscript).

Ethical consideration

The study was approved by the ethics committee of Santiago de Compostela (code 2020/389) and was performed in accordance with the ethical standards of the Declaration of Helsinki. All patients signed their informed consent before participating in the study.

Funding

Laboratorios Cinfa provided the blinded ampules of the treatment and control group. None of the authors received payment for conducting the study. This study did not receive any grants or external funding.

Declaration of competing interest

C. Calvo-Henriquez has received honoraria for consultancy and conferences from Sanofi, Astrazeneca, GSK, MSD, Cinfa, Forwardontics. García-Lliberós has received honoraria for consultancy and conferences from Sanofi, Astrazeneca and

GSK. J. Maza-Solano has received honoraria for consultancy and conferences from Sanofi, Astrazeneca, GSK, Faes Farma. I. Alobid has received honoraria for consultancy and conferences from Viatrix, Roche, Sanofi, GSK, MSD, Menarini, Salvat, and Novartis. Other co-authors do not report conflicts of interest.

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