CAMBRIDGE JOURNALS

Proof Delivery Form

Journal of Laryngology & Otology

Date of delivery: 22.02.2019

Journal and vol/article ref: jlo 18598(JLO1900044)

Number of pages (not including this page): 9

This proof is sent to you on behalf of Cambridge University Press.

Authors are strongly advised to read these proofs thoroughly because any errors missed may appear in the final published paper. This will be your ONLY chance to correct your proof. Once published, either online or in print, no further changes can be made.

Please return this proof within 2 working days

Dear contributor

Attached is a proof of the article you have written for publication in the **Journal of Laryngology & Otology** and is sent to you on behalf of Cambridge University Press.

If you wish to make corrections to your article, you can mark up the proof on screen using the freely available Adobe Reader software.

To mark up proofs electronically. Using your cursor select the text for correction and use the most appropriate tool (i.e. 'Replace', 'Cross out', 'Insert' or 'Add note to text') to note your correction.

Alternatively, you can print a copy of your proof, mark up your corrections with a black or blue pen and then scan it.

Please email your corrections to cambridgeproduction@novatechset.com
for the attention of Kalaivani Deveraj

Please do not provide corrections in your email message or in an attached document. Only corrections marked on the provided proof will be made to your article.

Your corrections (subject to journal style requirements) and those of an independent proof reader will be made to your article. Due to publication deadlines, you will not be sent a revised proof. Therefore, it is extremely important that any corrections are marked clearly.

If you have no corrections to make, please email cambridgeproduction@novatechset.com.

Copyright: if you have not already done so, please download a copyright form from:
http://journals.cambridge.org/images/fileUpload/documents/JLO_ctf.pdf

Please sign the form by hand and return by mail to the address shown on the form. Failure to send this form will delay the publication of your article.

CAMBRIDGE JOURNALS

Proof Delivery Form

Journal of Laryngology & Otology

Please note:

• The proof is sent to you for correction of typographical errors only. Revision of the substance of the text is not permitted, unless discussed with the editor of the journal. Only **one** set of corrections are permitted.

• Please answer carefully any author queries.

• Corrections which do NOT follow journal style will not be accepted.

• A new copy of a figure must be provided if correction of anything other than a typographical error introduced by the typesetter is required.

• If you have problems with the file please contact **jloproduction@cambridge.org**

Please note that this pdf is for proof checking purposes only. It should not be distributed to third parties and may not represent the final published version.

Important: you must return any forms included with your proof**.**

Please do not reply to this email

NOTE - for further information about **Journals Production** please consult our **FAQs** at http://journals.cambridge.org/production_faqs

Author Queries

Journal: JLO (The Journal of Laryngology & Otology)

Manuscript: S0022215119000446jra

Q1 The distinction between surnames can be ambiguous, therefore to ensure accurate tagging for indexing purposes online (eg for PubMed entries), please check that the highlighted surnames have been correctly identified, that all names are in the correct order and spelt correctly.

Q2 Acceptable/correct to change 'grade of recommendation A[1]' to 'grade 1A strength of recommendation'?

Q3 Note that citation number 18 has been changed to 19, as per references.

Q4 Note that references 20 and 21 have been swapped around so that the citation numbers are in numerical order.

Q5 The tables have been amended slightly, in line with JLO style – please check contents and footnotes.

Q6 Note that Figure 1 has been rekeyed for editing purposes; please check contents.

The Journal of Laryngology & Otology

cambridge.org/jlo

Double-blind, randomised controlled trial on the efficacy of saline nasal irrigation with sodium hyaluronate after endoscopic sinus surgery

F Mozzanica[1], A Preti[1,2], R Gera[1], C Bulgheroni[3], A Cardella[1], A Albera[1], F Collurà[1], N Mevio[4], A Dragonetti[4], A Schindler[5], U Milanesi[3] and F Ottaviani[1]

[1]Department of Clinical Sciences and Community Health, San Giuseppe Hospital, IRCCS Multimedica, University of Milan, [2]Department of Biotechnology and Life Sciences, University of Insubria, Varese, [3]Department of Otolaryngology, Desio Hospital, Monza, [4]Department of Otolaryngology, Niguarda Hospital, Milan and [5]Department of Biochemical and Clinical Sciences, Sacco Hospital, University of Milan, Italy

Main Article

Dr A Preti takes responsibility for the integrity of the content of the paper

Cite this article: Mozzanica F *et al*. Double-blind, randomised controlled trial on the efficacy of saline nasal irrigation with sodium hyaluronate after endoscopic sinus surgery. *J Laryngol Otol* 2019;1–9. https://doi.org/10.1017/S0022215119000446

Accepted: 4 December 2018

Key words:
Sinusitis; Surgery; Nose; Sodium Hyaluronate

Author for correspondence:
Dr Andrea Preti,
Department of Clinical Sciences and Community Health, Ospedale San Giuseppe, IRCCS Multimedica,
University of Milan,
Milan, Italy
E-mail: andrea.preti87@gmail.com
Fax: +39 0285 994 472

Abstract

Objective. There is a growing interest in sodium hyaluronate for the clinical management of patients who undergo functional endoscopic sinus surgery for chronic rhinosinusitis, because of the mucosal regenerative properties of this macromolecule. However, its role in post-operative care is still debated. This study aimed to evaluate the effect of sodium hyaluronate administered via nasal irrigation with saline, in the post-operative period, after functional endoscopic sinus surgery.

Methods. A multicentric, prospective, randomised, double-blind, parallel group study was conducted on 56 consecutive patients who underwent functional endoscopic sinus surgery for chronic rhinosinusitis without polyps. Group 1 received the standard therapy of normal saline; group 2 received saline plus sodium hyaluronate.

Results. Both objective and subjective measurements, in terms of endoscopic appearance and patient-reported satisfaction, were significantly better in group 2 compared to group 1.

Conclusion. Sodium hyaluronate may be a useful adjunct to nasal saline irrigation in the early post-operative period following functional endoscopic sinus surgery.

Introduction

Chronic rhinosinusitis is a common medical condition affecting up to 15 per cent of the Western population.[1] Chronic rhinosinusitis has a profound influence on the quality of life (QoL) of affected people because of nasal obstruction, impaired olfaction, fatigue, social dysfunction and emotional manifestations. Medical treatment for chronic rhinosinusitis can greatly improve symptoms and QoL.[2] However, in cases of medical treatment failure, functional endoscopic sinus surgery (FESS) represents a valuable alternative. The latter should not be considered as the only treatment, but rather as an adjuvant modality to remove the disease burden and increase the efficacy of post-operative medical therapy.[1] In fact, FESS improves the drainage of the nasal sinuses and the delivery of topical medication after surgery.[3]

Given the above, it is not surprising that post-operative management plays a pivotal role in the treatment of chronic rhinosinusitis. In particular, nasal irrigation represents a key element in the post-operative period following FESS (grade 1A strength of recommendation). Specifically, nasal irrigation has been demonstrated to promote cleansing of the nasal cavities, enhance wound healing, and reduce oedema and nasal discharge after surgery.[2,4] A variety of nasal irrigation solutions are available. These differ in terms of their composition (e.g. seawater, hypertonic, isotonic saline with or without additives), and the choice of solution will depend on the irrigation technique used (variations in pressure and/or volume).

As far as the irrigation technique is concerned, multiple studies have confirmed the benefit of high-volume, low-pressure douching over other methods of delivery.[2,3,5] In addition, Harvey *et al.*[3] investigated the paranasal sinus distribution of topical solutions following FESS in 10 cadavers. They reported that high-volume, low-pressure, gravity-dependent devices offer better delivery of solution in the paranasal sinuses than other methods.

However, information regarding the best solution composition for nasal irrigation after FESS is scarce and divergent,[6,7] and only few randomised controlled trials have been developed so far.[8–11] Freeman *et al.*[8] analysed the presence of adhesions, polyps, crusting, discharge and oedema post-operatively in a group of 22 patients who had only 1 nasal cavity irrigated with 2 ml of sterile saline via a mucosal atomisation device. The authors concluded that nasal saline douching improved the presence of discharge and oedema, but had no effect on adhesions or crusting. Low *et al.*[2] compared the efficacy of normal

saline, lactated Ringer's solution and hypertonic saline for nasal irrigation after FESS, administered via a squeeze bottle. They concluded that nasal irrigation with lactated Ringer's solution provides better results. Gelardi *et al.*[9] compared the effects of intranasal sodium hyaluronate and saline irrigation after FESS, and reported that sodium hyaluronate provided better results in terms of mucociliary clearance. Macchi *et al.*[10] reported that three-month intermittent treatment with nasal washes using 9 mg sodium hyaluronate plus saline solution after FESS was associated with significant improvements in nasal dyspnoea, nasal mucosa appearance on endoscopy and ciliary motility, compared to saline alone. Finally, Fong *et al.*[11] concluded, in a recent systematic review, that sodium hyaluronate appears to be clinically safe and well tolerated, and may be useful in the early stages after sinus surgery to limit adhesion rate, even if provided in different preparations.

The growing interest for sodium hyaluronate in the clinical management of patients who have undergone FESS is related to the mucosal regenerative properties of this macromolecule. Sodium hyaluronate, in fact, improves mucosal stability, lubrication, water homeostasis and molecule filtering, and promotes modifications in cell behaviour (such as anti-inflammatory modulation), because of its binding mechanisms and architectural configuration within the connective tissue.[11,12]

However, because of the variability in sodium hyaluronate preparations analysed so far (absorbable and non-absorbable dressings, and topical preparations such as cream, spray and nebulised ampules),[11] the role of sodium hyaluronate in the post-operative care of patients who have undergone FESS for chronic rhinosinusitis is still a matter of debate. In particular, no information is available regarding the effect of sodium hyaluronate administered via nasal irrigation with saline, using a high-volume gravity-dependent device (which can be considered one of the best irrigation techniques[3]).

A multicentric, randomised controlled trial was developed to gather information regarding the effects of sodium hyaluronate provided via nasal irrigation with saline on chronic rhinosinusitis patients post-FESS. In particular, the project aimed to compare the clinical effects of nasal irrigation with isotonic saline (0.9 per cent) versus nasal irrigation with isotonic saline plus sodium hyaluronate (9 mg) in patients who had undergone FESS. The study hypothesis was that normal saline plus sodium hyaluronate would provide better results with respect to objective and subjective evaluations than normal saline alone following FESS. A deeper understanding of the effects of sodium hyaluronate after FESS would help clinicians in the post-operative care of patients who have undergone FESS for chronic rhinosinusitis.

Materials and methods

The study was carried out according to the declaration of Helsinki, and was previously approved by the Institutional Review Boards of the enrolled hospitals. The research entailed a multicentric, prospective, randomised, double-blind, parallel group study, in which normal saline (standard therapy) was compared with normal saline plus sodium hyaluronate. All patients gave their written informed consent to participate in the study.

Participants

Fifty-six consecutive patients (28 females and 28 males) who underwent FESS for chronic rhinosinusitis without polyps were enrolled in the study. The mean age of the cohort was 43.8 ± 17.7 years (range, 11–75 years).

Inclusion criteria were: age over 18 years; diagnosis of bilateral chronic rhinosinusitis without polyps, as confirmed by endoscopy and computed tomography (CT); patients undergoing bilateral FESS as primary procedure for chronic rhinosinusitis without polyps not respondent to medical therapy; and a good understanding of written and spoken Italian.

Exclusion criteria were: previous trauma; congenital abnormalities of facial growth; systemic granulomatous disease; known mucociliary clearance disorders; known head and neck malignancies or a history of previous radiotherapy to the head and neck; any other nasal surgery performed concomitantly; and an inability to give informed consent because of mental impairment. In addition, patients who underwent surgery for conditions other than chronic rhinosinusitis without polyps, or who underwent revision, unilateral or anterior (only middle meatal antrostomy and/or anterior ethmoidectomy) FESS, were also excluded.

All patients had undergone bilateral FESS, involving conservative mucosa-sparing antrostomy, and anteroposterior ethmoidectomy with preservation of the middle turbinate. Frontal and sphenoid sinuses were drained when needed. The patients underwent the sinus surgery in three different, high-volume rhinological centres, between December 2017 and March 2018. All surgical procedures were performed by three experienced surgeons (one for each centre, all with 10 years or more of FESS experience). These surgeons were blind to the douching solution used by the patients and were not involved in the post-operative evaluation of the patients.

Nasal douching

Douching was performed using a high-volume, 250 ml, low-pressure, gravity-dependent device. A member of the secretarial staff assigned 70 numbers to either a douching solution comprising normal saline alone (Nasir Isotonic; EP Medica, Fusignano, Italy) or a solution comprising normal saline plus 9 mg of high molecular weight sodium hyaluronate (Nasir Plus; EP Medica), using simple randomisation. Numbers from 1 to 70 were randomly assigned to the recruited patients using a randomised, computer-generated table held by secretarial staff. Similar to the study of Freeman *et al.*,[8] ward staff telephoned the secretarial staff following surgery and allocated patients consecutively. Randomisation was performed independently for each centre.

At discharge, participants were given both written advice and a practical demonstration on how to carry out nasal douching. In particular, patients were advised to irrigate their nasal cavities twice a day for six weeks after surgery. Nasal irrigation solutions were provided by nursing staff on the day of surgery, using numbered boxes containing unmarked sacks of the same douching solution. Surgeons and patients were blind to the treatment allocation.

Compliance to the assigned treatment was evaluated by counting the amount of dispensed and returned sacks. The post-operative care of the patients was the same in the three centres. Nasal packing was maintained for 2 days; no oral antibiotics or oral steroids were prescribed. Post-operative follow up was performed at three and six weeks after surgery. During these visits, routine nasal toileting was kept to a bare minimum, so as not to influence the effectiveness of the nasal douching.

Nasal assessment

Each patient was evaluated before surgery, and at three and six weeks after surgery, using a set of objective and subjective (self-assessed) measurements. Pre-operative evaluation was performed the day before the surgical procedure, while post-operative assessments were carried out during the follow-up visits, before the application of any topical local anaesthetic.

For the objective evaluation, the Lund–Mackay radiological scoring system and Lund–Kennedy endoscopic scoring system were used.[13,14] The latter rates each sinonasal area on the basis of the degree of scarring, crusting, oedema, polyps and discharge. The total possible score is 20. The former consists of six items, with a total score ranging from 0 to 24, with higher scores representing worse radiological appearance of the sinonasal cavities. Both Lund–Mackay and Lund–Kennedy scores were assessed jointly by the two senior authors at the conclusion of the study, using digital videos recorded during the clinical evaluation (for the Lund–Kennedy scoring system) and the pre-operative CT scans of the paranasal sinuses (for the Lund–Mackay scoring system). All CT scans were performed on high-speed spiral CT scanners using non-contrast, axial, 1.5 mm sections. The morphological evaluation was performed on high-resolution coronal and sagittal sections, using a specialised computer software picture archiving and communication system ('PACS').[15] The investigators who performed the objective evaluation were blind to the douching solution used by the patients and were not involved in the surgical procedures.

For the subjective evaluation, the Italian versions of the Sino-Nasal Outcome Test 22 (SNOT-22)[16] and of the Nose Obstruction Symptom Evaluation ('NOSE') scale[17] were used. The latter is a simple and fast questionnaire composed of five obstruction-related items which evaluate the severity of complaints that the patient has been experiencing over the past month as a result of nasal obstruction. The former is a questionnaire structurally composed of 22 chronic rhinosinusitis related items which evaluate the severity of complaints that the patient has been experiencing over the past weeks a result of chronic rhinosinusitis. In addition, similar to the study of Low *et al.*,[2] six visual analogue scales (VASs) measuring the severity of symptoms (overall symptoms, nasal obstruction, headache, facial pain, smell alteration and nasal discharge) were used. These comprised 100 mm lines with the extremes 'as bad as it can be' (100 mm) and 'no symptoms' (0 mm).

Statistical analysis

Similar to the study of Salib *et al.*,[18] the Lund–Kennedy post-operative score was considered the primary endpoint, and a difference of 1 point between the two groups was considered clinically significant. For the study to have a power of 80 per cent, 26 patients would need to be recruited to demonstrate a statistically significant difference between the 2 treatments ($\alpha = 0.05$, two-sided), assuming a standard deviation of 1.5.

The results are given as arithmetic mean ± standard deviation. The Kolmogorov–Smirnoff test was used to test the normality of distribution in each group. As this test demonstrated a normal distribution of the variables, parametric tests were used to evaluate the differences between the two groups of patients. In particular, subjective and objective scores obtained before and after surgery were compared using a paired *t*-test. The *t*-test and the chi-square test were used when appropriate to compare the two groups. A significance level of 0.05 for all testing was used. Statistical analyses were performed using the SPSS® version 25.0 statistical software package.

Results

Of the 56 patients (28 males and 28 females), 30 (14 males and 16 females) were randomly allocated to the normal saline arm (group 1), and 26 (14 males and 12 females) were randomly allocated to the normal saline plus sodium hyaluronate arm (group 2) (Figure 1). No difference in sex distribution between the two groups was demonstrated with the chi-square test ($p = 0.487$). Allergy was reported by 15 patients (9 in group 1 and 6 in group 2), while asthma was reported by 6 patients (4 in group 1 and 2 in group 2). A total of 13 patients were active smokers (7 in group 1 and 6 in group 2). No differences between the two groups in the distribution of patients with allergy, asthma or smoking habit were demonstrated on chi-square tests ($p = 0.449$, $p = 0.722$ and $p = 811$, respectively).

Each patient underwent FESS for chronic rhinosinusitis without polyps. No complications were reported during surgery or the follow-up period. All patients attended the follow-up appointments; no patients were lost during the six-week follow-up period. All patients tolerated the nasal irrigation well and none of them discontinued the treatment.

Demographic data, and the distributions of objective and subjective scores pre-treatment, are depicted in Table 1. No significant differences were demonstrated in terms of age, or pre-operative Lund–Mackay, Lund–Kennedy, VAS, Nose Obstruction Symptom Evaluation and SNOT-22 scores, suggesting a similarity between the two study arms.

Objective assessment

Objective assessment was performed using both the Lund–Mackay radiological scoring system and the Lund–Kennedy endoscopic scoring system in the pre-operative period, while only the Lund–Kennedy scoring system was utilised during follow up (at three and six weeks post-surgery). In group 1 and group 2, there was a significant deterioration in the Lund–Kennedy total score at three weeks. At six weeks, the Lund–Kennedy total score was significantly better than the scores obtained in the pre-operative period and at three weeks (see Table 2 for group 1 and Table 3 for group 2).

When the two groups were compared, patients in group 2 scored significantly better in the crusting and scar subdomains of the Lund–Kennedy scoring system at three weeks, and in the secretion and scar subdomains at six weeks (see Table 4), on student's *t*-tests.

Subjective assessment

Regarding the subjective assessment, all patients autonomously completed the SNOT-22, the ~~Nose Obstruction Symptom Evaluation~~, and the six VASs, at the three assessment times (pre-operatively, and at three and six weeks after surgery). The time required to complete the subjective self-assessment never exceeded 10 minutes.

Sino-Nasal Outcome Test-22

The paired *t*-test demonstrated a significant improvement in SNOT-22 scores after surgery (Figure 2), in both groups. The results are reported in Table 2 (for group 1) and Table 3 (for group 2). In particular, significant differences

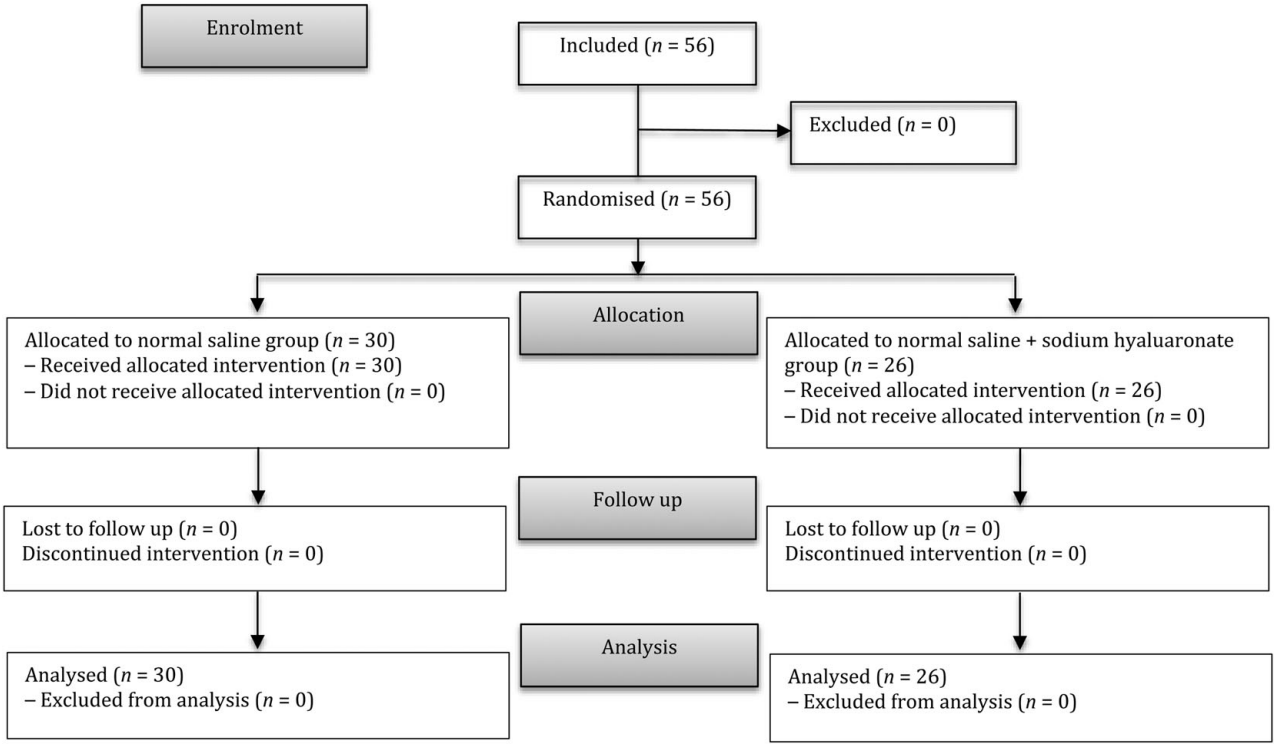

Fig. 1 - B/W online, B/W in print

Fig. 1. Flow diagram of the progress through the randomised trial phases of two groups.

Table 1. Distribution of age, and pre-operative objective and subjective evaluation scores in the two study arms

Parameter	Normal saline	Normal saline + sodium hyaluronate	*P* value*
Age (years)	42.8 ± 13.9	46.6 ± 15.5	0.825
Lund–Mackay radiological score	9.1 ± 3.7	8.1 ± 3.1	0.208
Lund–Kennedy endoscopic total score	3.6 ± 1.7	3.9 ± 2.3	0.136
SNOT-22 score	48.5 ± 21.1	48.8 ± 22.9	0.883
NOSE score	13.4 ± 4.4	13.6 ± 3.3	0.148
VASs†			
– Nasal blockage	4.9 ± 2.7	6.2 ± 2.8	0.183
– Nasal congestion	7.1 ± 2.2	8.1 ± 2.2	0.185
– Headache	5.7 ± 1.9	5.1 ± 3.7	0.166
– Facial pain	4.4 ± 2.9	3.3 ± 3.2	0.146
– Smell alteration	1.5 ± 1.9	2.1 ± 3.1	0.083
– Nasal discharge	5.6 ± 2.7	6.4 ± 2.9	0.948

Data represent means ± standard deviations, unless indicated otherwise. *Student's *t*-test. †Scores measured in centimetres. SNOT-22 = Sino-Nasal Outcome Test-22; NOSE = Nasal Obstruction Symptom Evaluation scale; VAS = visual analogue scale

were found between the SNOT-22 scores obtained in the pre-operative evaluation and those obtained at three and six weeks, in both groups. In addition, a significant difference was also demonstrated between the SNOT-22 scores obtained at three weeks and those obtained at six weeks, in both groups. However, no significant differences were demonstrated between the two groups at three or six weeks after surgery with the student's *t*-test (Table 4).

Nose Obstruction Symptom Evaluation

The paired *t*-test demonstrated a significant improvement in ~~Nose Obstruction Symptom Evaluation~~ scores after surgery (Figure 3), in both groups. The results are reported in Tables 2 and 3. In particular, significant differences were found between the ~~Nose Obstruction Symptom Evaluation~~ scores obtained in the pre-operative evaluation and those at three and six weeks, in both groups. Only in group 1 was a significant difference demonstrated between the ~~Nose Obstruction Symptom Evaluation~~ scores obtained at three weeks and those obtained at six weeks. Interestingly, at three weeks after surgery, the ~~Nose Obstruction Symptom Evaluation~~ scores obtained in group 2 were significantly lower than those in group 1, while there were no differences between the two groups at six weeks (Table 4).

Visual analogue scale

In group 1, significant improvements in VAS scores were demonstrated after three weeks for headache and facial pain only. However, six weeks after surgery, all the VAS scores improved significantly. Furthermore, significant improvements in VAS scores were demonstrated in the comparison between the third and sixth weeks, with the only exceptions being facial pain and nasal discharge (Table 2).

In group 2, improvements in VAS scores were demonstrated after three weeks for overall symptoms, nasal obstruction, headache and facial pain, while no ~~there were~~ significant improvements for smell alteration and nasal discharge. At six weeks after surgery, all the VAS scores improved significantly. No significant differences in headache, facial pain and smell alteration were found between VAS scores obtained at three and at six weeks (Table 3).

Significant differences were found between the two groups in the VAS scores for headache and smell alteration at three weeks (Figure 4). Specifically, patients in group 2 scored

Table 2. Comparison of pre- and post-operative evaluation scores for group 1 (normal saline)

	Scores (mean ± SD)			*P* values (paired *t*-test)		
Evaluation scale	Pre-op	3 wk post-op	6 wk post-op	Pre-op *vs* 3 wk post-op	Pre-op *vs* 6 wk post-op	3 wk *vs* 6 wk post-op
Lund–Kennedy endoscopic subscale						
– Polyps	–	–	–	–	–	–
– Inflammation	1.9 ± 0.9	1.6 ± 0.5	0.3 ± 0.5	0.677	0.231	0.009*
– Secretion	1.7 ± 0.9	1.5 ± 1.4	0.5 ± 0.8	0.331	0.671	0.003*
– Scar	0 ± 0	1.3 ± 0.9	0.7 ± 0.5	0.001*	0.001*	0.001*
– Crusting	0 ± 0	2.3 ± 1.1	0.7 ± 0.5	0.001*	0.001*	0.001*
– Total	3.6 ± 1.7	6.7 ± 3.1	2.4 ± 1.6	0.001*	0.032*	0.003*
SNOT-22	48.5 ± 21.1	22.9 ± 8.1	14.9 ± 11.4	0.001*	0.001*	0.048*
NOSE	13.4 ± 4.4	5.8 ± 4.1	2.7 ± 2.5	0.001*	0.001*	0.001*
VASs†						
– Overall symptoms	4.9 ± 2.7	3.6 ± 2.5	1.1 ± 1.6	0.862	0.010*	0.003*
– Nasal obstruction	7.1 ± 2.2	3.6 ± 2.3	1.2 ± 1.5	0.636	0.033*	0.011*
– Headache	5.7 ± 1.9	3.8 ± 3.4	1.5 ± 2.1	0.001*	0.048*	0.002*
– Facial pain	4.4 ± 2.9	1.8 ± 1.9	1.1 ± 1.9	0.039*	0.010*	0.855
– Smell alteration	1.5 ± 1.9	2.2 ± 2.7	0.9 ± 1.5	0.105	0.036*	0.004*
– Nasal discharge	5.6 ± 2.7	3.3 ± 2.4	1.6 ± 1.7	0.267	0.001*	0.069

*Indicates a statistically significant difference. †Scores measured in centimetres. SD = standard deviation; pre-op = pre-operation; wk = weeks; post-op = post-operation; SNOT-22 = Sino-Nasal Outcome Test-22; NOSE = Nasal Obstruction Symptom Evaluation scale; VAS = visual analogue scale

Table 3. Comparison of pre- and post-operative evaluation scores for group 2 (normal saline plus sodium hyaluronate)

	Scores (mean ± SD)			*P* values (paired *t*-test)		
Evaluation scale	Pre-op	3 wk post-op	6 wk post-op	Pre-op *vs* 3 wk post-op	Pre-op *vs* 6 wk post-op	3 wk *vs* 6 wk post-op
Lund–Kennedy endoscopic subscale						
– Polyps	–	–	–	–	–	–
– Inflammation	2.1 ± 1.1	1.7 ± 0.5	0.5 ± 0.6	0.106	0.289	0.048*
– Secretion	1.4 ± 1.2	1.6 ± 0.5	0.3 ± 0.3	0.214	0.001*	0.046*
– Scar	0 ± 0	0.7 ± 0.7	0.5 ± 0.6	0.001*	0.001*	0.595
– Crusting	0 ± 0	1.3 ± 0.9	0.8 ± 0.6	0.001*	0.001*	0.034*
– Total	3.9 ± 2.3	6.9 ± 3.1	3.1 ± 1.6	0.047*	0.038*	0.001*
SNOT-22	48.8 ± 15.5	24.4 ± 8.4	15.6 ± 13.4	0.002*	0.001*	0.022*
NOSE	13.6 ± 3.3	4.4 ± 1.5	3.7 ± 3.3	0.001*	0.001*	0.366
VASs†						
– Overall symptoms	6.2 ± 2.8	3.9 ± 3.6	1.1 ± 0.9	0.046*	0.001*	0.001*
– Nasal obstruction	8.1 ± 2.2	3.3 ± 3.1	1.7 ± 1.4	0.042*	0.001*	0.001*
– Headache	5.1 ± 3.7	1.9 ± 1.8	1.3 ± 1.3	0.005*	0.001*	0.086
– Facial pain	3.3 ± 3.2	1.1 ± 1.4	1.2 ± 1.1	0.001*	0.001*	0.891
– Smell alteration	2.1 ± 3.1	1.9 ± 1.5	1.1 ± 1.1	0.069	0.001*	0.575
– Nasal discharge	6.4 ± 2.9	2.6 ± 1.9	1.3 ± 1.1	0.230	0.001*	0.001*

*Indicates a statistically significant difference. †Scores measured in centimetres. SD = standard deviation; pre-op = pre-operation; wk = weeks; post-op = post-operation; SNOT-22 = Sino-Nasal Outcome Test-22; NOSE = Nasal Obstruction Symptom Evaluation scale; VAS = visual analogue scale

significantly better than patients in group 1. At six weeks, there were no differences between the two groups in the VAS scores (Table 4).

Discussion

In the present study, the effect of nasal irrigation using either normal saline or normal saline plus sodium hyaluronate was

Table 4. Comparison of evaluation scores between groups at three and six weeks post-surgery

	3 wk post-op scores (mean ± SD)			6 wk post-op scores (mean ± SD)		
Evaluation scale	Group 1	Group 2	*P* values*	Group 1	Group 2	*P* values*
Lund–Kennedy endoscopic subscale						
– Polyps	–	–	–	–	–	–
– Inflammation	1.6 ± 0.5	1.7 ± 0.5	0.303	0.3 ± 0.5	0.5 ± 0.6	0.059
– Secretion	1.5 ± 1.4	1.6 ± 0.5	0.472	0.5 ± 0.8	0.3 ± 0.3	0.028†
– Scar	1.3 ± 0.9	0.7 ± 0.7	0.008†	0.7 ± 0.5	0.5 ± 0.6	0.011†
– Crusting	2.3 ± 1.1	1.3 ± 0.9	0.009†	0.7 ± 0.5	0.8 ± 0.6	0.306
– Total	6.7 ± 3.1	6.9 ± 3.1	0.511	2.4 ± 1.6	3.1 ± 1.6	0.872
SNOT-22	22.9 ± 8.1	24.4 ± 8.4	0.933	14.9 ± 11.4	15.6 ± 13.4	0.175
NOSE	5.8 ± 4.1	4.4 ± 1.5	0.001†	2.7 ± 2.5	3.7 ± 3.3	0.092
VASs‡						
– Overall symptoms	3.6 ± 2.5	3.9 ± 3.6	0.115	1.1 ± 1.6	1.1 ± 0.9	0.143
– Nasal obstruction	3.6 ± 2.3	3.3 ± 3.1	0.163	1.2 ± 1.5	1.7 ± 1.4	0.539
– Headache	3.8 ± 3.4	1.9 ± 1.8	0.011†	1.5 ± 2.1	1.3 ± 1.3	0.125
– Facial pain	1.8 ± 1.9	1.1 ± 1.4	0.145	1.1 ± 1.9	1.2 ± 1.1	0.094
– Smell alteration	2.2 ± 2.7	1.9 ± 1.5	0.049†	0.9 ± 1.5	1.1 ± 1.1	0.638
– Nasal discharge	3.3 ± 2.4	2.6 ± 1.9	0.519	1.6 ± 1.7	1.3 ± 1.1	0.052

Group 1 = normal saline; group 2 = normal saline plus sodium hyaluronate. *Student's *t*-test. †Indicates a statistically significant difference. ‡Scores measured in centimetres. wk = weeks; post-op = post-operation; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test-22; NOSE = Nasal Obstruction Symptom Evaluation scale; VAS = visual analogue scale

Fig. 2 - B/W online, B/W in print

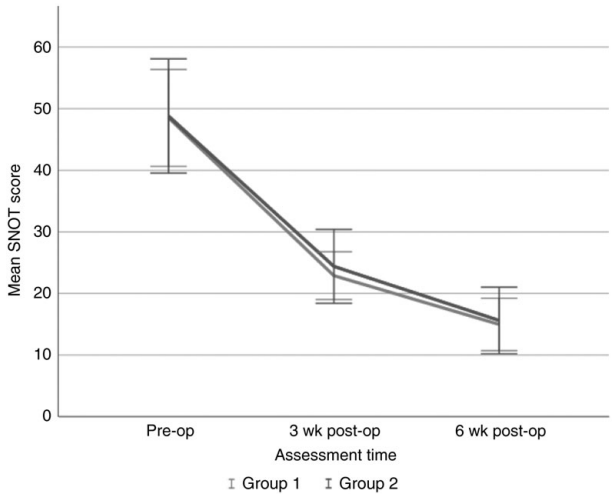

Fig. 2. Changes in Sino-Nasal Outcome Test 22 (SNOT-22) scores in patients treated with normal saline (group 1) or normal saline plus sodium hyaluronate (group 2). Data are presented as mean and confidence intervals (95 per cent). Pre-op = pre-operation; wk = weeks; post-op = post-operation

Fig. 3 - B/W online, B/W in print

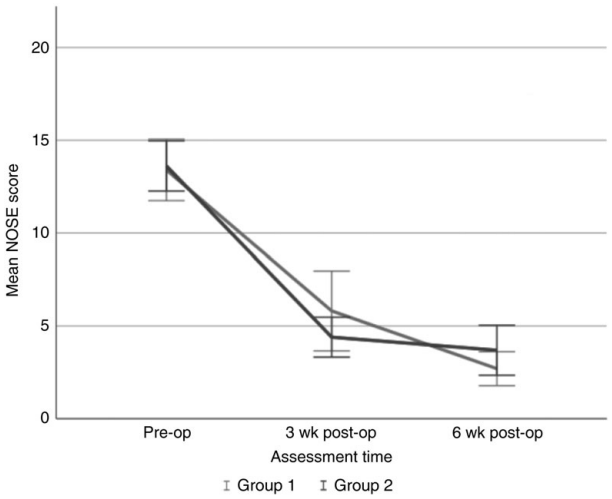

Fig. 3. Changes in ~~Nasal Obstruction Symptom Scale~~ (NOSE) scores in patients treated with normal saline (group 1) or normal saline plus sodium hyaluronate (group 2). Data are presented as mean and confidence intervals (95 per cent). Pre-op = pre-operation; wk = weeks; post-op = post-operation

analysed in a group of 56 patients who underwent FESS for chronic rhinosinusitis without polyps at 3 different centres. To our knowledge, this study is the first to investigate the clinical effect of high-volume, low-pressure, gravity-dependent nasal irrigation using saline plus sodium hyaluronate in patients who underwent FESS for chronic rhinosinusitis without polyps.

The results reported here are noteworthy. All patients tolerated the nasal irrigation well; none of the patients dropped out of the study. Furthermore, the subjective and objective scores improved during the six weeks of follow up in both treatment arms. These data further support the benefits of high-volume, low-pressure nasal saline irrigation post-FESS. Similar findings were reported by Salib *et al.*,[18] who demonstrated the superiority of high-volume, low-pressure nasal saline irrigation over low-volume, high-pressure nasal saline irrigation following FESS. It is possible that the positive effect of nasal irrigation is related to an increase in mucociliary clearance and to the physical effects of hydrostatic pressure, which improves the removal of crusts and thick, tenacious secretions.[4,18]

Besides the positive effects of nasal irrigation post-FESS, specific findings related to the composition of the nasal irrigation solution are interesting. As far as the objective assessment is concerned, in the pre-operative condition no differences in the Lund–Mackay and Lund–Kennedy scores were demonstrated, suggesting a similarity between the two study arms.

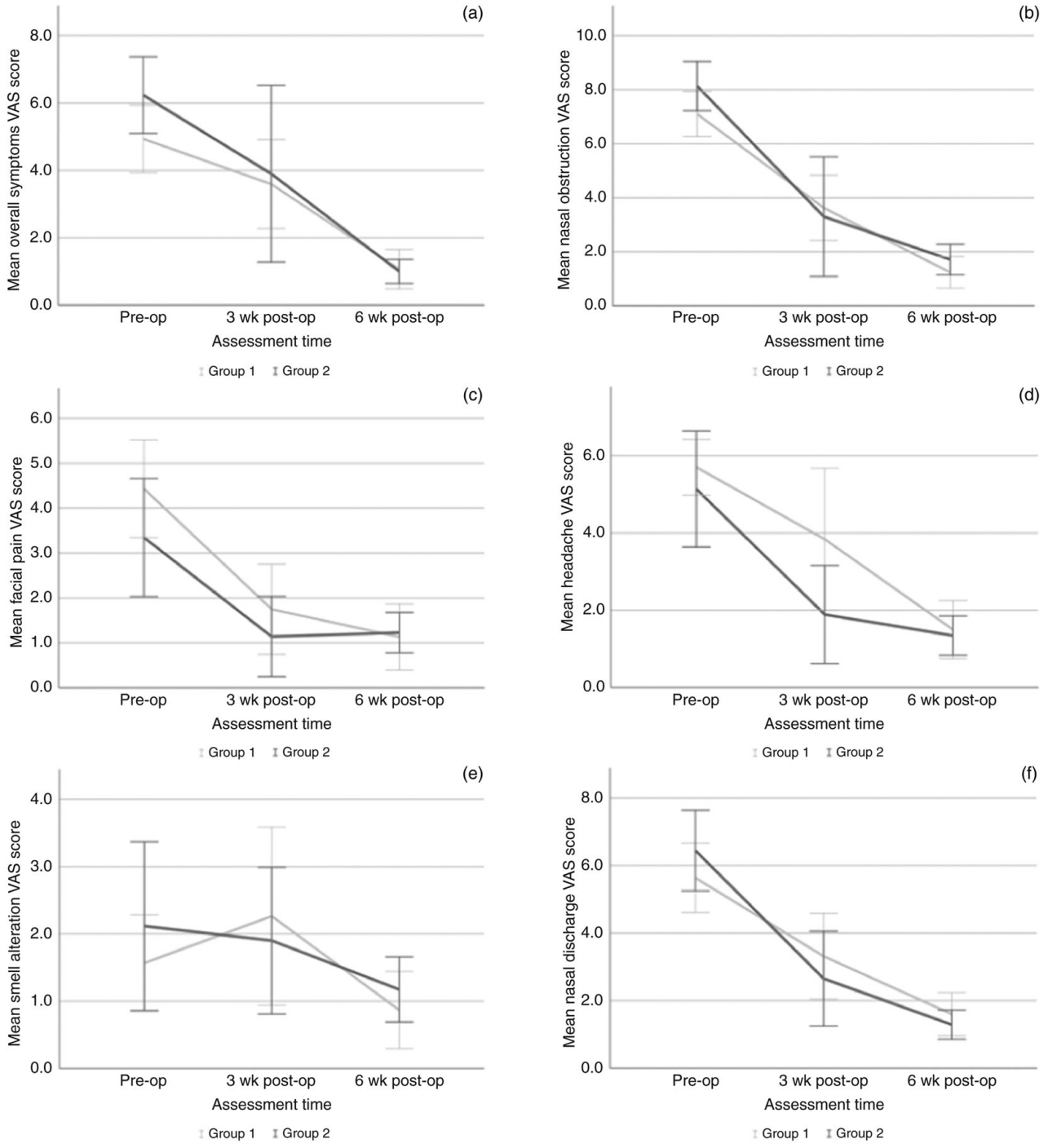

Fig. 4 - B/W online, B/W in print

Fig. 4. Changes in visual analogue scale (VAS) scores in patients treated with normal saline (group 1) or normal saline plus sodium hyaluronate (group 2), for: (a) overall symptoms, (b) nasal obstruction, (c) facial pain, (d) headache, (e) smell alteration and (f) nasal discharge. Data are presented as mean and confidence intervals (95 per cent). Pre-op = pre-operation; wk = weeks; post-op = post-operation

At three weeks after surgery, Lund–Kennedy scores were significantly increased in both groups. This finding is probably related to oedema, crust formation, mucosal alterations, secretions and impaired sinonasal ventilation, which frequently occur during the first month after FESS.[19] Nonetheless, at three weeks after surgery, there were significant differences between the two groups for the Lund–Kennedy crusting and scar subdomain scores. Specifically, patients treated with normal saline plus sodium hyaluronate (group 2) scored significantly better than patients treated with normal saline alone (group 1). Similarly, at six weeks after surgery, patients in group 2 scored significantly better in the Lund–Kennedy scar and secretion subdomains than patients in group 1. These findings suggest a positive effect of sodium hyaluronate in reducing secretions, crusts and scar formation post-FESS.

Similar results were reported by Cantone *et al.*,[19] who compared the effects of saline solution (2 ml) plus 9 mg of sodium hyaluronate (3 ml) versus saline solution alone (5 ml) on the improvement of post-operative discomfort and short-term QoL following FESS in a group of 124 patients. The authors found that Lund–Kennedy scores were better in patients treated with saline solution plus sodium hyaluronate than in those treated with saline solution alone 30 days after surgery. Gelardi *et al.*[9] compared saline irrigation versus intranasal sodium hyaluronate nebulised twice a day in a group of 36 patients. They found that patients receiving sodium hyaluronate had a

significantly faster mucociliary clearance time, a lower incidence of rhinorrhoea, less nasal obstruction and a lower incidence of exudate on endoscopy than control subjects at one month. In addition, Macchi *et al.*[10] compared the effect of nebulised sodium hyaluronate plus saline solution versus saline solution alone, given for 15 days per month over 3 months, in a group of 46 patients. They found that significantly more patients in the saline group than the sodium hyaluronate group had catarrhal, purulent or haematic nasal secretions.

It is consequently possible to speculate that the application of sodium hyaluronate through nasal irrigation improved recovery of the nasal mucosa, as suggested by the better Lund–Kennedy scores of patients who used nasal saline plus sodium hyaluronate. This hypothesis is in agreement with the findings of Dal and Bahar[20] who reported faster wound healing and re-epithelisation in patients treated with a cross-linked hyaluronan gel post-FESS.

- Nasal irrigation is crucial for post-operative care after functional endoscopic sinus surgery (FESS)
- High-volume, low-pressure, gravity-dependent irrigation devices offer better solution delivery in paranasal sinuses
- Sodium hyaluronate may be useful in the early stages after sinus surgery, even if provided in different preparations
- Sodium hyaluronate improves mucosal stability, lubrication, water homeostasis and molecule filtering, and promotes cell behaviour modification
- The adjunct of sodium hyaluronate to high-volume, low-pressure, gravity-dependent saline irrigation in the early post-FESS period resulted in a better endoscopic appearance
- Furthermore, it increased patient-reported satisfaction for perceived nasal obstruction, headache and smell alteration

Regarding the subjective assessment, the SNOT-22 scores significantly improved after surgery in both groups, thus suggesting the efficacy of FESS in the treatment of chronic rhinosinusitis without polyps. The Nose Obstruction Symptom Evaluation scores also significantly improved post-operatively in both groups, but there was a significant difference between the groups in the scores at three weeks post-surgery. Specifically, patients in group 2 scored better than those in group 1, suggesting that the sensation of nasal patency was better in the patients treated with nasal saline plus sodium hyaluronate. Similarly, three weeks after surgery, patients in group 2 scored significantly better in VASs for headache and smell alteration than patients in group 1. No differences between groups were found in Nose Obstruction Symptom Evaluation and VAS scores at six weeks. Similar results were reported by Cantone *et al.*,[19] who found that patients treated with saline solution plus sodium hyaluronate reported significantly higher scores in QoL at 30 days after surgery than patients treated with saline solution alone.

The presence of significant differences at three weeks post-surgery between the two groups of our sample suggests that sodium hyaluronate might provide a faster improvement of some nasal symptoms after FESS. It might be speculated that the application of sodium hyaluronate, by favouring nasal mucosa tissue repair, promotes wound healing and reduces crust formation. The reduced crusting could have played a role in improving the perception of nasal patency, and in reducing smell alteration and headache.

This study has several limitations. First of all, the number of enrolled patients is quite small, even if it is in line with previous reports. For this reason, caution should be used when interpreting the results. Moreover, similar to the study of Macchi *et al.*,[10] the control group of this study cannot be considered a placebo arm, as patients received the standard therapy of normal saline. For this reason, the possibility of detecting statistically significant differences between the groups might have been reduced. However, the inclusion of a control group of patients not undergoing nasal irrigation would be difficult to justify, as nasal irrigation has been found to be beneficial in the post-operative period.[18] An additional potential criticism of the study concerns the choice of primary outcome instrument. We decided to use the Lund–Kennedy score for two reasons: first, it remains the most commonly used endoscopic scoring system; second, it contains items that specifically address the post-surgical status of patients.[21] Finally, the follow-up period was short (only six weeks); consequently, no information regarding the effect of nasal saline irrigation with or without sodium hyaluronate over a longer time period is available.

Conclusion

Sodium hyaluronate might be a useful adjunct to high-volume, low-pressure, gravity-dependent saline irrigation in the early post-operative period following FESS performed for chronic rhinosinusitis without polyps. Sodium hyaluronate seems to result in a better endoscopic appearance, and higher patient-reported satisfaction in terms of perceived nasal obstruction, headache and smell alteration. However, the clinical benefit appears limited, and further studies with a longer follow-up period are needed.

Acknowledgement. The nasal saline irrigations used in this study (Nasir Isotonic and Nasir Plus) were donated by EP Medica (Fusignano, Italy).

Competing interests. None declared

References

1 Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F *et al.* EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;**50**:1–12
2 Low TH, Woods CM, Ullah S, Carney S. A double-blind randomized controlled trial of normal saline, lactated Ringer's, and hypertonic saline nasal irrigation solution after endoscopic sinus surgery. *Am J Rhinol Allergy* 2014;**28**:225–31
3 Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008;**139**:137–42
4 Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope* 2000;**110**:1189–93
5 Wormald PJ, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. *Laryngoscope* 2004;**114**:2224–7
6 Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2007;(18):CD006394
7 Chong LY, Head K, Hopkins C, Philpott C, Glew S, Scadding G *et al.* Saline irrigation for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016;(26):CD011995
8 Freeman SR, Sivayoham ES, Jepson K, de Carpentier J. A preliminary randomized controlled trial evaluating the efficacy of saline douching following endoscopic sinus surgery. *Clin Otolaryngol* 2008;**33**:462–5
9 Gelardi M, Guglielmi AV, De Candia N, Maffezzoni E, Berardi P, Quaranta N. Effect of sodium hyaluronate on mucociliary clearance after functional endoscopic sinus surgery. *Eur Ann Allergy Clin Immunol* 2013;**45**:103–8

10 Macchi A, Terranova P, Digilio E, Castelnuovo P. Hyaluronan plus saline nasal washes in the treatment of rhino-sinusal symptoms in patients undergoing functional endoscopic sinus surgery for rhino-sinusal remodeling. *Int J Immunopathol Pharmacol* 2013;**26**:137–45
11 Fong E, Garcia M, Woods CM, Ooi E. Hyaluronic acid for post sinus surgery care: systematic review and meta-analysis. *J Laryngol Otol* 2017;**131**: S2–11
12 Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med* 1997;**242**:27–33
13 Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;**107**:183–4
14 Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. *Ann Otol Rhinol Laryngol Suppl* 1995;**167**:17–21
15 Gera R, Mozzanica F, Karligkiotis A, Preti A, Bandi F, Gallo S *et al*. Lateral lamella of the cribriform plate, a keystone landmark: proposal for a novel classification system. *Rhinology* 2018;**56**:65–72
16 Mozzanica F, Preti A, Gera R, Gallo S, Bulgheroni C, Bandi F *et al*. Cross-cultural adaptation and validation of the SNOT-22 into Italian. *Eur Arch Otorhinolaryngol* 2017;**274**:887–95
17 Mozzanica F, Urbani E, Atac M, Scottà G, Luciano K, Bulgheroni C *et al*. Reliability and validity of the Italian nose obstruction symptom evaluation (I-NOSE) scale. *Eur Arch Otorhinolaryngol* 2013;**270**:3087–94
18 Salib RJ, Talpallikar S, Uppal S, Nair SB. A prospective randomized single-blinded clinical trial comparing the efficacy and tolerability of the nasal douching products Sterimar™ and Sinus Rinse™ following functional endoscopic sinus surgery. *Clin Otolaryngol* 2013;**38**:297–305
19 Cantone E, Castagna G, Sicignano S, Ferranti I, Rega F, Di Rubbo V *et al*. Impact of intranasal sodium hyaluronate on the short-term quality of life of patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2014;**4**:484–7
20 Dal T, Bahar S. The clinical outcomes of using a new cross-linked hyaluronan gel in endoscopic frontal sinus surgery. *Eur Arch Otorhinolaryngol* 2017;**274**:3397–402
21 Psaltis AJ, Li G, Vaezeafshar R, Cho KS, Hwang PH. Modification of the Lund-Kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures. *Laryngoscope* 2014;**124**: 2216–23