Self-cross-linked hyaluronic acid hydrogel in ethmoidectomy: A randomized, controlled trial

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ABSTRACT

Background: *This study was designed to evaluate the safety and efficacy of a novel, self–cross-linked hyaluronic acid (HA) hydrogel compared with carboxymethylcellulose (CMC) viscous foam in promoting healing when applied after ethmoidectomy. A prospective, randomized, controlled, blinded clinical trial was performed. The study was performed by four surgeons operating in two community hospitals.*

Methods: *Thirty patients with bilateral chronic rhinosinusitis underwent bilateral total ethmoidectomy. Intraoperatively, each patient received 5 mL of HA hydrogel in one ethmoid cavity and 5 mL of CMC contralaterally. The material applied within each ethmoid cavity was randomly assigned before surgery. An independent surgeon, blinded to the material used to treat each ethmoid cavity, evaluated postoperative endoscopic video at 1 and 2 weeks for edema, crusting, and mucopurulence and at 6 and 12 weeks for remucosalization and scarring/synechiae. Twenty-item Sino-Nasal Outcome Test SNOT-20 data were collected at each visit. A small sample underwent endoscopic mucosal biopsy.*

Results: *Twenty-nine of 30 patients completed the protocol. The difference in edema, crusting, and mucopurulence at 1 and 2 weeks was not statistically significant; however, at 6 and 12 weeks, the HA hydrogel showed statistically significant reduction in both overall endoscopic grade ($p < 0.05$), as well as synechiae formation ($p < 0.05$), with a trend toward superiority in remucosalization ($p = 0.08$). Histological analysis of six subjects at 12 weeks showed a nonsignificant trend toward a greater amount of regenerated cilia present with the HA hydrogel ($p = 0.23$). SNOT-20 scores declined 78.8% from preoperative scores.*

Conclusion: *Self–cross-linked HA hydrogel provides superior wound healing to CMC after ethmoidectomy.*

(Am J Rhinol Allergy 28, 508–513, 2014; doi: 10.2500/ajra.2014.28.4106)

Chronic rhinosinusitis, as defined by the European position paper on rhinosinusitis and nasal polyps 2012 (EPOS 2012), is a significant cause for physician visits, health-care expenditures, and reduced productivity of the workforce in the United States each year.[1] Approximately 600,000 nasal and sinus surgeries are performed each year,[2] with the likelihood that many additional viable surgical candidates elect to continue to manage their disease nonsurgically, with varying degrees of success and satisfaction. Part of this hesitancy to proceed with sinus surgery is based on the propensity for historical and current techniques to stimulate scarring within the sinus cavities or outflow tracts.[3] This scarring may result in recurrent disease or worsening of symptoms, necessitating revision surgical procedures, which may, in turn, result in further scar formation.[3]

The concept of nasal packing to minimize complications such as perioperative hemorrhage and to improve wound healing after sinus surgery can be traced back as far as the origins of intranasal surgery itself. However, over the past 20 years, multiple materials, both nonresorbable and bioresorbable, have been researched in earnest. Multiple clinical trials have examined contemporary materials for their positive wound-healing attributes such as promotion of hemostasis and regeneration of cilia within the mucosa, as well as their unintended contributions to known complications of endoscopic sinus surgery (ESS) such as synechiae formation.[3–7]

The ideal postsurgical device or dressing would be absorbable; promote both hemostasis and wound-healing; and would not contribute to infection, scarring, or recurrent disease. Although many current products and devices satisfactorily address one or multiple of these issues, they uniformly possess negative characteristics such as requiring removal at a later date, becoming infected, or actually promoting scar formation.[6,7] There remains great potential for improvement.

Various forms of hyaluronic acid (HA) have been developed and used successfully to promote wound healing and hemostasis in the nasal cavities, as well as other parts of the body.[8–19] A unique, self–cross-linked HA hydrogel (PureRegen Gel Sinus, BioRegen Biomedical Co., Ltd., Changzhou, China) has shown favorable outcomes in both remucosalization as well as the minimization of bleeding in the sinus cavities in prior animal studies, as well as in a previous human randomized, prospective clinical trial.[18–20]

The goal of this trial was to evaluate, in a blinded fashion, head to head, whether this particular formulation of HA applied to a freshly dissected ethmoid cavity, imparts improvement in early and late wound healing and therefore surgical outcomes, over another widely used material. Carboxymethylcellulose (CMC) viscous foam (Stammberger Sinu-Foam; ArthroCare ENT, Austin, TX) was chosen because of its current widespread clinical use, its similarity in appearance to the HA hydrogel in the surgical bed after deployment, and the similarity in expected time required for both HA and CMC to be cleared from the nasal cavity. Both materials typically dissolve and disappear because of natural mucociliary clearance mechanisms within the first 7–10 days postoperatively.[20–22] These similarities in appearance and clearance optimized the blinding, and thus the objectivity, of the endoscopic evaluator.

METHODS

A prospective, individual, randomized, controlled, blinded clinical trial was performed (level Ib). Institutional Review Board (IRB) approval was obtained through the independent Aspire IRB, Santee, CA. The 30 subjects presented to one of four otolaryngologist–head and neck surgeons in a community practice setting with bilateral chronic rhinosinusitis, based on clinical presentation and computed tomography findings per the EPOS 2012 guidelines.[1] These subjects were screened per the IRB-approved criteria, their consent was obtained, and they were enrolled in the trial. Subjects with primarily

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Accepted for Oral Presentation at the annual meeting of the American Academy of Otolaryngology–Head and Neck Surgery and OTO EXPO, Orlando, Florida, September 23, 2014

Funded by BioRegen Biomedical Co., Ltd., Changzhou, China

The authors have no conflicts of interest to declare pertaining to this article

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Published online September 11, 2014

unilateral disease and those with comorbid disease states that would undermine wound healing such as diabetes mellitus, autoimmune diseases, or other steroid-dependent chronic diseases were excluded. The subjects then underwent bilateral total ethmoidectomy. Concurrent nasal procedures, as well as revision ethmoidectomies, were permitted, provided there was substantial ethmoid disease bilaterally. The optimal sample size was determined to be between 25 and 30 patients to provide statistical power of >90%.

The sides of instillation for each material were randomly assigned before surgery based solely on chronological surgical scheduling among the four surgeons, with no regard to preoperative level or laterality of disease state. The patients were blinded as to which material was used in each side for the duration of the trial. Each patient served as their own control by receiving 5 mL of self–cross-linked HA hydrogel in one ethmoid cavity intraoperatively at the conclusion of ethmoidectomy, while the other ethmoid cavity was filled with 5 mL of CMC intraoperatively (Fig. 1). None of the surgical cases happened concurrently, so no deviations from this randomization occurred. Because of different packaging and instillation devices, the surgeons were not blinded to which material they were instructed by the randomization protocol to apply to each ethmoid cavity.

Patients received parenteral antibiotics (such as 2 g of cefazolin) and 10 mg of dexamethasone intraoperatively. Patients were instructed to use saline rinses two times daily throughout the 12 postoperative weeks. Treatment with oral antibiotics and oral steroids were permitted as indicated, because the patient served as their own control and both ethmoid cavities would receive the drug.

Nasal endoscopy, with individual video recording of each side, was performed at 1, 2, 6, and 12 weeks postoperatively, based on the typical postoperative management course of the surgeons. Routine postoperative debridement was performed at each visit, if necessary, only after the video was captured. Any residual HA or CMC present at 1 week was suctioned. Crusting was debrided and any synechiae were lysed at each visit, as is customary with routine postoperative ESS surveillance and management. No additional HA or CMC was applied. Twenty-item Sino-Nasal Outcome Test (SNOT-20) data were collected preoperatively and after each postoperative visit.

An independent, experienced rhinologic surgeon, blinded to the operating surgeon, the concurrent procedures in addition to bilateral total ethmoidectomy, and the material used to treat each ethmoid cavity, as well as the preoperative level of disease, evaluated the postoperative endoscopic video according to the novel scoring scale developed for this trial shown in Fig. 2. This novel scale was designed to capture features of both the early perioperative period and the phenomena seen after healing of the ethmoid cavities. The endoscopic evaluator was allowed to follow the progression of healing in each patient chronologically. Each subject was compared individually to their own corresponding side at the same time point. At 1 and 2 weeks, numerical scores were assigned for the amount of edema, crusting, and mucopurulence present. At 6 and 12 weeks, numerical scores were given for the degree of remucosalization and scarring.

To further characterize the nature of the ethmoid cavity healing, the protocol was expanded in the midst of the trial (with Aspire IRB approval of this amendment) to allow histological analysis of a sample of the ethmoid cavities. Mucosal biopsy specimens were obtained for six of the subjects by endoscopically sampling a representative area of the mucosa in each ethmoid cavity at 12 weeks. These biopsy specimens captured mucosa as anterior and inferior as possible to avoid the sensory neuroepithelium around the superior turbinate and the skull base. An independent pathologist, blinded to preoperative level of disease, surgeon, and which material was used on each side, performed hematoxylin and eosin staining of the biopsy specimens, and then graded the tissue specimens for regeneration of features of healthy mucosa such as the presence of cilia in the brush border and goblet cell formation. These mucosal features were graded on a numerical scale as found in the publication by DePoortere *et al.*, for statistical comparison, with 0 indicating a complete lack of cilia, 1 for <30% of the mucosa with cilia, 2 for 30–60% of the mucosa with cilia, and 3 for >60% of the mucosa with cilia.[23] A representative histological comparison sample is provided for reference purposes (Fig. 3).

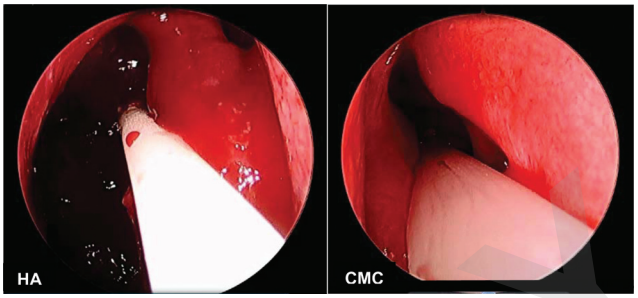

Figure 1. *Subject 004 instillation of hyaluronic acid (HA) hydrogel into the right ethmoid cavity and carboxymethylcellulose (CMC) viscous foam into the left ethmoid cavity.*

All data were included in this analysis according to the intent-to-treat principle. Comparison of data between the two sides from the postoperative endoscopic video grading, as well as the histological analysis, was performed by the paired Wilcoxon–Mann–Whitney test, using the SPSS 18.0 Statistical Software package (IBM, Armonk, NY). A value of $p < 0.05$ was considered statistically significant.

RESULTS

Twenty-nine of 30 subjects completed the entire 12-week postoperative course. Subject 014 was lost to follow-up after the 1-week endoscopic debridement. Baseline characteristics of the cohort are provided in Table 1. Twenty of the 30 patients were male subjects, with an average age of 45.33. Seventeen of the 30 (56.7%) patients had nasal polyposis. The mean Lund–Mackay score was 12.5 (SD, 3.2). Ten of the 30 patients underwent revision bilateral total ethmoidectomies. The most common concurrent procedure overall was maxillary antrostomy (95%).

The HA hydrogel showed a statistically significant improvement in overall total endoscopic grading score at both 6 and 12 weeks ($p < 0.05$; Fig. 4). HA hydrogel also showed statistical significance in prevention of synechiae formation at both 6 and 12 weeks ($p < 0.05$), with a concurrent trend toward improved ethmoid remucosalization at 6 and 12 weeks when compared with the ethmoid cavities treated with CMC ($p = 0.08$; Fig. 5). No statistically significant difference in edema, crusting, or mucopurulence was observed in the early postoperative period. Histological analysis showed a nonsignificant ($p = 0.23$) trend toward a greater number of cilia present within the HA hydrogel–treated ethmoid mucosa, when compared with the cavities treated with CMC (Fig. 6).

Overall, patients in this cohort experienced an enormous improvement in quality of life based on SNOT-20 scores at their lowest postoperative level when compared with the preoperative state. A 78.8% improvement was shown (39.90 mean preoperative SNOT-20; 8.45 mean postoperative SNOT-20).

No adverse events were encountered related to either the HA hydrogel or the CMC.

DISCUSSION

In this trial, HA hydrogel (PureRegen Gel Sinus) conferred superior ethmoid cavity healing when compared with CMC (Stammberger Sinu-foam) after endoscopic ethmoidectomy (Fig. 7).

The use of nasal packing in an attempt to minimize complications such as postoperative epistaxis and to improve wound healing after sinus surgery has been used for decades. Unfortunately, the benefits of currently available materials are also associated with some negatives such as the necessity for removal at a certain time interval after surgery, the risk of microbial colonization and infection, and the

ENDOSCOPIC GRADING SCALE

Subject Number: ☐ **Side:** ☐

Measure	1 WEEK	2 WEEK	6 WEEK	12 WEEK
Edema	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	X	X
Crust	Absent (1) Mild (2) Severe (3)	Absent (1) Mild (2) Severe (3)	X	X
Mucopurulence	Absent (1) Mild (2) Severe (3)	Absent (1) Mild (2) Severe (3)	X	X
Re-Epithelialization	< 25% (3) 25-75% (2) > 75% (1)	< 25% (3) 25-75% (2) > 75% (1)	< 25% (3) 25-75% (2) > 75% (1)	< 25% (3) 25-75% (2) > 75% (1)
Synechiae	Absent (1) Mild (2) Severe (3)	Absent (1) Mild (2) Severe (3)	Absent (1) Mild (2) Severe (3)	Absent (1) Mild (2) Severe (3)
Total Score				

Note: the alphabetic number in the bracket indicates the score assigned to each condition, which is used for statistical analysis.

Figure 2. *A novel grading scale for various early and late endoscopic outcome measures after endoscopic sinus surgery (ESS).*

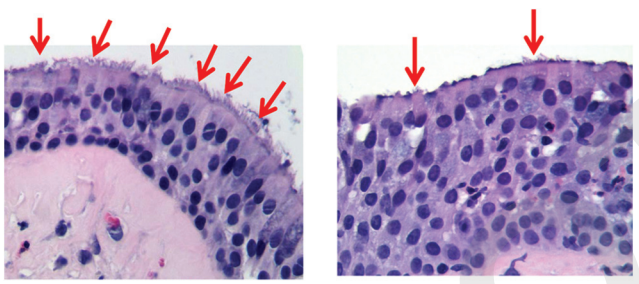

Figure 3. *Histological comparison of mucosal biopsy specimens in subject 025. The hyaluronic acid (HA) hydrogel–treated ethmoid mucosa (left) showed greater regeneration of the brush border with cilia than carboxymethylcellulose (CMC) (right).*

Table 1 **Baseline demographics and clinical characteristics**

n	30
Age (yr), mean (range)	45.33 (21,75)
Male, *n* (%)	20 (66.7)
SNOT-20 baseline total score, mean (SD)	39.90 (18.15)
CRSwNP, *n* (%)	17 (56.7)
CT Lund–Mackay score, mean (SD)	12.5 (3.2)
Primary ESS, *n* (%)	20 (66.7)
Concurrent procedures, *n* (%)	
Maxillary antrostomy	57 (95)
Frontal sinusotomy	34 (57)
Septoplasty	15 (50)
Sphenoidotomy	17 (28)

CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; ESS = endoscopic sinus surgery; SNOT-20; 20-item Sino-Nasal Outcome Test.

tendency to actually promote scarring.[3–6] The ideal postsurgical device or dressing would be absorbable, promote both hemostasis and wound healing, and would not contribute to infection, scarring, or recurrent disease. There remains great potential for improvement.[6,7]

A representative, but nonexhaustive, list of commonly used products includes hemostatic agents derived from gelatinous materials (FloSeal Hemostatic Matrix; Baxter, Deerfield, IL), CMC (Stammberger Sinu-foam), and chitosan (Xerogel; CogENT Therapeutics, Hayward, CA; PosiSep; Hemostasis LLC, St. Paul, MN). Unfortunately, many of these hemostatic agents such as FloSeal and CMC have been shown to actually promote fibrosis in the healing wound, resulting in synechiae and sinus ostial restenosis, which, in turn, may lead to recurrent rhinosinusitis and the need for revision ESS.[7,20–22,24–29]

Other agents may be chosen for their hypothetical activity or proven capability to promote remucosalization and regeneration of cilia after ESS, as well as their ability to minimize synechiae formation in the surgical bed, restenosis of sinus ostia, or lateralization of the middle turbinate. Examples would include esterified HA (MeroGel and MeroPak; Medtronic ENT, Jacksonville, FL), polyvinyl acetate (Merocel, Medtronic ENT), and various proprietary fibrous materials (Nasopore; Polyganics BV, Groningen, The Netherlands; Surgicel; Ethicon, Somerville, NJ). Various clinical trials have concluded that many of these materials either have no statistically significant beneficial effect on remucosalization or regeneration of cilia or have been shown to also contribute to scar formation.[7–12,30,31] As with the hemostatic agents, these types of agents may potentially result in recurrent disease and indications for revision surgery.

More recently, a different type of postoperative nasal device has been approved. A biodegradable, drug-eluting stent, designed to deliver mometasone locally to sinus mucosa during the postoperative period, is in widespread use to prevent synechiae, recurrent polyposis, and middle turbinate lateralization (Propel and Propel mini; Intersect ENT, Menlo Park, CA). This drug-eluting stent possesses perhaps the highest level of both evidence and degree of success, to date, in attaining this aforementioned ideal for a postoperative nasal treatment that is resorbable, imparts beneficial wound-healing effects, and has minimal risk of adverse events.[32–37]

Despite the equivocal data for esterified HA, other forms of HA have been developed and used successfully to promote wound healing and hemostasis in other parts of the body.[13–19] The unique self–cross-linked version of HA in the form of a hydrogel used in this particular clinical trial has shown favorable outcomes in both remucosalization as well as the minimization of bleeding in the sinus cavities in prior animal studies, as well as in a previous human randomized, prospective clinical trial.[18,19,22,38] Although this particular trial reproduced similar findings, the first human trial, performed separately and independently from this trial, was not blinded to the evaluator (the operating surgeons in the previous trial scored the wound healing in their own subjects themselves), and the

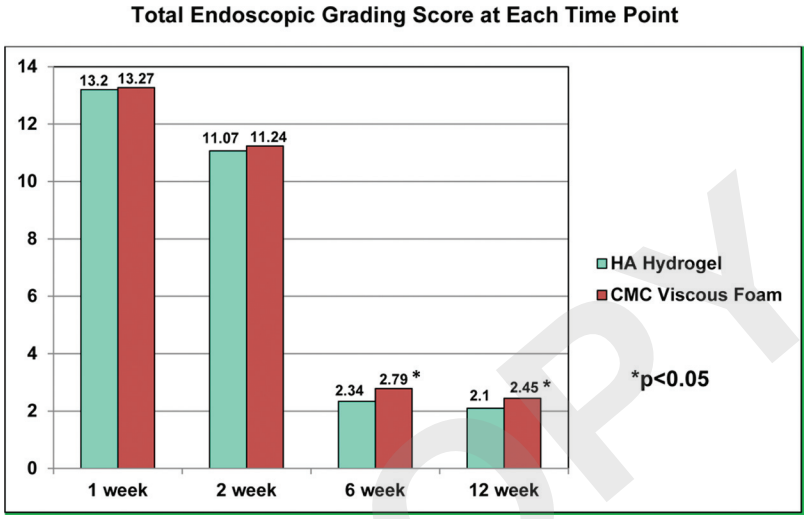

Figure 4. *Average total endoscopic score at each time point. A lower total score is indicative of more favorable wound healing.*

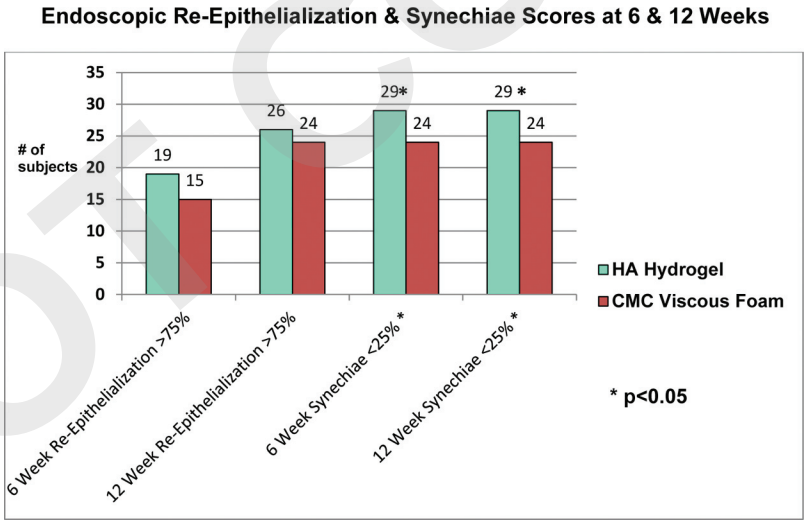

Figure 5. *Number of ethmoid cavities with endoscopic grading scores for reepithelialization >75% and synechiae formation <25% at 6 and 12 weeks.*

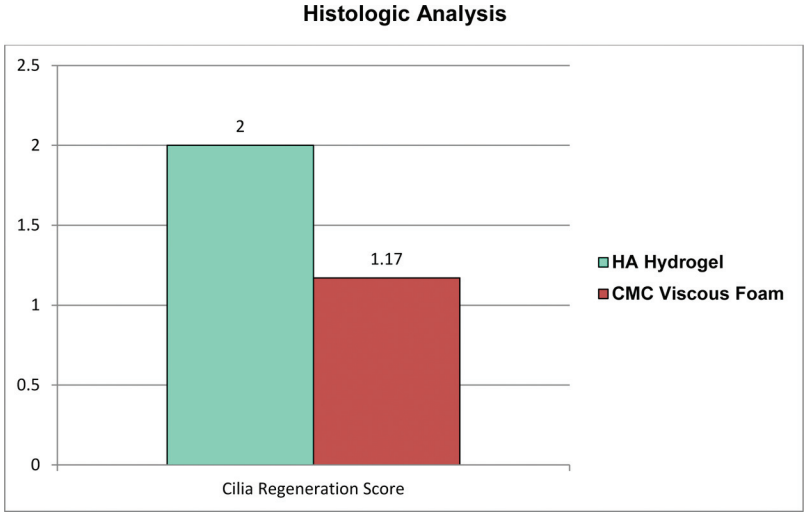

Figure 6. *Average histological scoring comparison based on amount of ciliary regeneration in the ethmoid cavities treated with hyaluronic acid (HA) hydrogel versus carboxymethylcellulose (CMC). A higher score indicates greater ciliary regeneration.*

control was the contralateral untreated ethmoid cavity. Untreated ethmoid cavities have a higher propensity for developing synechiae and have inferior degrees of mucosal regeneration relative to ethmoid cavities treated with a material that promotes positive wound healing.[39,40]

This trial was designed to minimize the weaknesses of the prior HA hydrogel trials by comparing the HA hydrogel to a widely used material (CMC), rather than leaving the contralateral ethmoid cavity untreated. By blinding both the study subjects and the endoscopic evaluator, objectivity was fostered within the data. The operating

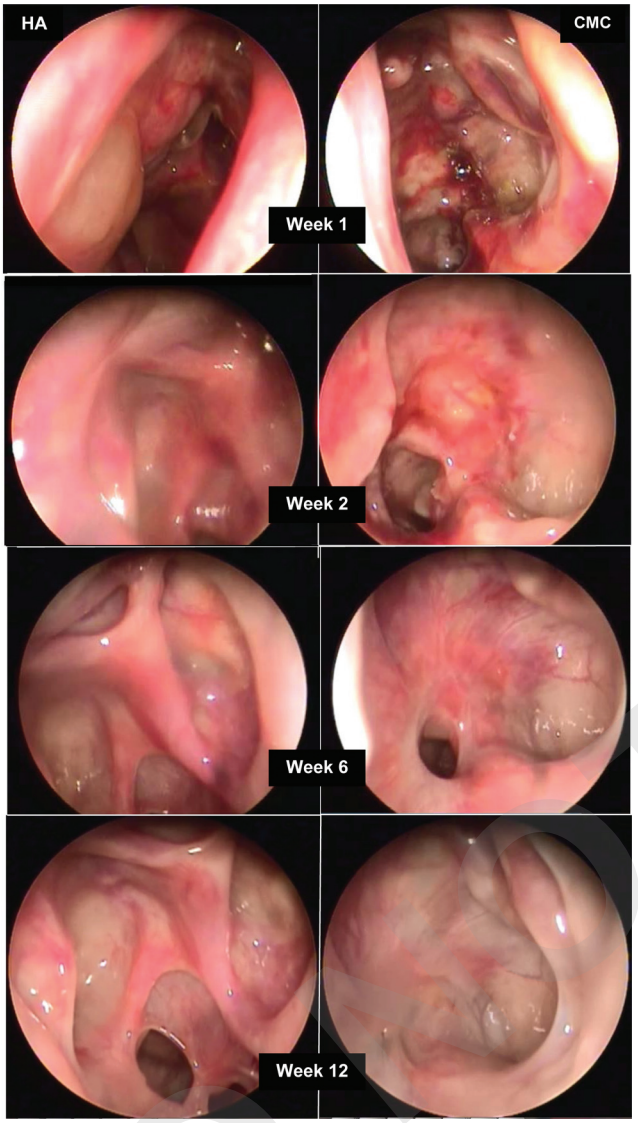

Figure 7. Subject 004 chronologically throughout the four time points of endoscopic evaluation. The hyaluronic acid (HA) hydrogel–treated ethmoid cavity is on the left, with the carboxymethylcellulose (CMC) on the right.

surgeons were not blinded, because the intraoperative preparation and the application devices themselves for the HA hydrogel and the CMC vary substantially, but they were ethically bound to operate on and debride each ethmoid cavity to the best of their clinical judgment. The operating surgeons did not have any role in endoscopic grading or histological analysis to further eliminate the biases of prior trials.

The findings in this study are significant, because much of the prior data on postoperative nasal packing materials are equivocal at best. This self–cross-linked HA hydrogel confers beneficial effects to the ethmoid cavity without some of the negative sequelae associated with the other materials, including acute postoperative bleeding and long-term scarring.

Future trials comparing the HA hydrogel head to head with other widely used postoperative packing materials, using HA in conjunction with the biodegradable mometasone-eluting ethmoid stents, or even investigations into the HA hydrogel's ability to promote closure of septal perforations or tympanic membrane perforations, would potentially be of great interest to clinicians seeking better materials to treat their patients.

ACKNOWLEDGMENTS

The authors thank clinical trial coordinators for Collin County ENT, Jennifer Owens and Wendy Willaby, L.V.N. They also thank Michael Deck, M.D. for his histological analysis and Brad Bader, M.D., of Collin County ENT for review of the article. Author Contributions: K.E. Matheny, substantial contributions to conception and design, acquisition of data and analysis/interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published; E.Y. Tseng, substantial contributions to acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published; K.B. Carter, Jr., substantial contributions to acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published; W.B. Cobb, substantial contributions to acquisition of data, revising the article critically for important intellectual content, final approval of the version to be published; K.J. Fong, substantial contributions to design, acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published.

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Erratum

In the article *Spreader flaps do not change early functional outcomes in reduction rhinoplasty: A randomized control trial* Am J Rhinol Allergy 28, 70–74, 2014; doi: 10.2500/ajra.2014.28.3991, the medical degrees listed for the authors in the author line and one of the author's name, Amin Amali, were incorrect. This is the correct author line: Babak Saedi, M.D.,[1] Amin Amaly, M.D.,[1] Venus Gharavis, M.D.,[1] Batool Ghorbani Yekta, M.D.,[2] and Sam P. Most, M.D.[3]

The authors regret the error.