



# Product Comparison Model in Otolaryngology: Equivalency Analysis of Absorbable Hemostatic Agents After Endoscopic Sinus Surgery

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**Objectives/Hypothesis:** Evidence-based medicine in otolaryngology literature continues to be lacking, especially with regard to new products brought to market. The marketing of products often includes statements of benefit that have limited objective support in research or literature. To address this, and to adequately determine product equivalency/superiority, careful evaluation must be made. In order to establish standards for this process in rhinology products, we directly compare three different absorbable hemostatic agents in patients with chronic rhinosinusitis (CRS) after undergoing endoscopic sinus surgery (ESS), using both objective and subjective outcomes.

**Study Design:** Double-blinded prospective (level 1) comparison and equivalency analysis of three plant-based absorbable hemostatic agents (carboxymethylcellulose [CMC] gel, mucopolysaccharide hemospheres (MPH), and potato starch wafer) in patients undergoing bilateral ESS.

**Methods:** Patients with medically refractory CRS who underwent bilateral ESS were recruited and prospectively followed. At the conclusion of ESS, one of three different hemostatic agents was applied to each nasal passage. Subjective patient data was obtained using rated symptoms compared between the two sides (nasal obstruction, bleeding, pain, and nasal discharge) at baseline and on postoperative days 1, 7, and 14. Objective data was obtained by blinded endoscopic scoring to rate mucosal edema, inflammation, granulation, crusting, infection, and synechiae formation on postoperative weeks 1, 3, and 6.

**Results:** Forty-eight patients who underwent ESS for CRS were included. There is no statistical difference in subjective scores for any of the variables measured, although (MPH) nearly reached statistical significance at postoperative day 7 for increased pain ( $P = 0.06$ ) and obstruction ( $P = 0.22$ ). Objective measures showed equivalency between all products, except the CMC gel approached significance at week 3 for increased crusting ( $P = 0.10$ ), granulation ( $P = 0.24$ ), and debridement ( $P = 0.07$ ). At 6 weeks, increased debridement ( $P = 0.14$ ) also approached significance.

**Conclusion:** Careful and deliberate consideration should be taken when choosing products to assist our surgical endeavors. Subjectively, patients treated with MPH showed near-significant increases in pain and obstruction. In objective measures, CMC gel nearly reaches significance for more postoperative debridement, with increased crusting and inflammation. Product choice could consider these factors, although it remains at the discretion of the surgeon. This model of comparison allows careful product comparison and should be applied to other hemostatics, as well as other materials in use in otolaryngology.

**Key Words:** Hemostasis, biomaterials, absorbable nasal packing, endoscopic sinus surgery, chronic rhinosinusitis.

**Level of Evidence:** 1b.

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Additional Supporting Information may be found in the online version of this article.

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## INTRODUCTION

The impact of chronic rhinosinusitis (CRS) on society is substantial. The prevalence of CRS in the United States is  $4.9\% \pm 0.2\%$ , with significant activity, work, and social limitations.<sup>1</sup> Comparisons of CRS with other chronic diseases revealed significantly lower scores in measures of bodily pain and social functioning in CRS patients than in those patients with congestive heart failure, angina, chronic obstructive pulmonary disease, and back pain.<sup>2</sup> Patients with CRS often have severe forms and require surgical intervention. In those patients, yearly costs related to CRS approach \$2,449.<sup>3</sup> Each year in the United States alone, more than 250 thousand endoscopic sinus surgeries (ESS) are performed, which is a significant cost.<sup>4</sup> In the current era of medical cost awareness and requirements for evidence-based medicine (EBM), any aspect of treatment that adds to that cost must be carefully examined. The postoperative use of

absorbable hemostatics certainly falls into the category of increased cost for a procedure.

Over the last 25 years, sinus surgery has changed from a primarily open procedure to a nearly total endoscopic approach. Severe complications are rare, but relatively minor complications do occur. The most frequent complication of ESS is adhesion formation, occurring in up to 36% of patients.<sup>5</sup> Oftentimes patients are asymptomatic after formation of adhesion, but revision surgery can be necessary if the adhesion obstructs sinus drainage and/or medication delivery. Revision has been estimated to be necessary in up to 25% of patients with adhesions.<sup>6</sup> A second concerning complication after ESS is postoperative hemorrhage. This can be major and require transfusion, which occurs in 0.76%,<sup>7</sup> or it can be relatively minor, with patient reports of excessive perioperative bleeding in 5.0%.<sup>8</sup> To address these two concerns, traditionally nonabsorbable packing was used, such as strips of gauze or specially designed sponges. These devices, however, require postoperative removal that causes significant discomfort and reopens the wound bed. Much of the societal trepidation toward sinus surgery is due to the historical need for removal of this packing. In order to address these issues, many bioabsorbable hemostatics have been developed that do not require removal. The perfect ESS hemostatic would prevent adhesions by controlling the middle turbinate, allow for drug delivery if desired, prevent postoperative hemorrhage, promote mucosal regeneration/prevent inflammation, minimize patient discomfort, be affordable, and limit postoperative debridement.

Given that otolaryngology and sinus surgery comprise a relatively small area of the overall surgical field, products that come to market for use after ESS frequently have been adapted from other surgical fields. One of the first major products to make this transition was FloSeal (Baxter Healthcare Corporation, Deerfield, IL). Combining bovine collagen with human thrombin, it has excellent hemostatic properties; as a foam, it controls the middle turbinate well. It quickly became commonplace to use at the completion of ESS. With widespread intranasal use, however, it subsequently became clear that FloSeal (Baxter Healthcare Corporation) caused a brisk inflammatory response, and instead of preventing adhesions, it encouraged their formation.<sup>9</sup> Two studies using a rabbit model to simulate sinus surgery revealed that FloSeal (Baxter Healthcare Corporation) not only caused a brisk inflammatory response but also was incorporated into the healing mucosa with significant granulation tissue formation.<sup>10,11</sup> Although FloSeal (Baxter Healthcare Corporation) has subsequently fallen out of favor for intranasal use post-ESS, the damage had been done. Biomaterials continue to be adapted for intranasal use, and only a select few have done the due diligence to evaluate in animal model and subsequent critical evaluation in humans. Additionally, when choosing a particular product of those available for post-ESS, there is a dearth of available critical comparative evaluation. In order to address this lack of evidence-based medicine, we designed a study with three specific aims.

### ***Specific Aim 1***

The first aim was to critically evaluate the subjective differences patients observe between the two sides treated with different absorbable hemostatic agents. Equivalency versus superiority will be assessed.

### ***Specific Aim 2***

The second aim was to evaluate the objective differences observed on postoperative endoscopic examinations. Equivalency versus superiority in adhesion formation/prevention, the need for debridement, as well as other parameters, will be examined.

### ***Specific Aim 3***

The third aim was to establish a model for critically evaluating hemostatic agents used after ESS. There has been a proliferation of these materials, and there is tremendous variability of study of each product regarding sinonasal safety and efficacy for hemostasis/adhesion control. The primary goal of this study is to discuss ideal product evaluation from the initial steps prior to market introduction all the way through the evaluation performed in this study. Vital to evaluation of these materials is this process of critical comparative product evaluation, which allows for an informed EBM decision when choosing a hemostatic agent.

## **MATERIALS AND METHODS**

### ***Patient Selection***

Adult patients (> 18 years of age) with bilateral chronic rhinosinusitis recalcitrant to maximal medical therapy who had posttreatment computed tomography (CT) scan consistent with CRS were recruited. No patients were included unless they were recommended and had agreed to undergo ESS. A careful record of their medications and past medical history was made. Those with massive sinonasal polyposis, bleeding diatheses, history of severe immunodeficiency, immotile cilia syndrome, neutropenia, and/or known hypersensitivity to the study agents were excluded. Institutional review board (IRB) was obtained from both tertiary care hospitals at which the study was performed. No monetary compensation was offered to either the participants in this study, the investigators, the physicians, or other health care providers for identifying and enrolling subjects. The respective companies donated all hemostatic agents for the study. No company had any input in the design, recruitment, analysis of data, or decision to publish the data.

### ***Sample Size***

The study design was a prospective, double-blind comparison level 1 evaluation. Sample size was calculated using: <http://www.danielsoper.com/statcalc/calc01.aspx>. Statistical power was 85 or higher, with type 1 error rate ( $\alpha$ ) of 0.05, which meant the value should be less than or equal to 0.05 to claim statistical significance ( $p \leq 0.05$ ). We had three groups, and the anticipated effect size ( $f^2$ ) was expected to be medium (0.15). In this setting, the minimum number of anatomic for the study was 86. Thus, with a goal sample size of 45 patients and a total of 90 sides, sinus cavities were divided into three groups of 30. Our null hypothesis comes from the assumption of similar effects

and side effects of the three agents, which represents an equivalency analysis.

### ***Surgical Procedure***

Patients who agreed to participate underwent ESS using mucosal-sparing techniques, with meticulous hemostasis during and at the end of the procedure; J.L.A. or S.K. were senior surgeon. One of the hemostatic agents was placed on each side in a randomized fashion. Patients were blinded to which product they would receive and which side was treated with what product. No other packing or splints were used. All patients were discharged the same day with pain medication, a 7-day course of oral antibiotics, and instructions to begin saline irrigations on postoperative day (POD) 1. Patients returned for postoperative visits on postoperative weeks (POW) 1, 3, and 6 and were evaluated, debrided as needed, and medically managed as appropriate.

### ***Hemostatics***

Three absorbable hemostatic agents were evaluated: Sinufoam (Arthrocare, Austin, TX), Arista (Medafor Inc., Minneapolis, MN), and Nexfoam (Hemostasis LLC, St. Paul, MN). All three products are U.S. Food and Drug Administration approved for use as topical dressings for the treatment of moderate to severe bleeding wounds, such as surgical wounds. In this study, the agents were used according to package insert instructions to achieve hemostasis after ESS.

Sinufoam (Arthrocare) is a foam/gel made from a carboxymethylcellulose (CMC) derivative. Carboxymethylcellulose is able to absorb many times its weight in water; however, in the gel form it has already been hydrolyzed prior to placement in the nasal cavity. Thus, although it achieves some hemostasis by absorbing water in blood, it primarily achieves hemostasis by pressure. It also provides a moist wound environment and with its viscosity and density provides a scaffold for epithelialization. Carboxymethylcellulose is cleared primarily by mucociliary clearance and irrigation. Additionally, it provides pressure against surfaces to which it is applied, such as medializing the middle turbinate. Arista (Medafor Inc.) is a powder composed of potato starch-derived mucopolysaccharide hemospheres (MPH), which are rapidly cleared from the human body by mucociliary clearance and chemical breakdown of polysaccharides, with minimal interruption in wound healing. Hemostasis is achieved by absorption of water from the blood and providing scaffolding for clot formation. As it is a powder, there is no pressure applied, nor is the middle turbinate medialized. Nexfoam (Hemostasis LLC) (heretofore referred to as starch wafer) is a compressible wafer made from potato starch that expands when hydrolyzed. It is also rapidly cleared from the nasal cavity via mucociliary clearance and irrigation. It achieves hemostasis by absorbing water but is not hydrolyzed until after it is in place in the nasal cavity. It also applies pressure and medializes the middle turbinate.

### ***Specific Aim 1: Subjective Evaluation***

Patients were given an instruction sheet explaining the scale for each symptom to be rated. This was an attempt to normalize the data between patients. Rated symptoms were nasal obstruction, bleeding, pain, and nasal discharge on a visual analog scale ranging from 1 to 10. Each side of the nose/sinuses was evaluated independently. Patient questionnaires were completed on PODs 1, 7, and 14. This questionnaire was adapted from previously published literature on this topic.<sup>11,12</sup> See Supp. Appendix I for the patient instructions and questionnaire.

### ***Specific Aim 2: Objective Evaluation***

Objective evaluation was performed during routine postoperative visits 1, 3, and 6 weeks after surgery. Blinded physicians performed endoscopic examinations with debridement as needed. Parameters evaluated included synechiae formation, mucosal edema, evidence of infection, granulation tissue formation, crusting, and time required for debridement. This questionnaire is adapted from previously published literature on this topic.<sup>12,13</sup> See Supp. Appendix I for the physician questionnaires.

### ***Specific Aim 3: Exhibit Model for Product Evaluation in Rhinology Literature***

Extensive literature review and analysis was performed regarding current and previous materials available for post-ESS use. Critical review of these studies is below. The current model is discussed in detail regarding this study, as well as application toward future otorhinolaryngologic studies.

### ***Statistical Analysis***

Data were analyzed using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, NY). Comparisons were made using non-parametric tests (Kruskal-Wallis test) for ordinal data and one-way analysis of variance for continuous data.

## **RESULTS**

The study took place over 2 years, from May 2011 to November 2013. Fifty-two patients were enrolled in the study. Four patients failed to follow up postoperatively and did not complete any patient questionnaires; thus, they were removed from the study. Forty-eight patients (30 females and 18 males) were included in the study, split between two tertiary care institutions. The average age was 48 years (range 18–77 years). Each patient had a history of CRS without major comorbidities, with no prior history of coagulopathy, and none were pregnant. Fourteen patients (29%) had asthma, 18 (38%) had allergic rhinitis, and 19 (40%) had nasal polyposis. One patient (2%) had aspirin sensitivity, two (4%) had cystic fibrosis, one (2%) had IgG deficiency, and one (2%) had mild immunodeficiency. Twenty patients (39%) had previously undergone one or more sinus surgeries. The mean preoperative Lund-Mackay CT score was 14, which reflects bilateral disease involving the maxillary and ethmoid sinuses with frontal or sphenoid involvement. All patients had bilaterally symmetric disease, with the same extent of surgery performed on each side. The mean estimated blood loss was 132 mL. There were no intraoperative complications, and all patients were discharged home on the same day. There were no instances of significant postoperative bleeding requiring further intervention. Demographics are noted in Table I. There were no significant differences between the three groups with regard to demographics or severity of disease.

### ***Subjective Symptoms***

Analysis of the data was broken down into two parts. Regarding the subjective patient data, there were no statistically significant differences in any of the four variables measured at any point, although several

TABLE I.  
Patient Characteristics.

Age	48 yrs
Male sex	18 (38%)
Asthma	12 (29%)
Allergic rhinitis	18 (38%)
Nasal polyposis	19 (40%)
Lund-MacKay computed tomography	14
Primary ESS	29 (60%)
Revision ESS	19 (40%)

ESS = endoscopic sinus surgery.

variables approached significance. Pain (Fig. 1) showed that the starch wafer and CMC gel followed the same trend in general. Mucopolysaccharide hemospheres had similar scores on POD 1 and 14, but on POD 7 there were higher pain scores that approached significance ( $P = 0.06$ ). Obstruction (Fig. 2) once again showed similar curves for all three products, with MPH showing increased obstruction throughout all three data collection points. This was most noted on POD 7 with  $P = 0.22$ .

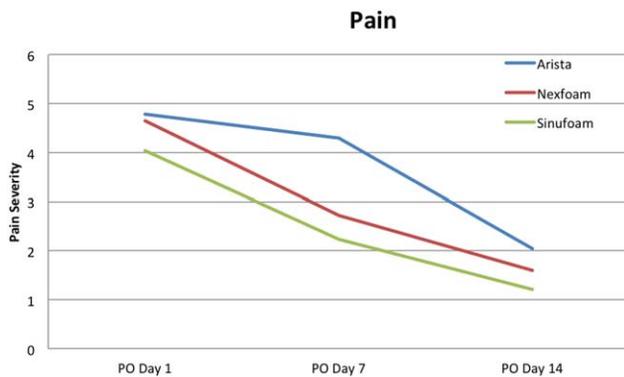


Fig. 1. Pain scores ranked subjectively scored by patients. POD 7 pain scores are higher in the Arista group ( $P = .06$ ). [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

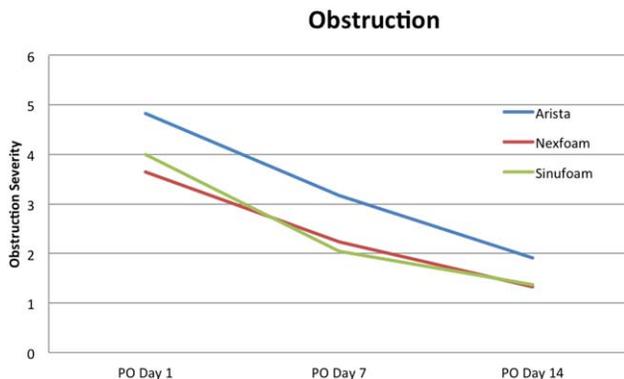


Fig. 2. Degree of obstruction subjectively scored by patients. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

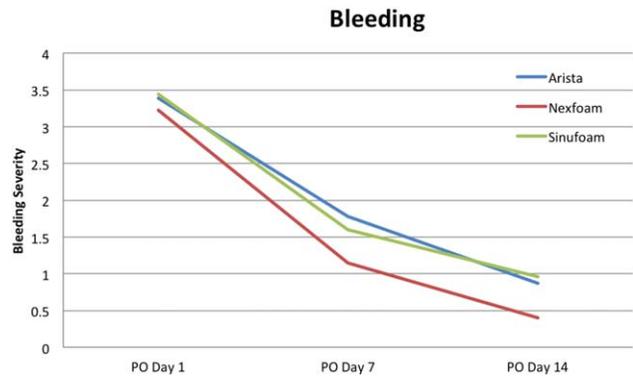


Fig. 3. Amount of bleeding subjectively scored by patients. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

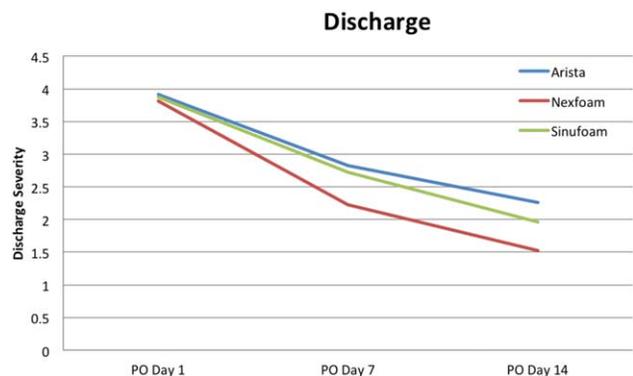


Fig. 4. Amount of discharge subjectively scored by patients. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

Regarding postoperative bleeding (Fig. 3), the three curves were mirror images with no significant differences. The starch wafer curve showed the least bleeding in general. Discharge (Fig. 4) showed nearly identical findings to bleeding with starch wafer curve the lowest.

### Objective Symptoms

The second aspect of data analysis was objectively reported blinded physician data from postoperative endoscopy. Six categories were scored according to the questionnaire in Supp. Appendix I. First, synechiae formation was not significantly different between the three groups at any of the three points (Table II). Given that synechiae are arguably the most important outcome, especially long-term, the POW 6 data are most important. Scores of 2 and above represent significant scarring. There was one patient in the MPH group with significant synechiae, two in the CMC gel group, and none in the starch wafer group. At POW 6, there was a 4.2% rate of significant synechiae formation, with an overall synechiae rate of 19.4%.

Debridement scores showed no significant difference at the POW 1. At POWs 3 and 6, there were increased

TABLE II.  
Objective Grading at Post-Operative Visits.

Synechiae												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	23	8	0	0	24	4	2	0	18	4	1	0
Nexfoam	25	4	2	0	22	6	0	0	20	3	0	0
Sinuf foam	29	5	0	0	26	5	1	0	20	4	2	0
Significance	$P = .55$				$P = .98$				$P = .59$			
Debridement												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	2	19	9	1	16	8	6	0	19	4	0	0
Nexfoam	3	19	8	1	17	8	3	0	20	3	0	0
Sinuf foam	2	20	10	2	10	15	5	2	17	8	1	0
Significance	$P = .77$				$P = .07$				$P = .14$			
Crusting												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	6	15	6	4	17	11	2	0	21	2	0	0
Nexfoam	7	18	6	0	20	7	1	0	20	3	0	0
Sinuf foam	1	25	8	0	14	15	3	0	20	5	1	0
Significance	$P = .30$				$P = .10$				$P = .34$			
Granulation												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	26	5	0	0	26	3	1	0	21	2	0	0
Nexfoam	27	3	1	0	25	3	0	0	23	0	0	0
Sinuf foam	29	2	2	1	24	5	1	2	24	2	0	0
Significance	$P = .94$				$P = .24$				$P = .37$			
Mucosal Edema												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	4	26	1	0	15	13	2	0	16	7	0	0
Nexfoam	5	23	3	0	13	12	3	0	15	8	0	0
Sinuf foam	7	27	0	0	13	17	2	0	14	12	0	0
Significance	$P = .43$				$P = .81$				$P = .50$			
Infection												
	1 week				3 weeks				6 weeks			
	0	1	2	3	0	1	2	3	0	1	2	3
Arista	30	1	0	0	28	2	0	0	22	1	0	0
Nexfoam	30	1	0	0	24	4	0	0	20	3	0	0
Sinuf foam	34	0	0	0	27	5	0	0	21	5	0	0
Significance	$P = .57$				$P = .52$				$P = .29$			

debridement requirement in the CMC gel group,  $P = 0.07$  and  $P = 0.14$ , respectively. The amount of crusting, which is related to the amount of debridement required, showed similar results. Throughout the entire 6 weeks, there was more crust noted in the CMC gel patients, most distinguished at POW 3 with  $P = 0.10$ . A third category, granulation, also showed an increase in CMC gel patients, peaking at POW 3 with  $P = 0.24$ .

The final two categories were mucosal edema and infection. These categories were consistent across all products at all time points. It is important to note that neither edema nor infection occurred frequently. As is the normal post-ESS course, mild mucosal edema was present at POW 1 and dissipated by POW 6.

## DISCUSSION

Evidence-based medicine has been defined by Sackett et al. as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”<sup>14</sup> In order to deliver the best possible care for our patients at the best value, quality EBM should be used to drive patient care decisions whenever possible. Current rhinology research is driving hard toward this goal with regard to many aspects of CRS care.<sup>15</sup> The present study is excellent EBM for evaluating these hemostatics and provides framework for further product comparison.

The subjective findings suggest that it is difficult for patients to distinguish between the three products. The starch wafer shows a trend to have less bleeding and discharge, although there is no statistically significant difference. The most important variable measured is bleeding; from a patient perspective, this is a primary reason for placing postoperative packing. Previous work with MPH showed that patients report a 40% decrease in bleeding on POD 1 when compared to the opposite control side that was untreated.<sup>16</sup> Previous work with CMC gel revealed that patients were unable to discern a significant difference in bleeding between the packed and untreated side, although there was a trend for less bleeding.<sup>17</sup> The starch wafer has not undergone similar study, although it is very similar to MPH in makeup. In general, the starch wafer does seem to show a general curve, with the lowest rate of bleeding and discharge. This possibly represents the fact that it combines the best aspects of the other two materials. It is placed dry, and thus can absorb water from the surrounding blood to maximally achieve hemostasis. It is then hydrolyzed, and thus can apply some pressure as well.

The other finding in the subjective scores was the increased pain scores at POD 7 for MPH, as well as the generally higher MPH curve for obstruction. The delivery of the three products is different. Available as a dry powder, MPH is placed and not hydrolyzed. This covers the mucosa uniformly in a dry manner but does not fill the space of the anterior middle meatus. Both the starch wafer and the CMC gel are hydrolyzed and fill the

anterior middle meatus, putting mild pressure on the anterior middle meatus and creating a moist covering. All three products are irrigated out to a degree, starting on POD 1. For what would be expected to be a more open sinus cavity with MPH, it is unclear why there would be more pain and obstruction. We postulate that either the dry crust creates more pain/obstruction sensation or that, during the early healing phase, having the anterior middle meatus blocked by the other products protects the sensitive postoperative mucosa from exposure to air. The confounding aspect is that, on the first postoperative visit, MPH does not show increased crusting or obstruction of the middle meatus. Further evaluation of this phenomenon is warranted.

The objective findings more strongly suggest a difference between the products. Several variables nearly reached significance, including increased crusting, granulation, and debridement for the CMC gel, suggest that this material is not as easily cleared with irrigations. The anecdotal experience of the blinded physicians was that one of the three products clearly required consistently more debridement. More extensive debridement is uncomfortable for the patient and incurs increased cost for the care of the patient. Increased granulation also suggests an inflammatory component associated with the continued presence of CMC. The evaluation of granulation tissue formation is of particular importance given previous findings in animal and human studies of FloSeal (Baxter Healthcare Corporation) having increased granulation formation in an animal model, and thus increased synechiae in humans. With regard to synechiae, the rates in this study of 4.2%, with significant synechiae formation and an overall synechiae rate of 19.4%, are well within previously reported rates.<sup>5,12,13</sup> Additionally, although synechiae was not statistically significant, two of the three significant synechiae occurred in the CMC group.

Previous work in the literature regarding nasal packing has been diverse, with conflicting findings. The two most cited studies that are not in favor of packing are by Eliashar<sup>18</sup> and Orlandi.<sup>19</sup> Eliashar et al. retrospectively reviewed a cohort on 92 consecutive ESS patients.<sup>18</sup> Patients were packed only if there was still bleeding 5 minutes after completion of ESS. Only 8% of patients were packed (microfibrillar collagen, tranexamic acid, or polyvinyl acetyl sponge), and none of the non-packed patients had a postoperative bleed. The authors postulate that nasal packing is not routinely necessary. General anesthesia and increased intraoperative bleeding were associated with a need for packing. In 2009, Orlandi and Lanza performed a retrospective review of 169 ESSs.<sup>19</sup> Only 2.4% of the patients had absorbable hemostatic agents placed; 11.2% had packing; and 87% had no material left in the nose. There were no postoperative bleeding complications, and the authors postulate that neither nasal packing nor hemostatic agents are not necessary for the majority of ESS.<sup>19</sup> However, there are two primary issues with both of these studies. First, they are both retrospective in nature, with each patient having been packed or not. Second, there is no randomization to the packing and no actual control group.

Patients need to serve as their own control. This leads to the second and more important issue: there is no patient evaluation of the degree of bleeding. Patients often experience a significant amount of bleeding that is distressing but not severe enough to require physician intervention. Neither of these studies evaluate from the patient perspective. As previously mentioned, more recent studies by Antisdell et al.<sup>11</sup> and Kastl et al.<sup>17</sup> used patient-reported surveys to evaluate the postoperative bleeding between treated and untreated sides. In the study by Antisdell et al., there was the aforementioned 40% reduction on the treated side, suggesting that at least one hemostatic material is effective for reducing the “nuisance bleed.”<sup>11</sup> For this reason, the current study incorporated this patient reported symptoms design.

Other studies have supported the use of nasal packing. Bugten et al. reported in 2009 regarding the use on nonabsorbable packing (NAP) for 5 days after ESS.<sup>20</sup> The randomized, controlled trial included 31 patients who had bilateral NAP and 28 who had no packing. The NAP group had significant decrease in adhesion formation and reported that NAP did not cause additional discomfort. In contrast, Franklin and Wright performed a prospective randomized study with NAP (polyvinyl acetate sponge) versus absorbable packing in each middle meatus post-ESS.<sup>21</sup> The absorbable packing was greatly preferred by the patients. Many subsequent studies have continued to use this NAP sponge as the control when comparing to a new hemostatic. Additionally, many surgeons advocate using NAP sponge in a glove finger. Kim et al. reported packing with glove finger resulted in less pain, less bleeding on packing removal, and improved postoperative wound healing.<sup>22</sup> Akbari et al. report that in their study, in which a gloved versus nongloved NAP sponge was placed on each side in the same patient,<sup>23</sup> there was equivalent mucosal inflammation and postoperative discomfort but significant reduction in pain on removal of the gloved NAP sponge.

There have been several review articles on the use of absorbable packing material. In 2008, Weitzel and Wormald reported that with regard to traditional agents such as oxidized regenerated cellulose, hyaluronic acid, porcine gelatin/collagen, and mitomycin C, there currently is no randomized controlled trial demonstrating any wound-healing advantages as compared with no treatment at all.<sup>24</sup> In 2010, this was reiterated by Valentine and Wormald in a best practices review,<sup>25</sup> as well as in another similar review.<sup>5</sup> The authors additionally review FloSeal (Baxter Healthcare Corporation), CMC, Nasopore (Polyganics, Groningen, The Netherlands), MPH, and chitosan dextran (CD). FloSeal (Baxter Healthcare Corporation) is discussed above in this article and is not recommended for post-ESS use because it is left in the nose. It is an excellent example of how some products will perform excellently in one area (hemostasis) but can have significant side effects (increased inflammation and synechia). Carboxymethyl-cellulose is also discussed in this article, and the studies showed no effect on wound healing or bleeding compared to untreated control sinuses.<sup>17,26</sup> Nasopore (Polyganics), a synthetic dissolvable biodegradable polyurethane foam,

was examined by Shoman et al.; when compared with gloved NAP sponge, it had worse endoscopic mucosal scores at 1 month that resolved by 3 months.<sup>27</sup> There were no other differences between the two groups. Verim et al. evaluated polyurethane foam versus nongloved NAP sponge and found no significant differences in healing or surgical outcomes.<sup>28</sup> Pain, bleeding, nasal blockage, and facial edema were lower with the polyurethane foam. Kastl et al. compared polyurethane foam to the untreated control side.<sup>29</sup> No difference in bleeding or nasal obstruction was noted, although there was less facial pressure on the polyurethane foam side.

The final hemostatics discussed in these reviews are CD and MPH. The research on these hemostatics provides a model with which to initially review materials for their use after ESS. Chitosan dextran has long been used in abdominal and pelvic surgery to prevent adhesions. Wormald et al. started their work in the ESS sheep model. Chitosan dextran significantly improved wound healing and reduced adhesion formation compared to other topical agents.<sup>30</sup> Chitosan dextran also significantly reduced intraoperative bleeding compared to no treatment control.<sup>31</sup> Following this work in the sheep model, human study showed that intraoperative hemostasis was significantly less than untreated control side. Postoperatively, the CD side showed significantly less adhesions than the control, with all other parameters (crusting, mucosal edema, infection, and granulation tissue) showing no difference between sides.<sup>12</sup> This was the first, and currently only, absorbable hemostatic to show decreased adhesions compared to untreated control. This study did not examine subjective patient rated symptoms. Most recent work on CD showed that CD safely controls the bleeding in brain tissue<sup>32</sup> and that CD gel produces significantly less stenosis of neoostia following ESS.<sup>33</sup> Similarly, MPH initially was studied in a rabbit ESS model, where it did not detrimentally affect sinus mucosa as compared to untreated controls.<sup>11</sup> As mentioned above, subsequent work revealed significant decreased POD 1 bleeding, with no increase in adhesions as compared to untreated control sides.<sup>13,16</sup> The first absorbable hemostatic to show decreased subjective postoperative bleeding was MPH.

We propose that biomaterials for the use in ESS follow the above model for initial evaluation. The final and most important step for product superiority is analysis in the same manner as the current study. This crucial step allows for an EBM decision of what can be a critical choice for both patient comfort and long-term surgical outcomes.

The hemostatics included in this study were chosen based on market popularity, availability in the United States at the time of study inception, and previous literature; all were plant-based. Polyurethane foam was not chosen due to its poor performance in previous studies, and CD was not yet available in the United States. Since the inception of this study, other forms of chitosan have come to market, but these are formulated differently and have not been adequately studied in ESS.

A final consideration regarding nasal packing is the delivery of medications. There are two aspects of this. First, drug-eluting stents are now available. These

stents are designed to deliver medication to the nasal mucosa during the postoperative period and then dissolve over time. The stents keep the middle turbinate medialized during this period. It is unclear how absorbable hemostatics will interact with these stents, with possible increased associated crusting as well as possible interference with elution of medication. It also raises the question of why have a hemostatic that medializes the middle turbinate if there already is a stent performing the function. Further study is warranted in this area.

The second aspect of delivery of medications is using the actual hemostatic to deliver the medication. Cote and Wright used polyurethane foam bilaterally on patients after ESS, with one side impregnated with triamcinolone and other with saline.<sup>34</sup> There was significant improvement in endoscopy scores at all points from POD 7 and lasting through 6-month endoscopies. Chang et al. examined the effect of Manuka honey-, gentamicin-, and budesonide-soaked NAP sponge versus untreated NAP sponge and found no difference with any of these medications.<sup>35</sup>

Mo et al. used polyurethane foam that was soaked in 2% lidocaine versus saline and showed significant decrease in postoperative pain.<sup>36</sup> On the other hand, Hong et al. examined the cortisol levels after using triamcinolone-impregnated absorbable dressing and found suppressed cortisol levels during the early postoperative period that normalized by 10 days.<sup>37</sup> Three studies additionally looked at polyurethane foam<sup>38</sup> and CMC foam<sup>39,40</sup> as steroid delivery vehicles in the office setting for exacerbations of nasal polyposis. All studies showed efficacy in decreasing polyposis and a need for oral prednisone use. The model of the current study should also be used to compare between hemostatics as medication delivery vehicles in both the office and the postoperative setting.

Even considering all the above discussion, there remains significant disagreement over whether packing should be used on a routine basis. Wang et al. performed a systematic review and meta-analysis of studies comparing absorbable to NAP.<sup>41</sup> The lack of homogeneity between studies made definitive conclusion impossible. To address the question of whether absorbable hemostatics should be routinely used after ESS, the authors of this study are currently performing a multi-institutional double-blinded control study of currently available absorbable hemostatics versus no treatment on the control side. Also, given the multiple studies regarding patient discomfort with NAP removal, we propose that when evaluating new hemostatics, the control side should be treated with no packing instead of NAP. This study suggests that both MPH and starch wafer are equal choices. Further comparison to CD is warranted; as new hemostatics are introduced, they should be critically evaluated. Until a definitive answer is reached regarding these questions, the choice of whether to pack and what to use for nasal packing remains at the discretion of the surgeon.

The limitations of this study are three-fold. First, despite the limitations shown in its initial studies, polyurethane foam has become increasingly popular. This material should undergo comparative evaluation with the materials evaluated in this study, as should CD

when it becomes available in the United States. Second, the patients for this study were carefully selected to rule out confounding variables and may not represent a real-world sample. For instance, many patients undergo concomitant septoplasty with possible stent placement. These patients may not be able to appreciate the differences noted when packed or not. The final concern is that there continues to be mixed views on the necessity of standard packing after ESS. We feel that, given the MPH study results combined with our current study results, their routine use is warranted. The aforementioned ongoing clinical trial should answer this question definitively. Other possible limitations would be surgeon differences and medical management. Two surgeons, J.L.A. and S.K., were primary surgeon on all the cases and use very similar techniques for ESS and medical management. Additionally, all patients received the same perioperative medical management.

The strengths of this study are as follows: The design was a randomized, controlled, double-blind level 1 study. Patients were carefully selected to eliminate confounding variables and underwent extensive subjective and objective evaluation. The study is appropriately powered. Compared to most previous studies that do not address patient bleeding concerns, the vital question of how the patient perceives the amount of postoperative bleeding is answered. Additionally, granulation and the amount of postoperative debridement required were carefully evaluated.

## CONCLUSION

The evaluated hemostatics are not statistically different in subjective or objective measures. Near-significant findings suggest that CMC gel remains in the nasal cavity longer and requires more debridement. Subjectively, patients treated with MPH reported near-significant increases in pain and obstruction. Although not conclusive for these hemostatics, this model has provided a starting point for choosing between these products. The decision of whether or not to use nasal packing, and what that packing is, remains at the discretion of the surgeon. Additionally, this model can and should be used for further development of EBM to compare other products for use in the nose, as well as in otolaryngology in general.

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