

Randomized Controlled Trial of a Bioabsorbable Steroid-Releasing Implant in the Frontal Sinus Opening

Timothy L. Smith, MD, MPH; Ameet Singh, MD; Amber Luong, MD, PhD; Randall A. Ow, MD;
Steven D. Shotts, MD; Nathan B. Sautter, MD; Joseph K. Han, MD; James Stambaugh, BS;
Aarthi Raman, PhD

Objectives/Hypothesis: To assess safety and efficacy of a steroid-releasing implant in improving surgical outcomes when placed in the frontal sinus opening (FSO) following endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis (CRS).

Study Design: Prospective, multicenter, randomized, blinded trial using an inpatient control design.

Methods: Eighty adult (≥ 18 years) CRS patients who underwent successful bilateral frontal sinusotomy were randomized to receive a steroid-releasing implant in one FSO, whereas the contralateral control side received no implant. All patients received standard postoperative care. Endoscopic evaluations recorded at 30-days postendoscopic sinus surgery (ESS) were graded real time by clinical investigators and by an independent, blinded sinus surgeon to assess the need for postoperative interventions in the FSO.

Results: Implants were successfully placed in all 80 frontal sinuses, resulting in 100% implant delivery success. At 30-days post-ESS, steroid-releasing implants provided a statistically significant ($P = 0.0070$) reduction in the need for postoperative interventions compared to surgery alone by an independent reviewer, representing 38% relative reduction. Clinical investigators reported statistically significant reduction in this measure at 30 days ($P < 0.0001$) and 90 days ($P = 0.0129$). Clinical investigators also reported a 55.6% reduction in the need for oral steroid interventions ($P = 0.0015$), 75% reduction in the need for surgical interventions ($P = 0.0225$), 16.7% reduction in inflammation score, 54.3% reduction in restenosis rate ($P = 0.0002$), and 32.2% greater diameter of FSO ($P < 0.0001$) on treated sides compared to control at 30 days. No implant-related adverse events were reported.

Conclusion: This study demonstrates the efficacy of steroid-releasing implants in improving outcomes of frontal sinus surgery.

Key Words: Corticosteroid, mometasone furoate, polyposis, inflammation, frontal sinusotomy, functional endoscopic sinus surgery (FESS), absorbable implant, frontal sinus.

Level of Evidence: 1b.

Laryngoscope, 00:000–000, 2016

From the Department of Otolaryngology–Head and Neck Surgery, Oregon Health Sciences University (T.L.S.); the Providence St. Vincent Medical Center (N.B.S.), Portland, Oregon; the Department of Surgery and Neurosurgery, George Washington Medical Faculty Associates (A.S.), Washington, DC; the Department of Otorhinolaryngology, McGovern Medical School at the University of Texas Health Science Center of Houston (A.L.), Houston, Texas; the Advanced ENT and Allergy (S.D.S.), Louisville, Kentucky; the Divisions of Rhinology and Endoscopic Sinus-Skull Base Surgery and Allergy, Eastern Virginia Medical School (J.K.H.), Norfolk, Virginia; the Sacramento ENT (R.A.O.), Roseville; and the Intersect ENT (J.S., A.R.), Menlo Park, California, U.S.A.

Editor's Note: This Manuscript was accepted for publication May 25, 2016.

The sponsor (Intersect ENT) provided funding for the investigation, as well as administrative and logistical support in coordinating the study across the study sites. J.K.H. was a consultant for Intersect ENT (Menlo Park, CA), T.L.S. (until February 2015) and R.A.O. (until January 2015) were consultants for Intersect ENT during the conduct of this study. J.S. and A.R. are employees of Intersect ENT. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Timothy L. Smith, MD, MPH, Oregon Health & Science University, Department of Otolaryngology–Head and Neck Surgery, Division of Rhinology and Skull Base Surgery, 3181 SW Sam Jackson Park Road, PV-01, Portland, OR. 97239. E-mail: smitht@ohsu.edu

DOI: 10.1002/lary.26140

INTRODUCTION

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses.¹ Endoscopic sinus surgery (ESS) is largely successful in treating CRS.² However, frontal sinusotomy has been shown to have a lower success rate^{3,4} depending on the preoperative conditions, extent of frontal sinusotomy, and postoperative medical management of the frontal recess.⁵ Reasons for failure of frontal ESS include persistent or recurrent inflammation and circumferential scarring at the frontal recess, leading to restenosis and occlusion of the frontal sinus opening (FSO), which may lead to the need for revision.^{5,6}

Success of frontal sinusotomy is in part dependent on optimization of the postoperative wound-healing process.^{7,8} Postoperative regimens of topical corticosteroids, saline irrigations, oral steroids, and immunomodulators to prevent adhesion and scarring⁸ and enhance mucosalization⁹ have been advocated.

Currently approved by the U.S. Food and Drug Administration, two steroid-releasing implants have been shown to significantly reduce the need for postoperative interventions in the ethmoid sinuses^{10–13} through

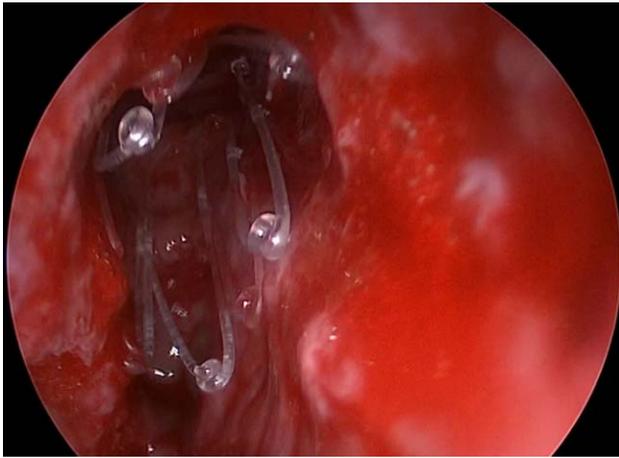


Fig. 1. Steroid-releasing sinus implant in the right frontal recess immediately following surgery. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

physical scaffolding of the middle turbinate and localized, controlled delivery of corticosteroid (370 μg of mometasone furoate [MF]). The current study was designed to assess the safety and efficacy of the steroid-releasing sinus implant in reducing the need for postoperative interventions when placed in the FSO of CRS patients undergoing ESS.

MATERIALS AND METHODS

Implant Description

The steroid-releasing sinus implants (PROPEL mini Sinus Implants, Intersect ENT, Menlo Park, CA) were supplied by Intersect ENT for investigational use. This implant is approved for use in adult (≥ 18 years) CRS patients to maintain patency of the ethmoid sinus cavity following ethmoid sinus surgery. The implant is composed of polylactide-co-glycolide polymer and is coated with 370 μg of the corticosteroid MF. The corticosteroid diffuses in a controlled manner over approximately 30 days into surrounding mucosa.¹⁴ Once inserted, the implant is designed to be self-expanding, allowing it to conform to the varying size and shape of the sinus opening (Fig. 1).

Study Design

This was a prospective, randomized, blinded, controlled, multicenter study enrolling 80 patients across 11 U.S. investigational centers, representing both academic and private practices. Participating clinical centers obtained institutional review board approval for the protocol and obtained written informed consent from all patients prior to study entry. The study was registered on ClinicalTrials.gov under identifier NCT02266810.

This study used an inpatient control design wherein after a successful bilateral frontal sinusotomy, one sinus side was randomly assigned using the envelop method to receive one steroid-releasing sinus implant (treatment side), whereas the contralateral side received surgery alone (control). The surgical technique used for frontal sinusotomy was required to be the same on both sides. Endoscopies at baseline and at 7, 21, 30, and 90 days postimplant placement were performed by clinical investigators and video recorded. The 30 day video-endoscopies were reviewed by the blinded independent reviewer.

Inclusion Criteria

The study population included adult (≥ 18 years of age) patients diagnosed with CRS based on American Academy of Otolaryngology–Head and Neck Surgery guidelines¹ who were scheduled to undergo primary or revision bilateral ESS and had evidence of bilateral frontal sinus disease based on computed tomography (Lund-Mackay score of ≥ 1 on each side). Frontal sinus surgery was required to be performed using Draf IIa or IIb procedure by traditional instrumentation, balloon, or a combination of both, as long as the same instrumentation was utilized on both sides. Septoplasty to access the ostiomeatal complex was permitted, as was treatment of other paranasal sinuses. The ESS procedure had to be successfully completed without complication, result in a minimum of 5-mm opening on both sides, and still be amenable to placement of the steroid-releasing sinus implant in both FSO for the patient to be enrolled in the study. Patients who had known history of immune deficiency or insulin-dependent diabetes, clinical evidence of acute bacterial or invasive fungal sinusitis, or any oral-steroid dependent condition were excluded from the study.

Prior and Concomitant Medications

Leading up to ESS there were no restrictions for oral or intranasal steroid use. No hemostatic packing materials of any kind were allowed to be placed within the study implants unless deemed medically necessary. Packing materials, including nasal splints, were allowed to be placed in the ethmoid cavity, if necessary.

Beginning at ESS (± 1 day), a 10-day course of antibiotics was required. Patients were maintained on standard medical regimen during the study. Intranasal steroid sprays were allowed starting 14 days post-ESS, and oral steroids were prescribed, if warranted, based on the investigator's discretion. Orally inhaled steroids for control of asthma were permitted. Patients were encouraged to use saline sprays or irrigation as needed during the follow-up period. All medications taken by the patient were documented throughout the study. Oral steroid interventions for sinus-related reasons were captured and were delineated from nonsinus-related reasons.

Efficacy Outcomes

The primary efficacy outcome of the study was the reduction in need for postoperative interventions at 30 days post-ESS based on video-endoscopic evaluation by an independent, blinded reviewer. Postoperative intervention was a composite endpoint defined as either surgical intervention required to debride obstructive adhesions or scar tissue formation in the frontal recess/FSO (defined as grades 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO. To maintain blinding of the independent reviewer, the implants were removed at day 21, and the day 30 video-endoscopies were edited to remove patient identifying information. The files were then randomly ordered and provided to the independent reviewer for grading without any additional clinical information. The 30-day time point was selected because it is beyond the acute phase of crusting and bleeding and represents the second phase of wound healing, which is characterized by edematous swelling of the residual mucosal tissue⁸ and is often a key decision point for commencement of postoperative interventions, as shown in previous studies.¹²

Endoscopic evaluation was performed using the following grading scales: *Adhesion/scarring* is defined as 0 = no visible granulation/scarring in the FSO; 1 = minimal amount of granulation, scarring, or contraction observed but not obstructing the

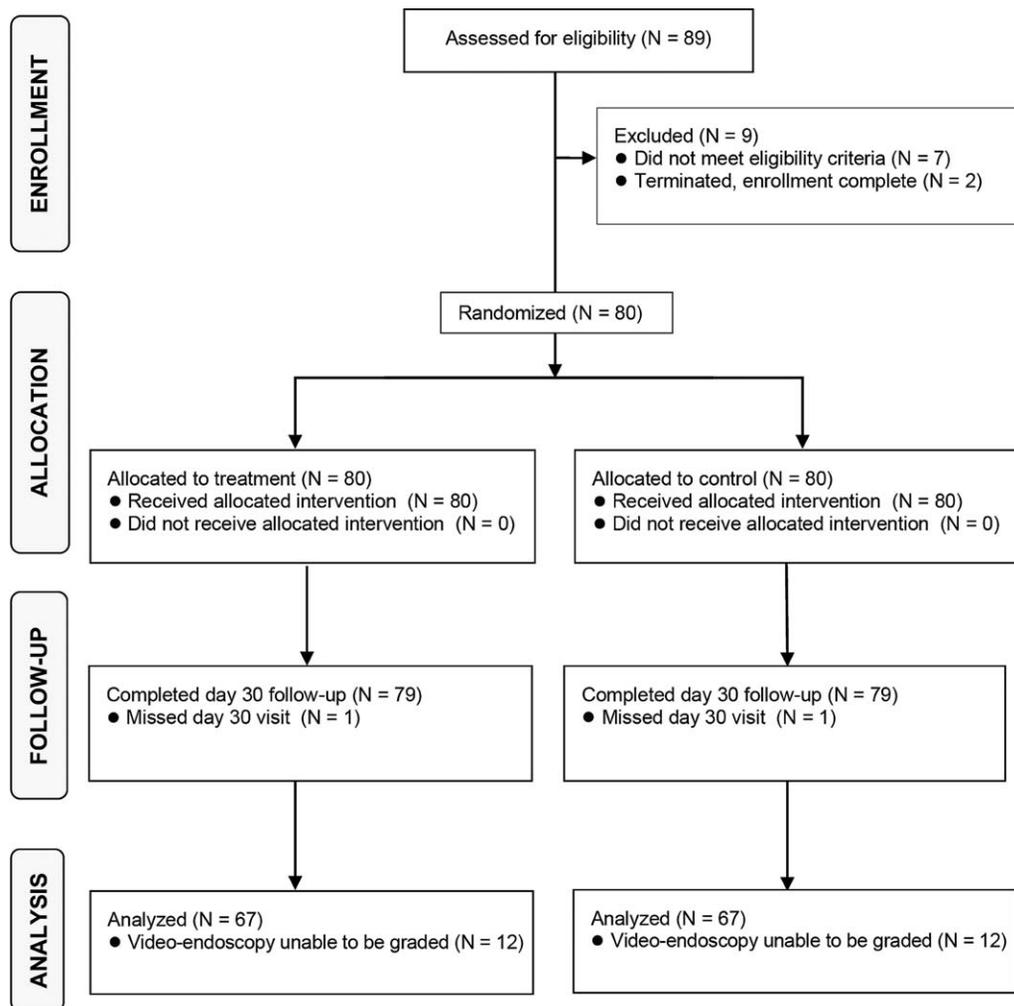


Fig. 2. CONSORT diagram.

FSO (intervention not warranted); 2 = moderate amount of obstructive granulation, scarring, or contraction present in the FSO (intervention is warranted); and 3 = significant amount of scarring or contraction causing obstruction of the FSO requiring intervention (likely to compromise patency if not removed). *Polypoid edema* is defined as 0 = normal mucosa, no visible polyps at the frontal recess or FSO; 1 = minimal amount of mucosal edema at the frontal recess or FSO; and 2 = expanded amount of polypoid edema at the frontal recess or FSO. *Patency of the FSO* is defined as 0 = patent; 1 = restenosed/partially occluded; and 2 = occluded. In addition, clinicians visually estimated the diameter of the FSO and the degree of inflammation using a 100-mm visual analog scale.

Safety assessment was based on all adverse events reported throughout the study.

Statistical Analysis

Randomization was stratified by clinical center and followed a block scheme of varying sizes. The ratio of left-to-right sinus randomization assignments was 1:1. Data were entered into a validated electronic database and analyzed by independent biostatisticians.

The primary efficacy hypothesis of the study was that the steroid-releasing sinus implant would reduce the need for

postoperative interventions in the FSO at 30 days compared to control sides. Only discordant pairs favoring the treatment side contributed to evidence of a treatment effect. Utilizing data from a previous study,¹² a 35% discordance with 80% of the discordant pairs favoring the treatment side was assumed. A total of 80 patients was required to achieve 20 discordant pairs with a two-sided α of 0.05 and 80% power. An exact version of McNemar's test was used, wherein the proportion of discordant pairs favoring the treatment side (out of all discordant pairs) was compared against a null value of 0.50. Categorical data that could be localized to a treatment or control side were analyzed using McNemar's test for correlated proportions. Continuous variables were compared using the two-sided t test with P values < 0.05 considered statistically significant.

Because interventions performed by clinical investigators prior to day 30 could potentially confound the primary efficacy outcome, an additional sensitivity analysis was performed after the primary analysis was conducted in order to test the robustness of the primary efficacy conclusion to interventions given for the treatment of the frontal recess/FSO. Data imputations were performed according to the following prespecified rule: if at day 7 or 21 a clinical investigator indicated that oral steroids or surgical intervention were warranted for any reason, and if that intervention was actually received, then the grades given by the independent sinus surgeon-reviewer at day 30 were

TABLE I.
Demographic and Baseline Characteristics.

N	80
Age (years), mean (SD)	49.9 (13.9)
Male	46 (57.5%)
Race	
White	62 (77.5%)
Black or African American	12 (15.0%)
Asian	6 (7.5%)
Number of prior ESS	
0	39 (48.8%)
≥ 1	41 (51.4%)
Medical history	
Asthma	30 (37.5%)
Aspirin exacerbated respiratory disease	6 (7.5%)
Expanded amount polypoid edema in frontal recess/FSO	61 (76.3%)
Control side	56 (72.7%)
Treatment side	53 (68.8%)
Total CT stage (Lund Mackay Score), mean (SD)	15.8 (4.8)
Frontal CT stage, mean (SD)	1.4 (0.5)
Control side	1.4 (0.5)
Treatment side	1.4 (0.5)

Values represent counts (percentage), unless specified otherwise
CT = computed tomography; ESS = endoscopic sinus surgery;
FSO = frontal sinus opening; SD = standard deviation.

replaced with the grades given by the clinical investigator at the preceding visit (day 7 or day 21) at which such intervention was given.

RESULTS

From September 2014 through June 2015, a total of 89 patients were consented for screening; of those, 80

met final eligibility criteria and were randomized (Fig. 2). Seventy-nine (99%) patients completed the follow-up visits through 90 days.

Baseline Characteristics

The mean (\pm standard deviation [SD]) age of patients randomized in the study was 49.9 years (13.9), and 57.5% were male (Table I). Of the 80 patients, 41 (51.2%) had undergone prior ESS. The study was well balanced in that similar proportion of sinuses had polypoid edema of grade 0 (control: 5 [6.5%] vs. treatment: 5 [6.5%]), grade 1 (control: 16 [20.8%] vs. treatment: 19 [24.7%]), and grade 2 (control: 56 [72.7%] vs. treatment: 53 [68.8%]) in the FSO at baseline. The mean total Lund-Mackay score at screening was 15.8 (4.8), with mean frontal (1.4 [0.5]) and ethmoid Lund Mackay scores (anterior [treatment: 1.5 [SD: 0.55]; control: 1.6 [SD: 0.55]] and posterior [treatment: 1.3 [SD: 0.61]; control: 1.4 [SD: 0.60]]) being comparable between the treatment and control sides.

All patients underwent frontal sinusotomies: 63.8% were performed with traditional rigid surgical instruments, 1.3% using only balloon dilation, and 35.0% using a combination of the two. Over ninety-seven percent (97.5%) of surgeries included bilateral ethmoidectomy. The implant was delivered in all 80 treated frontal sinuses, resulting in a 100% implant delivery success.

Efficacy Outcomes

Assessment of the primary efficacy outcome demonstrated that the proportion of patients needing postoperative interventions in the FSO on the treatment side was 38.8% compared to 62.7% on the control side, as judged by the independent reviewer (Table II) (Fig. 3). This difference was statistically significant ($P = 0.0070$) and represented a 38.1% relative reduction in the need for postoperative interventions on the treated sides.

TABLE II.
Endoscopic Efficacy Results at 30 Days.

	N Evaluable ^{§*}	Treatment	Control	Relative Change (%)	P Value ^{††}
Independent Reviewer ^{‡†}					
Need for postoperative interventions, n (%)	67	26 (38.8%)	42 (62.7%)	-38.1	0.0070
Clinical Investigators					
Need for postoperative interventions, n (%)	79	13 (16.5%)	33 (41.8%)	-60.6	< 0.0001
Need for oral steroid interventions, n (%)	79	12 (15.2%)	27 (34.2%)	-55.6	0.0015
Need for surgical interventions, n (%)	75	3 (4.0%)	12 (16.0%)	-75.0	0.0225
Inflammation (100 mm VAS), mean (SD)	77	24.7 (27.0)	41.3 (29.3)	-16.7	< 0.0001
Occlusion/restenosis, n (%)	76	16 (21.1%)	35 (46.1%)	-54.3	0.0002
Mean FSO diameter (mm), mean (SD)	75	5.9 (2.8)	4.4 (2.4)	32.2	< 0.0001

Relative change is calculated as a percentage of the mean difference between treatment and control groups divided by mean of control group.

*Seventy-nine patients returned for the day 30 visit and had their endoscopy recorded for grading by independent reviewer. Data were considered missing if the independent reviewer could not grade a video due to suboptimal video quality or inadequate imaging of the relevant anatomy. Because the planned statistical test required patients with an observed pair of outcomes, 12 patients could not be included in the test.

†McNemar's exact binomial test was employed to obtain the two-sided P -value at alpha level of 0.05 for the primary efficacy endpoint and other categorical efficacy endpoints. T tests were performed for all continuous efficacy data on the side-to-side difference in scores.

‡Number of patients with evaluable sinuses on both sides.

§FSO = frontal sinus opening; SD = standard deviation; VAS = visual analog scale.

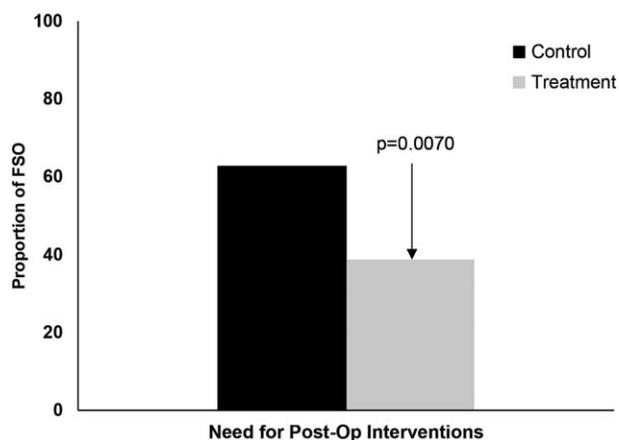


Fig. 3. Proportion of sinuses needing postoperative interventions in the frontal sinus opening (FSO) at day 30 following placement of a steroid-releasing sinus implant as determined by an independent, blinded sinus surgeon based on review of video-endoscopies. Postoperative intervention is a composite endpoint including surgical intervention required to debride obstructive adhesions/scarring formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO. *P*-values were obtained from a McNemar's test for correlated proportions, where only discordant pairs of observations contribute to evidence of a treatment effect. Arrow represents the percent relative reduction between treatment sides. FSO = frontal sinus opening.

To assess the potential confounding effect of other interventions, the primary endpoint was then analyzed following the prespecified data imputation rules for three patients who received oral steroids for the frontal recess/FSO prior to the 30 day follow-up. The results of the imputation demonstrated that the need for postoperative interventions remained significantly lower on the treatment sides compared to the control sides ($P = 0.0107$; 34.9% relative reduction).

The proportion of patients needing postoperative interventions on the treatment side (16.5%) was significantly ($P < 0.0001$) lower compared to the control side (41.8%), representing a 60.6% relative reduction as judged by clinical investigators. This reduction in the need for postoperative interventions on the treatment sides persisted through 90 days, demonstrating a sustained treatment effect ($P = 0.0129$).

Based on clinical investigator judgment, the reduction in need for postoperative interventions was driven by both components of the composite endpoint, with a 55.6% relative reduction in need for oral steroid intervention ($P = 0.0015$) and a 75.0% relative reduction in need for surgical intervention ($P = 0.0225$) (Table II). The treated sides showed a significantly lower inflammation score ($P < 0.0001$; 40.4% relative reduction); significantly lower number of restenosed or occluded sinuses ($P = 0.0002$; 54% relative reduction), and a significantly greater FSO diameter ($P < 0.0001$; 32.2% relative increase) compared to the control sides.

Additionally, the endoscopic assessments showed that the treated sides had a significantly lower frequency of adhesion and scarring warranting surgical

interventions ($P = 0.0225$; 75% relative reduction) and a significant reduction in expanded polypoid edema compared to the control sides at day 30 ($P = 0.0226$; 60% relative reduction) by clinical investigators.

Safety Outcomes

There were no implant-related adverse events in the study. Five adverse events (headache, left upper eyelid swelling, epistaxis, recurrent chronic sinusitis, and increased sinus pressure) were judged by the clinical investigators to have an indeterminate relationship to the implant. A total of four serious adverse events (diverticulitis, pulmonary fungal infection, two events of deep vein thrombosis) were reported among three patients in the study and were not related to the study implant.

DISCUSSION

This study was the first multicenter, randomized, controlled, blinded clinical trial that assessed the safety and efficacy of a steroid-releasing implant when placed in the frontal sinus opening following ESS. The study demonstrated that implant placement was safe and resulted in a statistically significant reduction in the need for postoperative interventions in the FSO at 30 days post-ESS, as judged by an independent, blinded reviewer. This statistically significant reduction in favor of the steroid-releasing implant was corroborated by clinical investigators who reported significant reductions in the need for postoperative and oral steroid interventions, adhesions and scarring, polypoid edema, inflammation, and restenosis rate.

The significant reduction in need for postoperative intervention in the FSO is consistent with previously reported efficacy outcomes in randomized controlled trials on steroid-releasing implants in the ethmoid sinuses.^{12,13} A meta-analysis of the 30-day results of these trials showed a 35% significant reduction in postoperative interventions ($P = 0.0008$), 51% significant reduction in adhesion and lysis ($P = 0.0016$), and 40% significant reduction in need for oral steroids ($P = 0.0023$) in treated sinuses that received a steroid-releasing implant compared to control sinuses that received a nondrug implant.¹⁰ Use of nondrug implants on control sinuses has been subject to criticism in the previous clinical trials. To address this question, the present study compared results of the steroid-releasing implant to sinusotomy alone while patients were maintained on a typical postoperative medical regimen. Despite this difference in study design, similar outcomes in the frontal sinuses were observed as previously reported in the ethmoid sinuses.^{10,12,13}

Topical steroids are known to promote early mucosalization and reduce edema, granulation tissue formation, and fibrin deposition after ESS; they are widely used postoperatively.⁸ However, studies have reported that topical nasal steroid sprays do not reach the frontal recess¹⁵⁻¹⁷ and hence are not effective in post-ESS management of patients with frontal sinusitis. Oral steroids, although beneficial in combating inflammatory response,

have been shown to have systemic risks to the patient and hence are prescribed with caution.¹⁸ Use of a steroid-releasing sinus implant provides localized topical steroid delivery to the frontal sinus opening and addresses the limitations of topical or oral steroid use. Patients in the present study remained on standard medical therapy¹⁹ wherein topical steroid sprays were allowed as early as 14 days postoperatively and oral steroids were permitted, if warranted, at any time during the study. Also, patients were encouraged to use saline sprays or irrigations as needed during the entire study follow-up. This allowed for comparison of steroid-releasing implants to the standard medical regimens typically employed in clinical practice. A limitation of the study is that the inpatient design precludes evaluation of the effect of treatment on patient symptoms and other quality-of-life assessments. However, the inpatient design was chosen to help minimize between-subject variability that is inherent in a parallel design, including concomitant medication usage or varying surgical techniques. The study implants or their remnants were required to be removed on day 21 to allow for blinded assessment of day-30 video-endoscopies. This implant removal procedure may have caused additional trauma to the adjacent mucosa; thereby hindering normal healing on the treatment sides. However, such implant removal is not obligatory in clinical practice. This study demonstrates that steroid-releasing implants improve surgical outcomes in the challenging area of frontal sinus surgery.

CONCLUSION

Placement of steroid-releasing sinus implants in the frontal sinus opening significantly reduces the need for postoperative interventions in CRS patients undergoing frontal sinus surgery and optimizes wound healing by reducing the potential for inflammation and scarring.

Acknowledgment

We thank the following research staff at the study centers for their efforts, commitment, and contributions toward recruitment and data collection: Cathy Garey, RN, BSN, CCRP, CCRC, of George Washington Medical Faculty Associates, Washington, DC; Sana Sarfaraz and Steven Dennis at UT Health Science Center of Houston, Houston, Texas; Bryan Hughes, CCRC, CRCP, of Sacramento Ear, Nose and Throat, Sacramento, California; Kathleen Sheeley, AHS, RRT, CCRC, of Advanced ENT and Allergy, Louisville, Kentucky; Jess C. Mace, MPH, CCRP, of Oregon Health and Science University, Portland, Oregon; Laura Stone, RN, BSN, CCRC, of Eastern Virginia Medical School, Department of Otolaryngology, Norfolk, Virginia;

Robert Weiss, MD (PI), Gena DeRibeux, and Micheal Cicirelli of The Connecticut Center for Advanced ENT Care, Norwalk, CT; J. Pablo Stolovitzky, MD (PI), and Anisa Daffari, PA-C, MPH, of ENT of Georgia, Atlanta, Georgia; Steven Miller, MD (PI), and Holly Featherstone of Intermountain/ENT Center, Salt Lake City, Utah; Robert Adelson, MD (PI), and Julie Baum of Albany ENT & Allergy, Albany, New York; and Steven E. Davis, MD (PI), and Gladys Sager, CCRC, of Breathe Clear Institute of Sinus and Allergy Relief, Torrance, California. We also thank Karen Fong, MD, of California Sinus Centers in Walnut Creek, California, for her role as the independent reviewer.

BIBLIOGRAPHY

- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg* 2015; 152:S1–S39.
- Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50:1–12.
- Hosemann W, Kuhnel T, Held P, Wagner W, Felderhoff A. Endonasal frontal sinusotomy in surgical management of chronic sinusitis: a critical evaluation. *Am J Rhinol* 1997;11:1–9.
- Valdes CJ, Bogado M, Samaha M. Causes of failure in endoscopic frontal sinus surgery in chronic rhinosinusitis patients. *Int Forum Allergy Rhinol* 2014;4:502–506.
- Chandra RK, Palmer JN, Tangsujaritham T, Kennedy DW. Factors associated with failure of frontal sinusotomy in the early follow-up period. *Otolaryngol Head Neck Surg* 2004;131:514–518.
- Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. *Laryngoscope* 1999;109:27–29.
- Hosemann W, Schindler E, Wiegrebe E, Gopferich A. Innovative frontal sinus stent acting as a local drug-releasing system. *Eur Arch Otorhinolaryngol* 2003;260:131–134.
- Hosemann W, Wigand ME, Gode U, Langer F, Dunker I. Normal wound healing of the paranasal sinuses: clinical and experimental investigations. *Eur Arch Otorhinolaryngol* 1991;248:390–394.
- Beule A, Scharf C, Biebler K-E, et al. Effects of topically applied dexamethasone on mucosal wound healing using a drug-releasing stent. *Laryngoscope* 2008;118:2073–2077.
- Han JK, Marple BF, Smith TL, et al. Effect of steroid-releasing sinus implants on postoperative medical and surgical interventions: an efficacy meta-analysis. *Int Forum Allergy Rhinol* 2012;2:271–279.
- Forwith KD, Chandra RK, Yun PT, Miller SK, Jampel HD. ADVANCE: a multisite trial of bioabsorbable steroid-eluting sinus implants. *Laryngoscope* 2011;121:2473–2480.
- Marple BF, Smith TL, Han JK, et al. ADVANCE II: a prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. *Otolaryngol HNS* 2012;146:1004–1011.
- Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. *Int Forum Allergy Rhinol* 2011;1:23–32.
- Li PM, Downie D, Hwang PH. Controlled steroid delivery via bioabsorbable stent: safety and performance in a rabbit model. *Am J Rhinol Allergy* 2009;23:591–596.
- Hong SD, Jang JY, Kim JH, et al. The effect of anatomically directed topical steroid drops on frontal recess patency after endoscopic sinus surgery: a prospective randomized single blind study. *Am J Rhinol Allergy* 2012;26:209–212.
- Aggarwal R, Cardozo A, Homer J. The assessment of topical nasal drug distribution. *Clin Otolaryngol Allied Sci* 2004;29:201–205.
- Kayarkar R, CLOPTON N, Woolford T. An evaluation of the best head position for instillation of steroid nose drops. *Clin Otolaryngol* 2002;27:18–21.
- Cope D, Bova R. Steroids in otolaryngology. *Laryngoscope* 2008;118:1556–1560.
- Orlandi RR, Kingdom TT, Hwang PH. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Executive Summary. *Int Forum Allergy Rhinol* 2016;6(suppl 1):S3–S21.