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Safety and Effectiveness of a Bioabsorbable Steroid-Releasing Implant for the Paranasal Sinus Ostia
A Randomized Clinical Trial

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Supplemental content

IMPORTANCE Suboptimal outcomes of endoscopic sinus surgery (ESS) are often associated with restenosis and inflammation of frontal sinus ostia. Steroid-releasing sinus implants have been shown to maintain sinus patency by minimizing inflammation and scar tissue formation. An hourglass-shaped, bioabsorbable, steroid-releasing implant was developed to provide mechanical support and optimize drug delivery to paranasal sinus ostia.

OBJECTIVE To assess the safety and efficacy of the hourglass-shaped, bioabsorbable, steroid-releasing sinus implant in improving postoperative outcomes when placed in the frontal sinus ostia (FSO) following ESS in patients with chronic rhinosinusitis (CRS).

DESIGN, SETTING, AND PARTICIPANTS In a prospective, multicenter, randomized clinical trial using an intrapatient control design (ESS followed by implant placement within 1 FSO vs ESS alone on the contralateral side) 80 adult patients, with a mean (SD) age of 49.5 (13.4) years and consisting of 53 (66%) men and 27 (34%) women, were enrolled and underwent bilateral frontal sinusotomies with 1 frontal sinus randomized to receive a steroid-releasing implant. The study was carried out in 12 US centers between July 2015 and March 2016.

INTERVENTIONS A bioabsorbable steroid-releasing implant with hourglass shape containing 370 µg of mometasone furoate. All patients received standardized postoperative care.

MAIN OUTCOMES AND MEASURES The need for postoperative interventions, medical and surgical, in the FSO at day 30, as determined based on review of video endoscopic findings by an independent blinded surgeon. Also, endoscopic grading by the independent reviewer and clinical investigators at day 30 and day 90 and computed tomographic scan at day 90.

RESULTS The mean (SD) age of patients was 49.5 (13.4) years, 53 (66%) were men. Implants were successfully placed in all 80 randomized treatment sinuses. At day 30, steroid-releasing implants significantly reduced the need for postoperative interventions to 11.5% compared with 32.8% by surgery alone (mean difference, −21.3%; 95% CI, −35.1% to −7.6%), as assessed by the independent reviewer. Real-time endoscopic assessment by clinical investigators at day 30 demonstrated significant reduction in need for postoperative intervention (mean difference, −17.3%; 95% CI, −27.9% to −6.7%), significant reduction in inflammation score (mean difference, −12.3 mm; 95% CI, −18.3 to −6.4 mm), and significant reduction in rate of frontal restenosis or occlusion (mean difference, −22.7%; 95% CI, −33.5% to −11.9%) on treated compared with control sides. The results favoring the treatment sides were sustained through day 90: reduced need for postoperative interventions (mean difference, −11.7%; 95% CI, −21.0% to −2.4%) and reduction in restenosis and/or occlusion of the frontal ostium (mean difference, −17.4%; 95% CI, −28.6% to −6.1%). No implant-related adverse events were observed.

CONCLUSIONS AND RELEVANCE The hourglass-shaped steroid-releasing sinus implant was safe and more effective in maintaining FSO patency and improving surgical outcomes compared with surgery alone in the setting where no other immediate postoperative corticosteroids were administered.

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Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa and associated symptoms for at least 3 months.[1] Initially treated with medical therapy, surgery represents a critical component of treatment should medical therapy fail. Of the paranasal sinuses addressed by surgery, the frontal sinus remains the most challenging to maintain patent after surgery given its hourglass configuration with the ostium at the narrowest portion. As such, the frontal sinus ostium is vulnerable to symptomatic consequences of stenosis associated with scarring and persistent or recurrent inflammation that often requires additional medical or surgical intervention.

To minimize possible postoperative stenosis of the frontal sinus neo-ostium and improve longer-term outcomes, surgeons follow 2 primary treatment strategies. The first is minimizing risk of scarring via meticulous atraumatic dissection of the frontal sinus ostium, requiring delicate endoscopic technique with specialized instrumentation to maximize the chance for long-term success. The other treatment option when inflammation or scarring is a concern even after careful dissection, or when addressing a narrow frontal sinus, is placement of a frontal sinus stent. Until recently, available options were nonabsorbable frontal stents that typically would be placed immediately after surgery and removed in the clinic 2 to 6 weeks later for significant crusting and/or symptomatic pressure. For these reasons, frontal sinus stents have been used sparingly.

Recently, a bioabsorbable steroid-releasing implant which has US Food and Drug Administration (FDA) approval for use in the ethmoid sinuses, was evaluated for postoperative placement in the frontal sinus.[2] The steroid-releasing implant resulted in a statistically significant reduction in need for postoperative intervention of the frontal sinus (either oral steroids or surgical intervention) compared with surgery alone with standardized postoperative care. To optimize drug delivery to the sinus ostia including the frontal sinus ostium, a similar bioabsorbable steroid-releasing implant eluting 370 µg mometasone furoate (MF) that differs only by its shape with an hourglass configuration, was developed. This study evaluated the safety and efficacy of the hourglass-shaped bioabsorbable steroid-releasing implant for the frontal sinus ostium (FSO).

Key Points

Question What is the safety and efficacy of an hourglass-shaped steroid-releasing implant on minimizing the need for postoperative intervention in a frontal sinus neo-ostium?

Findings In this randomized intrapatient-controlled clinical trial, there was a significant reduction in the need for postoperative interventions at day 30 to address scarring or inflammation of the frontal sinus neo-ostium implanted immediately after surgery with an hourglass-shaped steroid-releasing implant as assessed by an independent reviewer.

Meaning After a frontal sinusotomy, placement of a steroid-releasing implant in the neo-ostium minimizes scarring and inflammation, and significantly reduces the need for postoperative interventions in this region.

Methods

Implant Description

The hourglass-shaped steroid-releasing sinus implants (PROPEL Contour Sinus Implants, Intersect ENT) were supplied for investigational use. This implant is intended for use in adult patients with CRS to maintain patency of paranasal sinus ostia following sinus surgery and deliver steroid directly to the sinus mucosa. The implant is composed of a bioabsorbable 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 (**Figure 1**A).

Study Design

This was a prospective, 1:1 randomized, blinded, intrapatient-controlled, multicenter study, which enrolled 80 patients at 12 academic and private practice centers across the United States. Participating clinical centers obtained institutional review board approval for the protocol and obtained written informed consent from all patients prior to study entry. Participants were compensated with $350 Visa gift cards to cover reasonable expenses associated with 6 visits, such as parking. The study was registered on clinicaltrials.gov under identifier NCT02266810. The trial protocol is available in Supplement 1.

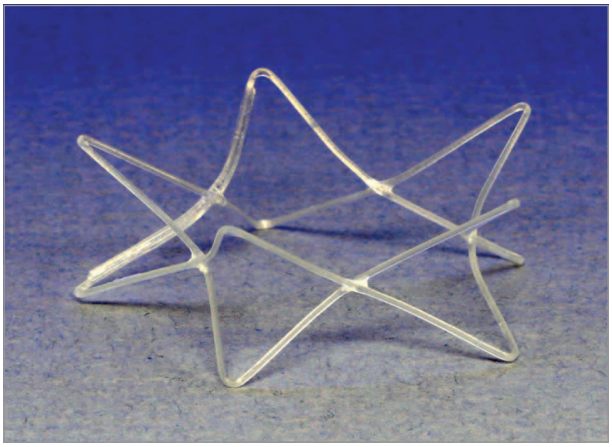
This study used an intrapatient control design identical to the study by Smith et al,[2] wherein after successful bilateral frontal sinusotomies were performed in the operating room, 1 sinus side was randomly assigned, using the envelope method, to receive the steroid-releasing sinus implant (treatment side) and the contralateral side received surgery alone (control). All patients received standardized postoperative care. The surgical techniques used for the frontal sinusotomies were required to be the same on both sides. The implant was removed at the 21-day visit by clinical investigators. Endoscopic examination with video recording at baseline and at 7, 21, 30, and 90 days after implant placement were performed by clinical investigators. The 30-day video endoscopic findings were reviewed by a blinded independent reviewer.

Inclusion Criteria

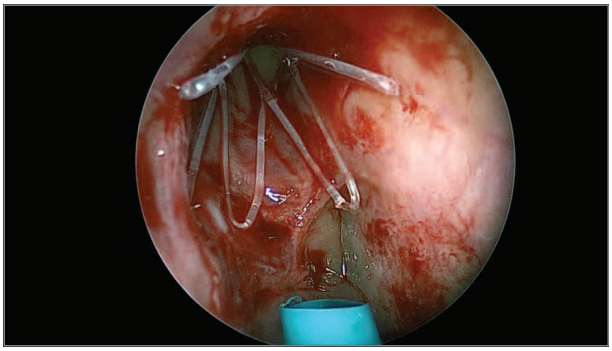
The study population included adult patients diagnosed with CRS based on AAO-HNS guidelines,[3] who were scheduled to undergo primary or revision bilateral ESS and had evidence of bilateral frontal sinus disease based on computed tomographic (CT) scan (Lund-Mackay [L-M] score of ≥1 on each side). Frontal sinus surgery was performed using Draf IIa or IIb procedure by traditional instrumentation, balloon dilation, or a combination of both, but the same method was always used 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 be amenable to placement of the steroid-releasing sinus implant in either FSO for the patient to be enrolled in the study. Patients who had known medical 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.

Figure 1. Hourglass-Shaped Steroid-Releasing Implant Designed to Optimize Apposition Within Paranasal Sinus Ostia

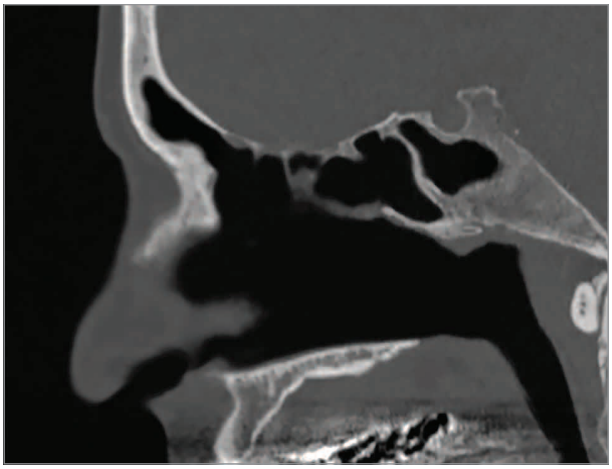
A Implant preplacement



B Implant after placement



C Computed tomographic image



A, Hourglass-shaped, bioabsorbable steroid-releasing sinus implant. B, Implant placed in the frontal sinus opening. C, Sagittal computed tomography image of an hourglass-shaped frontal sinus opening.

Prior and Concomitant Medications

Prior to ESS, there were no restrictions on oral or intranasal steroid use. No hemostatic packing materials of any kind were allowed to be placed in 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 (within 1 perioperative day), a 10-day course of antibiotics was required. Patients were maintained on a standard medical regimen during the study. Intranasal steroid sprays were allowed starting 14 days after ESS, and oral steroids were prescribed, if medically required. Orally inhaled steroids for control of asthma were permitted. Patients were encouraged to use saline sprays or irrigation during the follow-up period. All medications taken by the patient were documented throughout the study.

Efficacy Outcomes

The primary efficacy outcome of the study was the reduction in need for postoperative interventions at 30 days based on video endoscopic evaluation by an independent, blinded sinus surgeon 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. 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 typically characterized by edematous swelling of the residual mucosal tissue,[4] and is often a key decision point for commencement of postoperative interventions, as shown in previous studies.[5]

Endoscopic evaluation was performed using previously published[2] grading scales: (1) adhesion/scarring (0, no visible granulation/scarring in the FSO; 1, minimal amount of granulation, scarring, or contraction observed but not obstructing the FSO [intervention not warranted]; 2, moderate amount of obstructive granulation, scarring, or contraction present in the FSO [intervention is warranted]; 3, significant amount of scarring or contraction causing obstruction of the FSO requiring intervention [likely to compromise patency if not removed]); (2) polypoid edema (0, normal mucosa, no visible polyps at the frontal recess or FSO; 1, minimal amount of mucosal edema at the frontal recess or FSO; 2, expanded amount of polypoid edema at the frontal recess or FSO); and (3) patency of the FSO (0, patent; 1, restenosed/partially occluded; 2, occluded). Clinicians also visually estimated the diameter of the FSO (in millimeters) and the degree of inflammation using a 100-mm visual analog scale (VAS). Computed tomographic scans were obtained at day 90 to allow grading of frontal sinus opacification using the L-M staging method.

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

Statistical Analysis

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

Figure 2. CONSORT Diagram

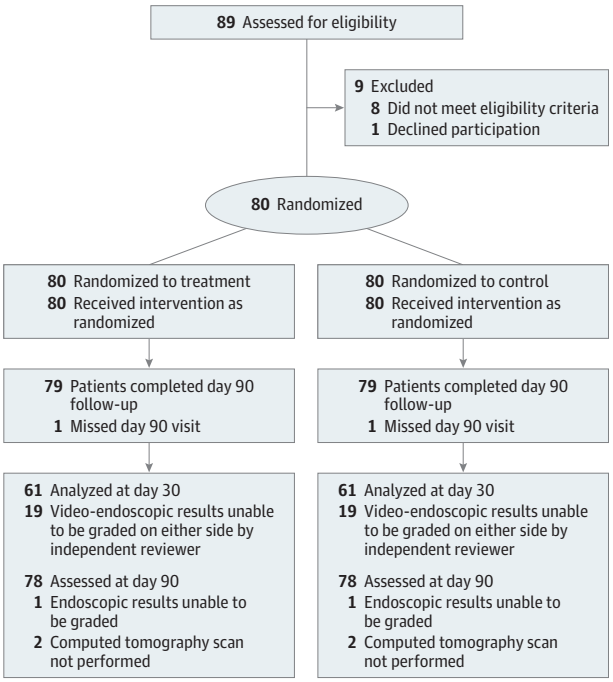


Table 1. Demographic and Baseline Characteristics

Characteristic	Value, No. (%)
No.	80
Age, mean (SD), y	49.5 (13.4)
Male	53 (66.3)
No. of prior ESS	
0	39 (48.8)
1	24 (30.0)
2	11 (13.8)
3	1 (1.3)
≥4	5 (6.3)
Medical history	
Aspirin intolerance or allergy	7 (8.8)
Asthma diagnosed by physician	36 (45.0)
Aspirin exacerbated respiratory disease	5 (6.3)
Current smokers	3 (3.8)
Polypoid edema in frontal recess/FSO, grade 2	44 (55.0)
Total (left + right) L-M score, mean (SD)[a]	14.8 (4.9)
Frontal L-M score, mean (SD)	1.4 (0.5)

Abbreviations: CT, computed tomography; ESS, endoscopic sinus surgery; FSO, frontal sinus ostia; L-M, Lund Mackay.

[a] L-M scores are based on CT scan within 6 months prior to implant placement.

interventions in the FSO at day 30 compared with control sides. The need for postoperative interventions was analyzed using an exact version of the McNemar test for correlated proportions where only discordant pairs favoring the treatment side contributed to evidence of a treatment effect. Other categorical data that could be localized to a treatment or control side were analyzed using the McNemar test for correlated proportions. Continuous variables were compared using the 2-sided *t* test with $P < .05$ considered statistically significant, and the results are displayed as means and 95% CIs of the mean difference.

Since interventions performed by clinical investigators prior to day 30 could potentially confound the primary efficacy outcome, an additional sensitivity analysis was performed to test the robustness of the primary efficacy conclusion. If at day 7 or 21 a clinical investigator indicated that oral steroids or surgical interventions were warranted for any reason, and if that intervention was actually received, then the data from the independent reviewer at day 30 were imputed with the data from the clinical investigator at the preceding visit (day 7 or day 21) at which such intervention was given.

Results

Patient Enrollment and Baseline Clinical Characteristics

Between July 2015 and March 2016, 80 patients consented, met all eligibility criteria, and were randomly assigned to receive a steroid-releasing implant in one of the frontal sinus ostia, after successful bilateral frontal sinusotomies (**Figure 2**). All 80 patients completed 30-day follow-up visit and 79 (99%) patients completed the 90-day follow-up. The mean (SD) age of patients was 49.5 (13.4) years, 53 (66%) were men, and 41 (51%) patients had at least 1 prior ESS. The study population included 44 (55%) patients with polypoid edema (grade 2) in the frontal recess/FSO, 36 (45%) with asthma, 7 (9%) with aspirin intolerance/allergy, and 5 (6%) with aspirin exacerbated respiratory disease (aspirin sensitivity, asthma, and chronic rhinosinusitis with nasal polyps). The mean (SD) total L-M CT score at baseline was 14.8 (4.9) with the treatment and control sides well balanced with respect to the frontal L-M CT stage (mean frontal L-M score, 1.4 on each side) (**Table 1**).

Of the 80 patients, 65 (81%) patients underwent traditional frontal sinusotomies with surgical instruments (42 [53%]) or surgical instruments and balloon dilation (23 [29%]), whereas 15 (19%) patients underwent frontal sinus balloon dilation alone. A total of 149 ethmoidectomies (76 [95%] anterior, 73 [91%] posterior), 69 (86%) maxillary antrostomies, and 61 (76%) sphenoidotomies were performed in most patients. The implant was placed in all 80 treatment sinuses resulting in 100% implant delivery success. Minor postplacement manipulation to position the device was required in 37 (46%) of cases, and on average, 92% of the implant was judged to be directly in contact with mucosal tissue.

Efficacy Data Accounting

Video endoscopies from 19 patients could not be evaluated by the independent reviewer for the primary efficacy endpoint (number of sinuses: treatment group, 61; control group, 61) owing to suboptimal video quality or inadequate imaging of the FSO. Given that the need for surgical intervention was based on assessing adhesion/scarring of the FSO, video endoscopic findings from an additional 3 patients could not be analyzed for need for surgical intervention because the FSO was obstructed by polyps resulting in 58 sinuses that could be analyzed for the need for surgical intervention (**Table 2**). For inflammation, as assessed by the independent reviewer at day

Table 2. Efficacy Results

Endpoints	Treatment (N = 80) No.[a]	Treatment (N = 80) Value	Control (N = 80) No.[a]	Control (N = 80) Value	Mean Difference (95% CI)
By Independent Reviewer at Day 30					
Primary efficacy endpoint, No. (%)					
Need for postoperative intervention[b]	61[c]	7 (11.5)	61[c]	20 (32.8)	−21.3% (−35.1% to −7.6%)
Need for surgical intervention	58[c]	4 (6.9)	58[c]	15 (25.9)	−19.0% (−32.8% to −5.1%)
Need for oral steroid intervention	61[c]	6 (9.8)	61[c]	10 (16.4)	−6.6% (−17.1% to 4.0%)
By Clinical Investigators at Day 30					
Secondary efficacy endpoints, No. (%)					
Need for postoperative intervention[b]	75[d]	12 (16.0)	75[d]	25 (33.3)	−17.3% (−27.9% to −6.7%)
Need for surgical intervention	75[d]	3 (4.0)	75[d]	11 (14.7)	−10.7% (−18.9% to −2.3%)
Need for oral steroid intervention	75[d]	11 (14.7)	75[d]	17 (22.7)	−8.0% (−17.4% to 1.4%)
Inflammation (100-mm VAS), mean (SD)	79[d]	23.1 (24.2)	77[d]	35.6 (31.1)	−12.3 (−18.3 to −6.4)
Occlusion/restenosis of FSO, No. (%)	75[d]	10 (13.3)	75[d]	27 (36.0)	−22.7% (−33.5% to −11.9%)
Estimated FSO diameter, mean (SD), mm	79[d]	6.3 (2.7)	75[d]	4.5 (3.2)	1.9 (1.3 to 2.5)
By clinical investigators at day 90					
Inflammation (100-mm VAS), mean (SD)	76[d]	26.0 (31.2)	77[d]	31.9 (32.1)	−5.5 (−11.3 to 0.3)
Occlusion/restenosis of FSO, No. (%)	69[d]	16 (23.2)	69[d]	28 (40.6)	−17.4% (−28.6% to −6.1%)
Estimated FSO diameter, mean (SD), mm	68[d]	5.7 (3.2)	68[d]	4.7 (3.4)	1.0 (0.2 to 1.7)
Frontal L-M CT stage, mean (SD)	78[d]	0.7 (0.6)	78[d]	0.9 (0.7)	−0.2 (−0.3 to −0.1)

Abbreviations: CT, computed tomography; FSO, frontal sinus ostia; L-M, Lund-Mackay; VAS, visual analog scale.

[a] No. of patients with evaluable sinuses.

[b] Postoperative intervention was a composite end point 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.

[c] The number of sinuses evaluable based on grading of video endoscopies by independent reviewer varied by parameter. Data were considered missing if the independent reviewer could not grade a video owing to suboptimal video quality or inadequate imaging of the relevant anatomy. Inadequate imaging of the relevant anatomy can occur when polyps in the ethmoid cavity or adhesions of the middle turbinate prevent visualization of the FSO.

[d] The number of sinuses evaluable varied by parameter based on ability to visualize relevant anatomy. For example, presence of polyps in frontal recess or a middle turbinate adhesion can prevent visualization of the FSO, and therefore, estimation of ostial diameter or patency.

30, only 10 video endoscopies could not be evaluated owing to inadequate imaging of the frontal recess and/or FSO resulting in 70 patients (eTable 2 in Supplement 2).

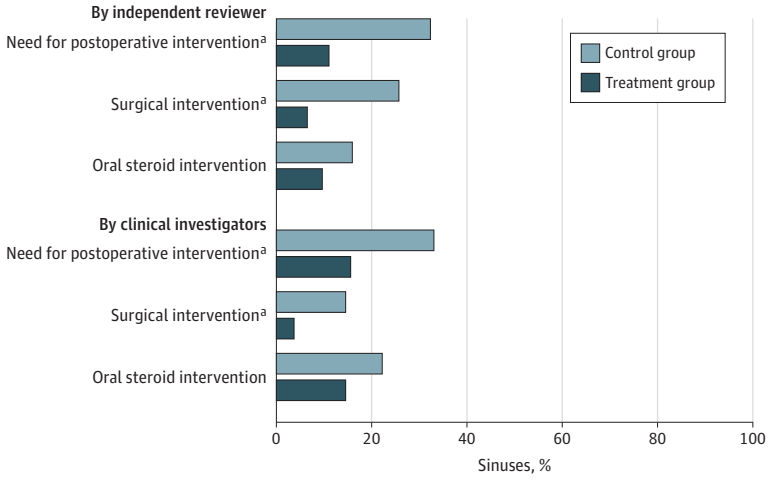
Inability to visualize the FSO by clinical investigators in some patients secondary to lateralization of middle turbinate or polyps in the ethmoid cavity resulted in fewer evaluable data for the need for postoperative, surgical, and oral steroid interventions (treatment group, 75; control group, 75); inflammation (treatment group, 79; control group, 77); occlusion/restenosis (treatment group, 75; control group, 75); estimated FSO diameter (treatment group, 79; control group, 75); adhesion/scarring (treatment group, 75; control group, 75); and polypoid edema (treatment group, 77; control group, 77) (Table 2; eTable 2 in Supplement 2) at day 30.

Efficacy

The primary efficacy outcome assessed by the independent reviewer demonstrated that the proportion of patients needing postoperative interventions in the FSO was significantly lower on the treatment sides at 11.5% compared with the control sides at 32.8% (mean difference, −21.3%; 95% CI, −35.1% to −7.6%) (Table 2) (**Figure 3**). The decrease in the need for postoperative intervention was driven largely by a significant reduction (mean difference, −19.0%; 95% CI, −32.8% to −5.1%) in the need for surgical intervention (6.9% on the treatment side vs 25.9% on the control side). Fewer treatment sides (9.8%) needed oral steroid intervention compared with control sides (16.4%), with a nonsignificant mean difference of −6.6% (95% CI, −17.1% to 4.0%). To assess the potential confounding effect of other steroid or surgical interventions, the primary endpoint was analyzed following the prespecified data imputation rules for 7 patients who received oral steroids or surgical interventions prior to day 30 (eTable 1 in Supplement 2). The results of this imputed analysis demonstrated that the need for postoperative interventions remained significantly lower on the treatment sides compared with the control sides (mean difference, −19.7%; 95% CI, −33.3% to −6.1%).

The clinical investigator assessments were very similar to those of the independent reviewer. At day 30, treatment sides showed a 16.0% need for postoperative interventions, compared with 33.3% on the control sides (mean difference, −17.3%; 95% CI, −27.9% to −6.7%); significantly reduced need for surgical intervention (mean difference, −10.7%; 95% CI, −18.9% to −2.3%); significantly reduced inflammation score (mean difference, −12.3 mm; 95% CI, −18.3 to −6.4 mm); significantly reduced rate of restenosis/occlusion (grade 1 or 2) (mean difference, −22.7%; 95% CI, −33.5% to −11.9%); and a significantly larger ostial diameter (mean difference, 1.9 mm; 95% CI, 1.3 to 2.5 mm) compared with the control sides (Table 2). Additional endoscopic endpoints as assessed by the independent reviewer and clinical investigators at day 30 are presented in eTable 2 in Supplement 2.

Figure 3. Need for Postoperative Interventions in the Frontal Sinus Opening at Day 30 as Judged by an Independent Reviewer and by Clinical Investigators



[a] Significant differences.

Results at 90 days continued to favor the steroid-releasing implant with significant reduction on the treated sides in need for postoperative interventions (mean difference, −11.7%; 95% CI, −21.0% to −2.4%), lower rate of restenosis/occlusion of the FSO (grade 1 or 2) (mean difference, −17.4%; 95% CI, −28.6% to −6.1%), significantly larger ostial diameter (mean difference, 1.0 mm; 95% CI, 0.2 to 1.7 mm), and a significant reduction in the frontal L-M CT stage (mean difference, −0.2; 95% CI, −0.3 to −0.1) compared with the control sides, as assessed by clinical investigators (Table 2).

In the subset of 15 patients who underwent frontal sinus balloon dilation alone, treated sinus sides had a lower inflammation score (19.5 mm vs 28.5 mm) and larger ostial diameter (7.3 mm vs 5.1 mm) compared with the control sides at day 30. Owing to the small sample size, no inferential statistical analyses were performed.

Safety Results

There were no implant-related adverse events in the study. There were 3 adverse events that were judged by clinical investigators to have an indeterminate relationship to the implant and drug from the implant (headache, epistaxis, and acute sinusitis).

Discussion

The frontal sinus outflow configuration is uniquely challenged by its anatomically narrow boundaries of the nasal beak, orbit, and skull base, leading to limited sinusotomy size and hence the risk of postoperative inflammation and restenosis. Studies within the past 10 years report patency rates after Draf II frontal sinusotomy ranging from 67.6% to 92%, with most in the mid-80% range.[6-9] Hosemann et al[10] followed frontal sinuses in 82 patients who underwent a Draf II dissection and reported an average intraoperative FSO diameter of 5.6 mm. The neo-ostial diameter decreased to a mean of 3.5 mm, representing a contraction of 37.5%. This group also found that a minimum 5-mm frontal neo-ostium was needed to significantly minimize the risk of FSO restenosis.[10]

Postsurgical stenting of the FSO is one technological attempt to address scarring while preserving drainage and ventilation as the neo-ostium heals.[11] Several pliable nonbioabsorbable frontal sinus stents are commercially available and typically used in a neo-ostium measuring less than 5 mm in the presence of denuded or osteitic bone or nasal polyps in the frontal recess, or in the presence of an unstable middle turbinate. These stents are typically removed within 6 months of placement, often as a result of crusting or recurrent infections incited by the foreign body. Given these various limitations, these frontal sinus stents are used sparingly.

Local drug delivery could improve outcomes for frontal sinus surgery by addressing the underlying inflammatory process during the postoperative healing period. Multiple randomized clinical trials on 3 different steroid-eluting sinus implants for the ethmoid and frontal sinuses have been conducted, including this study, showing the effectiveness of bioabsorbable steroid-releasing implants for the frontal sinus ostium. In this study, the primary outcome was the need for postoperative surgical and/or medical intervention at 30 days after frontal sinusotomies, as determined by an independent reviewer. The observed 21.3% reduction in the need for postoperative intervention in the FSO treated with the steroid-eluting implant relative to the untreated side corresponds to 4.7 patients needed to treat to prevent 1 patient from undergoing postoperative intervention. Evaluating the CI suggests that the reduction in postoperative interventions could be as high as 35.1%. But even the lower bound of the CI of 7.6% reduction is clinically meaningful because postoperative interventions pose additional risks to patients and consumption of health care resources. A similar reduction in postoperative intervention was observed by the on-site clinical investigators.

An objective outcome that influences need for postoperative interventions is the diameter of the frontal neo-ostium. In the present study, the baseline mean frontal neo-ostium was 7.5 mm on both sides. After 3 months, the control sides contracted down

by 37% to 4.7 mm, similar to the 37.5% reported by Hosemann et al.[10] However, the FSO implanted with the steroid-releasing implant only contracted by 24% to 5.7 mm, altering the typical course of contraction following a frontal sinusotomy. This translates clinically to a significant reduction in the need for postoperative interventions of the neo-ostium.

This intrapatient controlled, randomized, blinded clinical trial evaluated the safety and efficacy of an hourglass-shaped, bioabsorbable steroid-releasing implant designed for placement in paranasal sinus ostia after ESS. As discussed, the primary endpoint results are consistent with a clinically meaningful reduction in postoperative intervention, as assessed by a blinded independent reviewer. This was corroborated with the findings by on-site clinical investigators. In the present study, the treated sides at 30 days demonstrated a 12% reduction in inflammation and approximately 2-mm increase in estimated FSO diameter compared with the untreated FSO, supporting a clinically meaningful change. These findings are consistent with the primary outcome measure. Overall, the results from this study showed similar beneficial effect of a bioabsorbable steroid-releasing implant as was reported in previous studies with steroid-releasing sinus implants placed in the ethmoid and frontal sinuses.[2,12,13]

Comparing the steroid-releasing implants used in the 2 frontal sinus studies, 46% of the hourglass shaped implants required some minor manipulation once deployed compared with 68% of the implants studied by Smith et al.[11] On average, the hourglass-shaped implant had over a 90% apposition to the underlying mucosa. These observations suggest improved alignment of the hourglass-shaped implant to the FSO when its natural shape is retained after dissection (Figure 1C). However, the implant studied by Smith et al[11] provides another configuration for cases where the FSO has less of an hourglass shape, or where placement in the frontal sinus or recess is preferred.

Limitations

There are a couple of limitations of this study. First, the intrapatient control study design precluded evaluation of patient symptoms. However, this study design was chosen to minimize the considerable interpatient variability associated with comorbid diseases, differences in surgical techniques among surgeons, and concomitant medication usage. Also, a standardized postoperative medical regimen was followed, which may not reflect the variability of postoperative treatments used in practice, but was used to minimize bias from variable postoperative regimen. In the standardized regimen in this study, intranasal steroids were not started until after day 14, which is consistent with RCTs evaluating topical steroid sprays in the early postoperative period, and because early commencement of topical nasal steroid sprays (within 2 weeks) is limited by blood crusts that prevent the topical steroids from reaching the frontal sinus in meaningful quantities.[14] Finally, to allow blinded assessment of day 30 video endoscopies, the study implants or their remnants were required to be removed on day 21. This implant removal procedure, which is not obligatory in clinical practice, may have caused additional trauma to the adjacent mucosa, potentially affecting normal healing on the treatment sides. However, despite this the treated sides fared better than control sides.

Conclusions

Frontal sinus surgery followed by placement of a bioabsorbable steroid-releasing implant significantly minimizes scarring and/or inflammation, reducing the need for postoperative surgical and medical interventions compared with standard frontal sinus surgery without placement of a steroid-releasing implant in the setting where no other immediate postoperative corticosteroids are administered.

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Invited Commentary

Frontal Sinus Drug-Eluting Implants—Effective, but for Which Patients and at What Cost?

Stacey T. Gray, MD; Ahmad R. Sedaghat, MD, PhD

Surgical intervention for chronic rhinosinusitis (CRS) is an important treatment option for patients refractory to medical therapy. Despite advances in surgical techniques and operative technology, revision endoscopic sinus surgery (ESS) is necessary in 6% to 19% of patients.[1,2] Reasons for revision surgery include scarring and adhesion formation, recurrent polyposis, and persistent inflammation.[3] These issues are especially problematic in the frontal recess given the narrow anatomic boundaries that limit the size of the surgical sinusotomy that can be created. Long-term patency rates are reported in the range of 67% to 92%.[4] Attempts to improve the success of frontal sinus surgery by decreasing scarring and inflammation have been long standing and a variety of stenting options exist. Recent advancements in bioabsorbable and drug-eluting stents provide a new possibility for improving postoperative sinus surgery outcomes.

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In this issue of *JAMA Otolaryngology–Head & Neck Surgery*, Luong and colleagues[5] report their experience with the use of a bioabsorbable, steroid-releasing hourglass-shaped implant in the frontal sinus ostium. The authors conducted a prospective, randomized, intrapatient controlled multicenter study in 80 patients undergoing bilateral ESS for CRS. The same degree of frontal sinus surgery (Draf IIa or IIb via traditional surgical dissection, balloon dilation, or a combination of both procedures) was performed bilaterally with a resultant frontal sinusotomy of at least 5 mm. The treatment side (with placement of the implant) was randomly assigned and the contralateral side, which was treated with surgery alone, became the control side. The implant was removed at 21 days postoperatively. The primary efficacy outcome was based on review of video from the 30-day postoperative endoscopic examination by an independent reviewer to determine the need for postoperative intervention (defined as either the need for debridement of obstructive scar tissue/adhesion formation or the need for oral steroid therapy to resolve inflammation or polypoid edema of the frontal recess). Secondary outcome measures included endoscopic grading of the frontal recess by the investigators at 30 and 90 days, as well as frontal sinus opacification on computed tomography (CT) scan of the sinuses at 90 days. Compared with the control side, the need for postoperative intervention—the primary outcome measure—in the treatment (implanted) side was significantly lower (11.5% on the treatment side compared with 32.8% on the control side). Secondary outcome measures favored the treatment side as well.

This study by Luong et al[5] provides valuable evidence for the efficacy of a bioabsorbable, steroid-releasing hourglass-shaped implant in the frontal sinus ostium to reduce the need for debridement of obstructive scar tissue or the need for oral steroid therapy to address inflammation or polypoid edema