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Article

Eosinophilia and Quality of Life in Patients Receiving a Bioabsorbable Steroid-Eluting Implant during Endoscopic Sinus Surgery

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Abstract: Introduction: Bioabsorbable steroid-eluting implants are available as an adjunct for endoscopic sinus surgery (ESS) in the treatment of chronic rhinosinusitis (CRS). It is unclear which patients are most likely to benefit from this technology. We sought to determine if the severity of preoperative sinonasal inflammation influences the postoperative changes in patient-reported quality of life (QOL) and endoscopic appearance following ESS with implant placement; Methods: Consecutive adult patients undergoing ESS for CRS with ethmoidectomy and placement of a steroid-eluting implant over an 18-month period were prospectively included for study. Pre-operative sinus computed tomography (CT) opacification was evaluated using the Lund-Mackay score (LMS). Sinonasal Outcome Test (SNOT-22) scores and Lund-Kennedy endoscopic scores (LKES) for each patient were collected preoperatively and at three- and six-month intervals postoperatively. Serum eosinophilia (>6.0% on peripheral smear) and sinus tissue eosinophilia were recorded; Results: One hundred and thirty-six patients were included for analysis. Of these, 36.7% had polyposis, 15.4% had serum eosinophilia and 64.0% had tissue eosinophilia. The mean (standard deviation) SNOT-22 score was 45.5 (19.4) preoperatively, which improved postoperatively to 18.8 (14.1) at three months ($p < 0.001$) and 16.5 (14.0) at six months ($p < 0.001$). Similar results were found when stratified by the presence of polyposis, serum eosinophilia, tissue eosinophilia or high-grade CT findings (LMS > 6). Higher baseline LKES was observed for patients with eosinophilia or high-grade LMS, but these differences normalized at six months postoperatively; Conclusions: Patient-reported QOL and endoscopic appearance show improvement six months after placement of a steroid-eluting implant during ESS, irrespective of the presence of polyposis or eosinophilia.

Keywords: steroid-eluting implant; endoscopic sinus surgery; quality of life; eosinophil; chronic rhinosinusitis

1. Introduction

Chronic rhinosinusitis (CRS) is estimated to affect over 12% of adults in the United States [1]. The clinical manifestations of CRS are variable, though in nearly all cases quality of life (QOL) is diminished [2], with associations with impaired productivity, lost workdays, more healthcare visits, and increased spending on treatment. Validated metrics such as the 22-item Sinonasal Outcomes Test

(SNOT-22) have been created to determine the severity of disease, to monitor progression, and to demonstrate the response to medical and surgical treatment [3].

Endoscopic sinus surgery (ESS) has a role in the management of CRS to improve sinus ventilation and mucociliary clearance as well as to facilitate the topical administration of medication [4]. Adjunct, long-term medical therapy is necessary for the effective treatment and maintenance of CRS [5]. The beneficial effect of steroids is well-known in CRS; however, the side effects of long-term systemic steroid use are not desirable and can lead to serious complications [6]. Topical intranasal steroids can minimize systemic effects and are an integral component in treatment; however, penetration into the middle meatus and sinus cavities can be limited by postoperative edema and crusting [7]. Current efforts are focused on improving steroid delivery to the diseased sinuses while limiting their systemic effects [8].

Bioabsorbable steroid-eluting implants are a relatively new technology that may be utilized within the ethmoid sinus lumen following ESS [9,10]. Only one such implant is currently available, marketed under the trade name Propel (Intersect ENT, Menlo Park, CA, USA), which combines the release of 370 μg of mometasone furoate with a spring-like spacer activity that is designed for gradual release over 30 days [11]. This offers the potential benefits of decreasing postoperative inflammation and mucosal edema, reducing polyposis and adhesions, securing the middle turbinate in a medialized position, and separating raw mucosal edges [8,10].

Previous studies examining the utility of adjuvant use of a bioabsorbable steroid-eluting implant in ESS have demonstrated its safety and clinical effectiveness in CRS patients in general [6–8,12]. However, it is unclear which patient groups are most likely to benefit from this technology. Study of patient-reported QOL outcomes with use of this device has been limited, and the differential effect of this device upon phenotypes of CRS has not been fully studied. The aim of the present study was to determine if changes in patient-reported QOL after ESS with implant placement are related to the severity of baseline sinonasal inflammation. Objective measures of tissue eosinophilia, serum eosinophilia, polyposis and degree of radiographic sinus opacification were used as indicators of inflammation severity. A secondary aim was to determine if surgeon-reported endoscopic appearance showed similar postoperative improvements in patients with mild versus severe baseline inflammation.

2. Methods

A single-cohort before-after study design was utilized to evaluate outcomes of ESS for CRS performed by a single surgeon (EDM) from October 2014 to March 2016. During this time period, 151 consecutive adult patients undergoing ethmoidectomy for CRS had placement of a Propel implant. This implant is composed of a bioabsorbable polymer, poly-(LL-lactide-co-glycolide), woven into a scaffold and impregnated with 370 μg of mometasone furoate, and is deployed into the sinus cavity using an specialized catheter. ESS cases performed for other indications besides CRS did not receive an implant and were not included in the study. Patients were excluded who received postoperative systemic corticosteroids (nine cases), who had a diagnosis of cystic fibrosis (five cases), or who received an implant but were found incidentally to have a sinonasal neoplasm (one case). All included participants underwent unilateral or bilateral total (anterior and posterior) ethmoidectomy, and each operated ethmoid cavity received an implant. Treatment of other paranasal sinuses was permitted, as was concurrent septoplasty or inferior turbinate reduction. In addition to ethmoidectomy, 96.3% (131/136) underwent concurrent maxillary antrostomy, 83.8% (114/136) underwent frontal sinus exploration, and 56.6% (77/136) underwent sphenoidotomy.

CRS was defined as symptomatic mucosal inflammation of the paranasal sinuses of at least 12 consecutive weeks duration. Pre-operative sinus computerized tomography (CT) within three months of the procedure was reviewed. Opacification was evaluated for each patient using the Lund-Mackay score (LMS) on all preoperative CT scans, with LMS = 6 considered the median score in this cohort. Pre-operative Lund-Kennedy Endoscopic score (LKES) was determined on all patients with in-office nasal endoscopy performed by the senior author. The presence of preoperative serum

eosinophilia (>6.0% on peripheral smear) and presence of polyps were recorded. The presence of tissue eosinophilia (>10 cells/hpf) was documented on histopathologic examination of ethmoid tissue specimens. Relevant comorbidities were obtained from the medical history provided by the patient or recorded in the medical record.

Patients were seen approximately seven days and 28 days postoperatively for nasal endoscopy and debridement. If stent fragments were present on post-operative day 28, they were removed during the office visit. At 28 days all patients were then started on a daily application of an intranasal topical steroid. LKES was reported during nasal endoscopy at the three- and six-month post-operative visits. Patient-reported SNOT-22 scores were gathered preoperatively and at three and six months postoperatively, and were grouped for analysis relative to the median score of 45. The study was approved by the institutional review board of the senior author's primary institution.

Sample size calculation was based on the expected mean (SD) postoperative change score, previously reported in a large cohort as 16.2 (20.0) [13]. Assuming an alpha level of 0.05 and a power of 0.8, the calculated sample size was 48. A larger cohort was sampled to account for dropouts. Pre- and post-operative continuous variables were compared using two-tailed paired *t*-tests. Nonparametric variables were compared using Fisher's exact test. *p*-values less than 0.05 were considered significant. Statistical analysis was completed using SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

3. Results

One hundred and thirty-six patients met inclusion criteria. Of these, 50 (36.8%) had polyposis, 21 (15.4%) had serum eosinophilia and 87 (64.0%) had tissue eosinophilia. None of these cases received systemic steroids during the study period. Baseline characteristics of eosinophilic (serum eosinophilia >6.0% on peripheral smear) and non-eosinophilic (serum eosinophilia $\leq$ 6.0%) groups were comparable, although more males presented with high-grade LMS and lower preoperative SNOT-22 scores (Table 1). Comorbid conditions that could affect QOL were equally distributed. Patients with serum eosinophilia had a mean LMS of 11.9 versus 7.4 in patients without eosinophilia ($p = 0.003$), whereas those with and without tissue eosinophilia had LMS scores of 9.11 and 6.96, respectively ($p = 0.211$). Tissue eosinophilia and serum eosinophilia were weakly correlated (Spearman rho = 0.265). Two patients (1.5%) required revision ESS during the study period.

The mean (standard deviation) SNOT-22 score for all patients was 45.5 (19.4) preoperatively, which improved postoperatively to 18.8 (14.1) at three months ($p < 0.001$), and to 16.5 (14.0) at six months ($p < 0.001$). Similar results were found in the subgroup analysis of tissue eosinophilia, serum eosinophilia, the presence of polyps, and high-grade presentation of disease on CT (LMS > 6) (Figure 1A–D, Table 2). Three and six-month SNOT-22 scores were significantly lower than the preoperative SNOT-22 scores in all subgroups (Figure 1A–D). The presence or absence of serum eosinophilia and the grade of disease on CT did not significantly affect postoperative SNOT-22 scores (Figure 1A,D, Table 2). Three-month postoperative SNOT-22 scores were significantly higher in patients with tissue eosinophilia and polyps compared to those without; however, at six months, there was no significant difference (Figure 1B,C, Table 2).

Table 1. Baseline characteristics.

Basline Characteristic	Total Subjects, *n* (%)	Serum Eosinophilia Present, *n* (%)	*p*-Value [1]	LMS $\geq$ 6, *n* (%)	*p*-Value [2]	Preoperative SNOT-22 Score $\geq$ 45, *n* (%)	*p*-Value [3]
Sex							
Male	55/136 (40.4)	12/55 (21.8)	0.089	42/55 (76.4)	0.027	14/55 (25.5)	0.008
Female	81/136 (59.6)	9/81 (11.1)	-	47/81 (58.0)	-	49/81 (60.5)	-
Prior surgery							
Yes	47/136 (34.6)	10/47 (21.3)	0.171	34/47 (72.3)	0.219	25/47 (53.2)	0.242
No	89/136 (65.4)	11/89 (12.4)	-	55/89 (61.8)	-	38/89 (42.7)	-

Table 1. *Cont.*

Basline Characteristic	Total Subjects, *n* (%)	Serum Eosinophilia Present, *n* (%)	*p*-Value [1]	LMS ≥ 6, *n* (%)	*p*-Value [2]	Preoperative SNOT-22 Score ≥ 45, *n* (%)	*p*-Value [3]
Age							
>50 years	70/136 (51.5)	12/70 (17.1)	0.569	46/70 (65.7)	0.944	31/70 (44.3)	0.263
≤50 years	66/136 (48.5)	9/66 (13.6)	-	43/66 (65.2)	-	32/66 (48.5)	-
Asthma							
Present	21/136 (15.4)	4/21 (19.0)	0.617	17/21 (81.0)	0.103	12/21 (57.1)	0.280
Absent	115/136 (84.5)	17/115 (14.8)	-	72/115 (62.6)	-	51/115 (44.4)	-
AR							
Present	63/136 (46.3)	15/63 (23.8)	0.012	42/63 (66.7)	0.779	30/63 (47.6)	0.779
Absent	73/136 (53.7)	6/73 (8.2)	-	47/73 (74.6)	-	33/73 (45.2)	-
Anxiety							
Present	25/136 (18.3)	6/25 (24.0)	0.190	14/25 (56.0)	0.271	13/25 (52.0)	0.529
Absent	111/136 (81.6)	15/111 (10.8)	-	75/111 (67.5)	-	50/111 (45.0)	-
Depression							
Present	15/136 (11.0)	4/15 (26.7)	0.200	10/15 (66.7)	0.912	9/15 (60.0)	0.258
Absent	121/136 (89.0)	17/121 (14.0)	-	79/121 (65.3)	-	54/121 (44.3)	-
Migraine							
Present	19/136 (14.0)	1/19 (5.3)	0.187	9/19 (47.4)	0.073	12/19 (63.2)	0.112
Absent	117/136 (86.0)	20/117 (17.1)	-	80/117 (68.4)	-	51/117 (43.6)	-

LMS, Lund-Mackay Score; SNOT-22, Sinonasal Outcome Test; AR, Allergic Rhinitis; [1] *p*-value represents comparison of percentages of patients with serum eosinophilia; [2] *p*-value represents comparison of percentages of patients with LMS ≥ 6; [3] *p*-value represents comparison of percentages of patients with preoperative SNOT-22 ≥ 45.

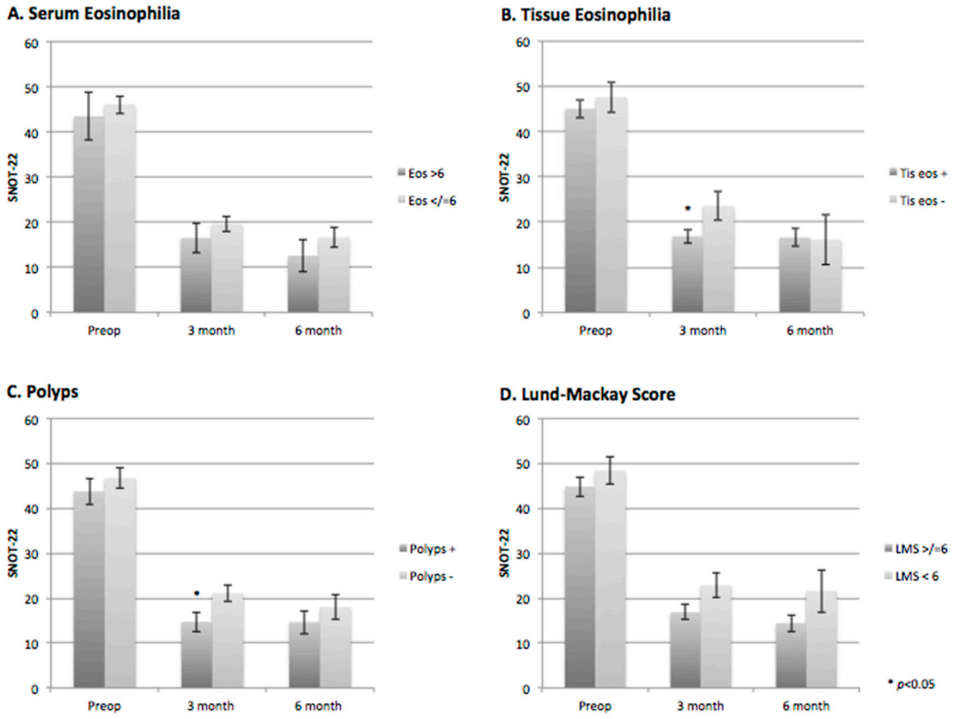

Figure 1. Comparisons of preoperative, three-month postoperative, and six-month postoperative SNOT-22 scores. (**A**) Presence versus absence of serum eosinophilia; (**B**) Presence versus absence of tissue eosinophilia; (**C**) Presence versus absence of polyposis; (**D**) High-grade versus low-grade Lund-Mackay score of CT opacification. * $p < 0.05$ for between-group comparisons. SNOT-22: Sinonasal Outcome Test; CT: computed tomography; LMS: Lund-Mackay Score.

The baseline LKES scores were significantly higher for patients with serum and tissue eosinophilia, polyps and high-grade CT disease (Figure 2A–D; Table 3). The three- and six-month LKES scores were

significantly lower for patients with and without serum eosinophilia, with no significant difference between the groups (Figure 2A, Table 3). Patients with tissue eosinophilia and high-grade CT disease had significantly higher three-month postoperative LKES scores (p = 0.017 and p = 0.006, respectively); however, this difference was not seen at six months postoperatively (p = 0.189 and p = 0.144, respectively) (Figure 2B,D; Table 3).

Table 2. Between-group comparisons of Sinonasal Outcome Test (SNOT-22) scores before and after endoscopic sinus surgery.

Disease Characteristic	Preop	*p*-Value [1]	3 Month Postop	*p*-Value [2]	6 Month Postop	*p*-Value [3]
Serum eosinophilia						
Present	43.44	0.609	16.5	0.461	12.57	0.474
Absent	46.01	-	19.6	-	16.61	-
Tissue eosinophilia						
Present	45.01	0.512	18.86	0.034	16.55	0.924
Absent	47.57	-	23.54	-	16.09	-
Polyps						
Present	43.74	0.419	14.71	0.032	14.63	0.362
Absent	46.67	-	21.08	-	17.97	-
Lund-Mackay score						
LMS $\geq$ 6	44.77	0.350	16.84	0.050	14.42	0.093
LMS < 6	48.33	-	22.82	-	21.6	-

LMS, Lund-Mackay score. [1] *p*-value represents comparison of preoperative SNOT-22 scores; [2] *p*-value represents comparison of three-month postoperative SNOT-22 scores; [3] *p*-value represents comparison of six-month postoperative SNOT-22 scores.

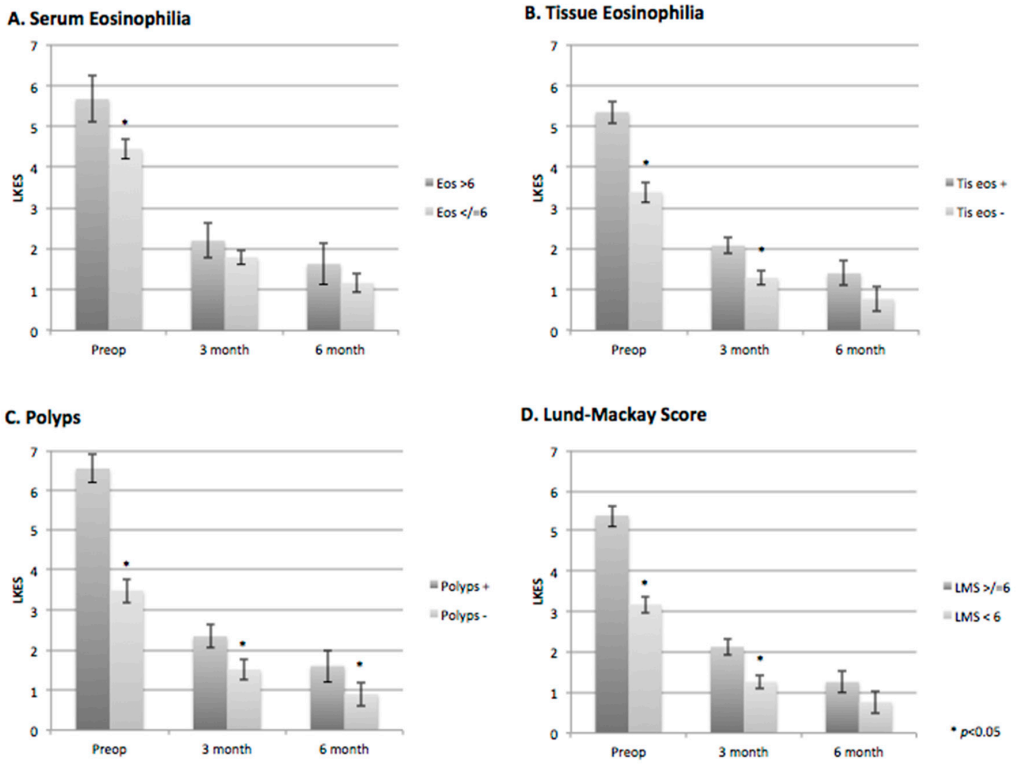

Figure 2. Comparisons of preoperative, three-month postoperative, and six-month postoperative Lund-Kennedy Endoscopic scores. (**A**) Presence versus absence of serum eosinophilia. (**B**) Presence versus absence of tissue eosinophilia. (**C**) Presence versus absence of polyposis. (**D**) High-grade versus low-grade Lund-Mackay score of CT opacification. * $p < 0.05$ for between-group comparisons.

Table 3. Between-group comparisons of Lund-Kennedy endoscopic score (LKES) before and after endoscopic sinus surgery.

Disease Characteristic	Preop	*p*-Value [1]	3 Month Postop	*p*-Value [2]	6 Month Postop	*p*-Value [3]
Serum eosinophilia						
Present	5.67	0.036	2.2	0.349	1.63	0.420
Absent	4.45	-	1.79	-	1.16	-
Tissue eosinophilia						
Present	5.35	<0.001	2.08	0.017	1.4	0.189
Absent	3.39	-	1.29	-	0.77	-
Polyps						
Present	6.56	<0.001	2.34	0.006	1.72	0.032
Absent	3.48	-	1.51	-	0.87	-
Lund-Mackay score						
LMS $\geq$ 6	5.37	<0.001	2.13	0.006	1.36	0.144
LMS < 6	3.17	-	1.26	-	0.73	-

LMS, Lund-Mackay score. [1] *p*-value represents comparison of preoperative LKES; [2] *p*-value represents comparison of three-month postoperative LKES; [3] *p*-value represents comparison of six-month postoperative LKES.

4. Discussion

CRS is a heterogeneous disease consisting of multiple variants with different underlying pathophysiologies [14]. In the United States and Europe, patients with CRS are classified into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps [15]. CRSwNP patients that have recurrence of nasal polyps after surgery are more likely to have pronounced eosinophilic infiltration of the nasal mucosa [15,16]. Eosinophilic CRS is a subtype of CRS that predicts less post-operative improvement in patient-reported QOL and disease-specific measures [17,18]. Peripheral blood eosinophilia and tissue eosinophilia are associated with more severe CRSwNP, higher recurrence rates of nasal polyps after surgery [14,15], and higher revision surgery rates [19].

The availability of bioabsorbable steroid-eluting implants in the treatment of CRS offers the potential for decreased inflammation, adhesions, recurrent polyposis, and improved sinus ostia patency in the postoperative period after ESS [10,20]. However, few studies have focused on patient-reported QOL outcomes with the use of this device, and the relative efficacy in the treatment of different phenotypes of CRS has not been analyzed in previous studies [6–8,12]. The goal of this study was to determine if a bioabsorbable steroid-eluting implant would have a differential effect on patient-reported QOL relative to the status of baseline eosinophilia. We found that QOL scores showed comparable improvement among patients with eosinophilic CRS and those without. Similar results were found when comparing low- versus high-grade sinus CT opacification, as well as patients with CRSwP versus those without polyps. These findings suggest that the benefit from these implants may not be limited to one particular CRS phenotype, and could be beneficial to a wider range of patients undergoing ESS.

In addition to patient-reported outcomes, the clinician assessment of endoscopic appearance may be a useful outcome to assess disease control. Patients with eosinophilic CRS are often noted to have persistent postoperative edema and polypoid changes on endoscopy during the postoperative period. As expected, our data showed higher preoperative LKES for patients with polyposis, eosinophilia or higher-grade CT opacification. Moreover, subsequent improvement in postoperative LKES was observed for patients with both low- and high-grade disease. At six months postoperatively, patients with preoperative eosinophilia or high-grade CT opacification were found to have an endoscopic appearance comparable to those without eosinophilia or with low-grade CT opacification. Though future controlled studies are necessary to better examine this effect, our data suggest that the steroid-eluting implant in conjunction with ESS might assist with suppression of

inflammation that persists for several months after implant degradation. Further studies are required to determine whether these effects are significantly better than surgery performed without placement of a bioabsorbable steroid-eluting implant.

Revision ESS rates as reported in the literature are variable. Patients with serum and tissue eosinophilia often require systemic steroids and have significantly higher recurrence and revision rates [15,21–23]. In a previous study of the steroid-eluting implant, revision ESS was indicated in 2.2% (2/90) of cases with use of the Propel stent, which is consistent with the revision rate (1.5%) in the present study [6]. Of this, only one patient of 21 (4.8%) with serum and tissue eosinophilia required revision surgery after one year, which is significantly less than revision rates reported in the literature, though long-term follow up is necessary.

Several notable limitations are relevant in the present study. As a single-armed study without a comparison treatment group, conclusions about causation and comparative effectiveness are not possible. Additionally, although approximately 80% of patients continued to follow up six months from the time of surgery, there is a risk of follow-up bias, as postoperative outcomes could have influenced both follow-up and completion of the forms. Finally, some patients in this study also received a septoplasty and/or inferior turbinate reduction, which may be a confounding variable that overestimates the improvement in QOL measures.

Although the present study indicates that improvements occur regardless of the severity of preoperative inflammation, it remains unclear how these effects would compare to cases in which an implant was not utilized. Future studies with controlled trials of patient-reported QOL following ESS with bioabsorbable steroid-eluting implants are needed, which may utilize postoperative objective markers of inflammation to supplement the effects on patient-reported QOL. Investigation of the effect of simultaneous additional symptom scores or QOL measures may help elucidate the confounding potential of septoplasty and inferior turbinate reduction in conjunction with ESS. Lastly, examination into specific items of the SNOT-22 score that are most affected by implant placement may result in better preoperative counseling and patient selection.

5. Conclusions

Irrespective of the presence of polyposis or eosinophilia, patient-reported QOL scores are improved up to six months after placement of a steroid-eluting implant during ESS for patients with CRS. Endoscopic appearance shows comparable normalization over time regardless of the extent of preoperative inflammation. Controlled studies are necessary to determine the comparative effectiveness of the steroid-eluting implant.

Author Contributions: Edward D. McCoul conceived and designed the study; Jason D. Pou, Charles A. Riley, Anna K. Bareiss, Kiranya E. Tipirneni and Edward D. McCoul collected the data; Jason D. Pou, Charles A. Riley and Edward D. McCoul analyzed the data; Jason D. Pou, Charles A. Riley and Edward D. McCoul wrote and revised the paper; all authors approved the final manuscript.

Conflicts of Interest: There was no financial or material support for the research of this work. Edward D. McCoul is a consultant for Acclarent, which is unrelated to the current study. The other authors have no financial affiliations to disclose. The authors declare no conflict of interest.

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