

Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease

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Background: In this study we assessed patient outcomes after complete endoscopic sinus surgery (ESS) and aspirin desensitization for patients with aspirin-exacerbated respiratory disease (AERD).

Methods: A retrospective chart review was conducted for patients with aspirin challenge-proven AERD who underwent complete ESS followed by aspirin desensitization. Outcomes assessed included need for revision surgery and quality-of-life measures using the 22-item Sino-Nasal Outcomes Test (SNOT-22). Data were collected preoperatively, postoperatively prior to desensitization, and then at intervals post-desensitization through 30 months after aspirin desensitization. A longitudinal linear mixed-effects model was used for data analysis.

Results: Thirty-four patients met the inclusion criteria for this study. Thirty-two patients successfully completed aspirin desensitization and were subsequently followed for 30 months after desensitization. Two patients were unable to complete desensitization. Five patients discontinued aspirin maintenance therapy due to gastrointestinal and respiratory side effects. Within the follow-up period, there were only 3 (9.4%) revision sinus surgeries. Notably, 1 of

these revision cases occurred in a patient who had discontinued aspirin maintenance therapy. After surgical treatment and prior to desensitization patients had significant reductions in SNOT-22 scores. Our results demonstrate that total SNOT-22 scores remained statistically unchanged from immediate post-desensitization throughout the 30-month follow-up period.

Conclusion: Complete sinus surgery followed by timely aspirin desensitization and maintenance therapy is an effective combination in the long-term management of sinus disease in patients with AERD. © 2017 ARS-AAOA, LLC.

Key Words:

aspirin desensitization; aspirin-exacerbated respiratory disease; nasal polyps; Samter's triad; SNOT-22

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Aspirin-exacerbated respiratory disease (AERD), previously known as Samter's triad, is an upper and lower airway inflammatory disease characterized by the triad of nasal polyposis, asthma, and respiratory reactions to cyclooxygenase 1 (COX-1)-inhibiting medications.¹ The chronic rhinosinusitis associated with AERD is notable for the severity of sinus disease, with aggressive nasal polyposis and higher rates of sinus surgery compared with non-AERD patients.² There is also a high rate of dependence on systemic corticosteroids for symptom management of AERD.³

Medical therapy is a key component in the management of AERD.¹ Oral aspirin desensitization has been shown to be a safe and effective tool for management of AERD.⁴ Sinonasal outcomes measured by quality of life and need for revision sinus surgery have been shown in multiple studies to improve with aspirin desensitization.⁴⁻⁷ Complete sinus

surgery has been associated with improved quality of life in AERD patients compared with patients who underwent more conservative sinus surgery.⁸ Cho et al showed aspirin desensitization after endoscopic sinus surgery (ESS) to be well tolerated and effective for controlling polyp recurrence and improving sense of smell and nasal obstruction at a follow-up of 30 months post-desensitization.⁷

In this study we examine our institution's long-term sinonasal outcomes after complete endoscopic sinus surgery and aspirin desensitization for AERD patients. Outcomes were measured using validated sinonasal symptom questionnaires and need for revision sinus surgery.

Methods

A retrospective review was conducted for all patients who underwent ESS followed by aspirin desensitization available in the University of Pennsylvania Hospital System rhinology database.

The following inclusion criteria were applied: (1) challenge-proven aspirin intolerance characterized by worsening of upper and/or lower airway symptoms with ingestion of aspirin; (2) a diagnosis of asthma; (3) chronic rhinosinusitis refractory to maximal medical therapy; (4) preoperative endoscopic evidence of pansinusitis with bilateral nasal polyposis; and (5) post-desensitization follow-up of 30 months. Exclusion criteria included age < 18 years, pregnancy, immunodeficiency, cystic fibrosis, and negative aspirin challenge.

All patients underwent complete ESS, which we have defined as removal of all polyp burden followed by wide bilateral maxillary antrostomy, total sphenoidotomy, and frontal sinusotomy. This includes removal of all residual bony partitions, thereby skeletonizing the skull base.¹ Postoperatively, all patients were given oral prednisone taper as well as topical budesonide irrigation that was continued post-desensitization.

Three to 6 weeks after ESS, patients underwent oral aspirin challenge and desensitization. All aspirin desensitization was performed with continuous vital sign monitoring in an outpatient surgicenter setting. Prior to 2012, a standardized oral aspirin desensitization protocol was followed, as described by Stevenson.⁹ After 2012, the modified intranasal ketorolac and aspirin challenge protocol was followed, as described by Lee et al.¹⁰ For maintenance therapy, patients were started on aspirin 650 mg twice daily, with attempted titration down based on patient response and tolerance, to a goal of 975 mg to 325 mg/day gradually over a period of months. By 6 months post-desensitization, patients are typically on a stable dose of aspirin for maintenance therapy (325 mg to 1300 mg daily).

Baseline patient demographics collected included age, gender, race, comorbidities, and number of prior sinus surgeries.

Subjective sinonasal outcomes were assessed using the 22-item Sino-Nasal Outcomes Test (SNOT-22). The SNOT-22 is a validated, symptom-based patient

questionnaire that assesses 22 nasal, sinus, psychological, and behavioral metrics on a scale from 0 (no problem) to 5 (worst problem). SNOT-22 scores were taken preoperatively, 4 weeks postoperatively but pre-desensitization, and then post-desensitization at 1, 6, 12, 18, 24, and 30 months. Objective sinonasal outcomes were measured by the need for revision sinus surgery within the follow-up period.

A longitudinal linear mixed-effects regression model was used for analysis of SNOT-22 scores across time. There was no discernible pattern of missingness in the data, so the model utilized all available data. Both random slopes and intercepts were modeled to represent the within-subject correlation that exists in repeated-measures quality-of-life survey data. Time was measured as a categorical variable to account for nonlinearity in the SNOT-22 trajectory over time after surgery. The α was set to 0.050, and all reported *p* values are 2-tailed. Statistical analysis utilized STATA 14.2/SE (StataCorp LP, College Station, TX).

Results

Thirty-four patients with AERD met inclusion criteria for the study. Two patients were unable to complete the initial aspirin desensitization. The remaining 32 patients successfully completed post-ESS aspirin desensitization and were followed for the 30-month post-desensitization window.

Within the 30-month follow-up period, 3 (9.4%) patients needed revision sinus surgery. Notably, 1 of these revision cases occurred in a patient who had discontinued aspirin maintenance therapy due to worsening asthma symptoms. Approximately 1 year after discontinuing aspirin the patient underwent revision sinus surgery for complaints of worsening nasal obstruction and objective findings of worsening nasal polyposis. The second revision case was performed for recurrent sinus infections, thick nasal discharge, and anosmia with objective recurrent nasal polyposis. The third revision case was performed for a symptomatic frontal sinus mucocele causing supraorbital headaches. This patient had a history of multiple prior frontal sinus surgeries. The mean (with 95% confidence interval [CI]) SNOT-22 score at the time of revision for the 3 patients just described was 53.3 (95% CI, 40.1-66.5). A total of 5 patients (16.6%) discontinued aspirin maintenance therapy. Two patients discontinued for worsening asthma, 1 discontinued for gastric pain, 1 discontinued for upcoming gastric bypass surgery, and 1 patient did not have a reason recorded for discontinuation.

The longitudinal linear mixed-effects regression model was used to analyze subjective sinonasal outcomes as measured by SNOT-22 responses. The mean (with 95% CI and *p* value comparing post-desensitization scores to 1-month post-operative scores in parentheses) preoperative SNOT-22 scores was 47.0 (95% CI, 39.0-55.1). Four-week postoperative SNOT-22 scores taken prior to aspirin desensitization showed a significant decrease to 15.2 (7.3-23.1; *p* < 0.001). After aspirin desensitization, SNOT-22 scores for the most part remained statistically unchanged from

TABLE 1. Mixed-effects model estimates for SNOT-22 subscales*

	Pre-ESS	1 month post-ESS	1 month post-desensitization	30 months post-desensitization
SNOT-22 total	47.0 (39.0-55.1)	15.2 (7.3-23.1)***	20.7 (12.1-29.3)	22.6 (11.6-33.7)
Subscales				
Rhinologic (0-35)	17.8 (15.1-20.5)	4.3 (1.7-6.9)***	6.6 (3.9-9.4)	10.1 (6.5-13.7)**
Extranasal (0-15)	7.3 (5.8-8.8)	1.8 (0.3-3.3)***	2.5 (0.9-4.0)	3.7 (1.6-5.7)
Ear/facial (0-25)	7.3 (5.3-9.3)	2.2 (0.2-4.2)***	3.8 (1.7-5.9)	4.5 (1.8-7.2)
Psychological (0-35)	12.2 (9.2-15.2)	4.2 (1.3-7.2)***	5.5 (2.4-8.5)	6.1 (2.3-9.8)
Sleep (0-25)	12.5 (9.8-15.3)	5.1 (2.4-7.9)***	6.2 (3.4-9.0)	6.9 (3.4-10.3)

*The *p* values at 1 month post-ESS compare estimates to pre-ESS (time = 0); *p* values at 1 and 30 months post-desensitization compare estimates to 1 month post-ESS to assess for a difference in the SNOT-22 trajectory over time after aspirin desensitization.

***p* < 0.010.

****p* < 0.001.

ESS = endoscopic sinus surgery; SNOT-22 = 22-item Sino-Nasal Outcomes Test.

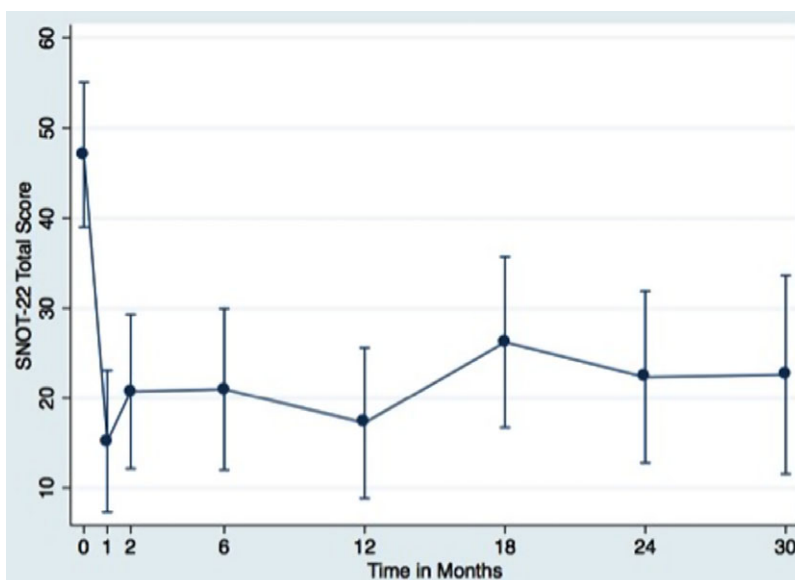


FIGURE 1. Total SNOT-22 scores are displayed with average score and 95% confidence interval over the study time-points. Time 0 is preoperative, time 1 is 4-week post-ESS (prior to desensitization), and time 2 is 1-month post-desensitization. Subsequent time-points refer to the number of months after ESS. ESS = endoscopic sinus surgery; SNOT-22 = 22-item Sino-Nasal Outcome Test.

the 4-week postoperative average with total scores of 20.7 (12.1-29.3; *p* = 0.241), 21.0 (12.0-30.0; *p* = 0.245), 17.2 (8.8-25.6; *p* = 0.669), 26.2 (16.7-35.7; *p* = 0.037), 22.3 (12.8-31.9; *p* = 0.188), and 22.6 (11.6-33.7; *p* = 0.218) at 1, 6, 12, 18, 24, and 30 months post-desensitization, respectively. Summary results of the mixed-effects linear regression model are provided in Table 1 and Figure 1.

SNOT-22 subscale analyses were also performed for rhinologic, extranasal, ear/facial, psychological, and sleep categories. All categories had significant improvement from preoperative to 4-week postoperative scores. The rhinologic subscale showed a statistically significant increase in scores from 4 weeks postoperatively to 30 months post-desensitization (*p* = 0.003). The extranasal, ear/facial, psychological, and sleep subscales showed no

significant increase from 4-week postoperative scores to 30-month post-desensitization scores (*p* = 0.105, *p* = 0.129, *p* = 0.335, and *p* = 0.319, respectively).

Discussion

AERD is a challenging disease process to manage, characterized by the triad of chronic sinusitis with nasal polypsis, asthma, and respiratory reactions to COX-1-inhibiting medications such as aspirin. Medical management is a cornerstone in the treatment of AERD, with aspirin desensitization being a major tool in the medical management armamentarium. Aspirin desensitization has been shown to be safe and effective for improving disease control and optimizing patient status. Studies have shown a statistically

significant improvement in the number of sinus infections per year, sinus surgeries needed, olfactory symptoms, and nasal symptoms for patients who have undergone aspirin desensitization.⁴

Regarding the role of surgery in the treatment of AERD, current treatment recommendations in the literature advise aspirin desensitization several weeks after ESS for AERD patients with recalcitrant rhinosinusitis.^{11,12} Surgical intervention with ESS followed by aspirin desensitization has been shown to be an effective treatment regimen for AERD.^{7,8,13} Cho et al showed improved quality-of-life metrics among AERD patients for >2 years after desensitization.⁷ Our findings show that SNOT-22 scores were most improved immediately postoperatively at the 4-week postoperative follow-up. Subsequently, after undergoing desensitization, there was no significant increase in total SNOT-22 scores through the 30-month follow-up period. These findings are in agreement with previous studies showing durable improvement in quality-of-life metrics after desensitization.^{7,13}


Within our cohort there were 3 patients (9.4%) who underwent revision sinus surgery within the follow-up period. Notably, 1 of the 3 patients who required revision surgery had previously discontinued aspirin therapy due to worsening asthma symptoms. Another patient had revision surgery for a symptomatic frontal sinus mucocele. This patient had multiple prior osteoplastic flap procedures that may have increased his risk of a mucocele and the revision surgery may not reflect a failure of aspirin maintenance therapy. The third patient who required revision did not have an identifiable risk factor that predisposed him to needing revision surgery. Our data show that, at the time of revision, the mean SNOT-22 score for those 3 patients had risen to 53.3 (95% CI, 40.1-66.5). McMains et al compared AERD patients treated with surgery and aspirin desensitization vs surgery alone and found a 0% revision rate in the surgery-plus-desensitization group compared with an 80% revision rate in the surgery-alone group ($p = 0.003$).⁶ Fruth et al showed a trend toward significance for lower polyp recurrence among patients who underwent aspirin desensitization followed by daily aspirin therapy when compared with a placebo group (28% vs 62%; $p = 0.0785$). In that study, Kaplan-Meier analysis showed polyp recurrence occurred earlier and more often in the placebo group compared with the aspirin-desensitization group.¹³

Aspirin desensitization and subsequent maintenance therapy has been shown to be well tolerated among AERD patients.⁴ There are variations in the exact protocol and maintenance regimen used. Our group recommends an aspirin dose range of 325–1300 mg/day for maintenance therapy, depending on patient response and tolerance.¹ Gastrointestinal discomfort is the most common side effect of aspirin maintenance therapy, limiting continuation of the treatment regimen.¹⁴ In a study of 172 AERD patients who had undergone desensitization and maintenance therapy, 14% stopped due to the side effects of aspirin.¹⁵ Five patients (16.6%) in our study had to discontinue maintenance therapy during the follow-up period, including 1 with gastric discomfort, 2 with worsening respiratory symptoms, and 1 who could not take aspirin after undergoing gastric bypass surgery.

An important consideration in the surgical management of AERD is that more extensive surgical procedures may be required to clear the severe sinonasal disease burden. DeConde et al demonstrated greater quality-of-life improvements in AERD patients who underwent complete sinus surgery compared with a more focused sinus surgery.⁸ Patients who underwent endoscopic modified Lothrop procedures (Draf III) for recalcitrant frontal sinusitis also had improved outcomes.¹⁶ As outlined earlier, we define complete sinus surgery as removal of all polyp burden followed by wide bilateral maxillary antrostomy, total sphenoidectomy, and frontal sinusotomy. This includes removal of all residual bony partitions.¹ The effectiveness of this approach may be multifaceted by first removing obstructive polyps and inflamed mucosa and subsequently allowing increased penetration of topical steroid therapy.¹

Limitations of our study include the retrospective nature of the review. We did not have standardized endoscopic grading data collected for all patients, which limits objective measures that could be assessed in our study.

Conclusion

AERD patients with recalcitrant sinusitis require a multifaceted treatment regimen. This includes complete sinus surgery, topical steroid therapy, and postoperative aspirin desensitization. Our findings demonstrate long-lasting improvements in quality-of-life measures for AERD patients treated with this regimen. 

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