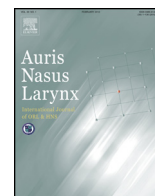




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Objective and subjective sinonasal and pulmonary outcomes in aspirin desensitization therapy: A prospective cohort study[☆]

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ABSTRACT

Objective: Aspirin exacerbated respiratory disease (AERD) patients are challenging to manage with sinonasal and pulmonary symptoms refractory to maximal medical and surgical therapies. Our objective was to comprehensively examine objective and validated, disease-specific subjective sinonasal and pulmonary outcomes of aspirin (ASA) desensitization therapy in this patient population.

Methods: Prospective cohort study at an academic tertiary center. AERD patients with a history of chronic rhinosinusitis with nasal polyposis (CRSwNP), prior diagnosis of asthma, and a history of ASA sensitivity were eligible for inclusion. Patients underwent ASA desensitization using an established institutional protocol and continued on a 650 mg twice daily maintenance dose. Baseline Sinonasal Outcome Test (SNOT-22) and Asthma Control Questionnaire (ACQ) responses, acoustic rhinometry, peak flow readings, and endoscopic scoring of nasal polyps were recorded prior to desensitization and after 6 months of maintenance therapy.

Results: Twelve patients were recruited for participation and underwent desensitization. Eight patients continued maintenance therapy and follow up at 6 months. Prior to desensitization, patients reported bothersome sinonasal symptoms with a median SNOT-22 score of 30.0 ± 34.5 (interquartile range (IQR)). There was significant improvement after 6 months of maintenance therapy to a median SNOT-22 score of 18.5 ± 17.3 ($p = 0.025$, Wilcoxon signed rank test). Acoustic rhinometry, endoscopic scores, ACQ and forced expiratory volume values remained stable at 6 months.

Conclusions: AERD patients may benefit from ASA desensitization with subjective sinonasal symptom improvement at 6 months and stable asthma and objective sinonasal measures. Further discussion is needed in the otolaryngology community regarding ASA desensitization in AERD management.

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Abbreviations: ACQ, Asthma Control Questionnaire; AERD, aspirin exacerbated respiratory disease; ASA, aspirin; CRSwNP, chronic rhinosinusitis with nasal polyposis; FEV1, force expiratory volume 1 second; IQR, interquartile range; POSE, perioperative sinus endoscopy scoring system; SNOT-20, Sinonasal Outcome Test-20; SNOT-22, Sinonasal Outcome Test-22.

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1. Introduction

The management of patients with Samter's triad – consisting of asthma, nasal polyposis, and aspirin (ASA) sensitivity – involves a multidisciplinary approach. Aspirin exacerbated respiratory disease (AERD) is another term to describe this clinical presentation involving an upper and lower airway inflammatory reaction triggered by ASA or other cyclooxygenase-1 inhibitors [1]. These patients often have severe sinonasal symptoms refractory to conventional medical management and surgery [2,3]. They often require numerous courses of systemic steroids for severe nasal polyposis and multiple endoscopic sinus surgeries. Despite this, patients have ongoing symptoms and reduced quality of life [1].

ASA desensitization was first described by Widal et al. [4] and was later pioneered as a treatment for AERD in the 1980's, predominantly from the perspective of asthma management [5–7]. The pathophysiologic process behind AERD is believed to involve an imbalance of eicosanoid inflammatory mediators, including cysteinyl leukotrienes, which promote airway hyper-responsiveness, bronchoconstriction, and eosinophil activation [8]. These leukotrienes are over-expressed at baseline and further increase in production with exposure to ASA in patients with AERD [8]. However, the mechanism behind ASA desensitization therapy is not well understood.

While the current literature supports ASA desensitization as an effective adjuvant in the management of sinonasal complaints and asthma symptoms in AERD patients, the early literature was predominantly focused on subjective, non-validated sinonasal symptom scoring, quality of life scores, and pulmonary outcomes with more recent attention to validated subjective sinonasal outcomes and objective measures [2,9–18]. It was therefore our objective to measure both objective and subjective, disease-specific validated sinonasal and pulmonary outcomes to evaluate the efficacy of ASA desensitization therapy in a prospective cohort of patients.

2. Materials and methods

This is a prospective clinical cohort study of patients with AERD. Institutional ethics review board approval with the Human Ethics Research Online system was obtained prior to commencement of the study (Pro0052194). All patients provided informed, written consent prior to inclusion in the study. Patients were identified through the practices of two academic rhinologists and one academic general otolaryngologist at our institution from October 2014 to December 2015. AERD patients 18 years of age and older who were being considered for ASA desensitization by their surgeon based on their clinical status were eligible for recruitment in the study. Our definition of AERD included documented nasal polyposis on either endoscopic examination or CT scan, a previous diagnosis and active management of asthma, and a history of sensitivity reaction to ASA. Sensitivity to ASA included a clear history of previous asthma exacerbation or naso-ocular reaction within 3 h of ingestion of ASA.

Patients were excluded if they had a history of gastrointestinal bleeds, a bleeding disorder, or cystic fibrosis. Patients who

were pregnant or planning to become pregnant within the next year were also excluded.

Patient demographics, current asthma and chronic sinusitis with nasal polyposis (CRSwNP) management, history of emergency room visits and hospitalization for asthma exacerbation, history of sinus surgery, and smoking history were collected. Patients were administered the Sinonasal Outcome Test (SNOT-22) [19] and Asthma Control Questionnaire (ACQ) [20]. Acoustic rhinometry was performed to measure nasal volumes at a depth from 2 to 5 cm from the nostril as described in previous literature [21] using an A1 acoustic rhinometer (gm instruments, Kilwinning, Scotland, United Kingdom). The depth of 2 to 5 cm was selected to reduce the impact of the nasal valve on the measurements and to emphasize evaluation of mucosal changes related to AERD [21]. Patients were measured in their non-decongested state to assess changes in edema and congestion independent of response to decongestants. All measurements were performed by a single technician. The average from three readings was recorded for each side with the sum of each side used as the total nasal volume. Patients underwent endoscopic examination using a 30-degree 3 mm Hopkins rigid endoscope and their nasal polyposis was scored using the scale proposed by Vendelo Johansen et al. [22] and the Perioperative Sinus Endoscopy (POSE) [23] scoring system. Nasal endoscopy videos were recorded using a Mediap USB300 recorder (Mediacapture, Plymouth Meeting, PA) and two surgeons blinded to patient identification and pre-and post-desensitization status evaluated the POSE score. Endoscopic scores were reported as the average sum of the right and left sided scores by the two surgeons.

Prior to undergoing ASA desensitization, all patients were reviewed by an asthma specialist. Patients required well-controlled asthma based on reported symptoms and pulmonary function tests prior to being approved to proceed with desensitization as judged globally by the asthma specialist.

All patients were prescribed montelukast 10 mg daily for seven days prior to desensitization to reduce the risk of severe ASA-induced bronchospasm [24] and recorded peak flow readings diurnally to ensure stability. ASA desensitizations were performed according to an established protocol in a supervised medical outpatient setting within the hospital over a two-day period to reach a final dose of 650 mg without an adverse response. The protocol is a modification of the Scripps protocol [25] with doses given in 2-h intervals with 5 mg, 40 mg, 80 mg, and 160 mg doses administered on the first day and 160 mg, 325 mg, and 650 mg doses on the second day. Sequential ASA doses were delayed or repeated if required for significant or non-resolving sinonasal or pulmonary symptoms. Following desensitization, patients were maintained on an ASA dose of 650 mg twice daily.

Patients were seen in follow-up at 1 month, 3 months, and 6 months post-desensitization. Self-reported compliance with ASA maintenance dosing was recorded along with adverse events, current asthma and CRSwNP treatment and medications. SNOT-22 and ACQ questionnaires were administered. Acoustic rhinometry and nasal endoscopy were performed.

An ad hoc sample size calculation was performed using change in SNOT-22 as the primary outcome measure in paired samples. Using $\alpha = 0.05$ and $\beta = 0.80$ with an estimated effect difference in SNOT-22 score of 9 corresponding to a clinically significant change [19] and an estimated standard deviation of 10, a sample size of 12 patients was determined.

Individual patient data forms were used for initial data collection and then data were transferred into a computer database. Descriptive statistics including medians, interquartile ranges, and frequencies were calculated. Statistical analysis was performed comparing pre- and post-desensitization values for patients completing follow-up using the non-parametric Wilcoxon signed rank test. Statistical significance was accepted at $p < 0.05$ in all cases. Statistical analyses were performed using SPSS software version 23 (SPSS Inc., Chicago, IL).

3. Results

Twelve patients were recruited and completed the desensitization protocol. Two patients did not have any evidence of a sensitivity reaction to the escalating ASA doses and were thus excluded from the study (Fig. 1). In the remaining 10 patients, the median age was 51.0 ± 5.5 years ($\pm$ interquartile range (IQR)) (Table 1). Six of the patients were female and four were male. All patients had a history of endoscopic sinus surgery with a median number of 2.5 prior surgeries. The median period since their last surgery at the time of desensitization was 460 days. All patients were using daily saline nasal rinses with budesonide nebulas. Eight of the patients had at least one course

Table 1

Baseline demographics and sinonasal scores of patients undergoing ASA desensitization.

N	10
Age(range)	51.0 ± 5.5 years (46–66 years)
Gender (n)	
Males	4
Females	6
Courses of systemic steroids in previous year	1.0 ± 1.5
Smoking status	
Never smoked	6
Former smoker	4
Number of prior surgeries	2.5 ± 2.5
Time since last endoscopic sinus surgery (days)	460 ± 1092

Measures of central tendency recorded as median $\pm$ interquartile range.

of systemic steroids in the preceding year. Four of the patients received courses of oral steroids after recruitment into the study but prior to pre-desensitization data collection and ASA desensitization, including one following a hospitalization for pneumonia and the another for a rheumatoid arthritis flare.

With regards to asthma management, 6 patients had previous emergency room visits or hospitalizations for their asthma but only one patient visited the emergency room in the last year for asthma. All patients were on inhaled corticosteroids as well as long or short acting β_2 -agonists. No patients were current smokers but 4 had a prior history of smoking ranging from 5 to 35 pack year histories (Table 1).

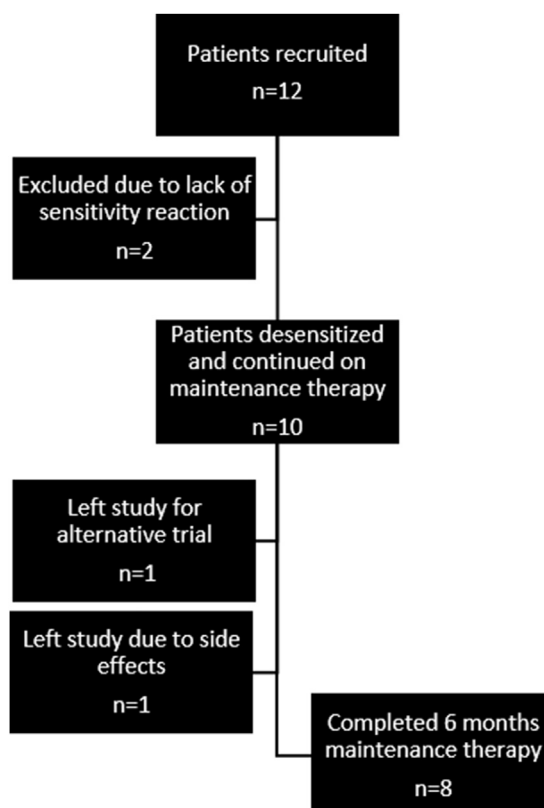


Fig. 1. Study flowchart.

Table 2

Pre- and post-desensitization subjective and objective sinonasal and asthma outcomes in patients completing 6 months of ASA maintenance therapy and follow-up.

Characteristic	Pre-desensitization	6 Months maintenance therapy	P value
SNOT-22	30.0 ± 34.5	18.5 ± 17.3	0.025
ACQ	0.43 ± 0.32	0.21 ± 0.79	0.833
Acoustic rhinometry volume (cm ³)	9.37 ± 5.38	7.51 ± 7.99	0.779
Percent predicted FEV1	111 ± 17	102 ± 33	0.123
POSE	20.5 ± 18.5	27.0 ± 18.5	0.483
Polyp score	1.5 ± 2.8	2.0 ± 3.5	0.157

Measures of central tendency recorded as median ± interquartile range. P value based on Wilcoxon signed rank test. N = 8 patients completing follow-up at 6 months. SNOT 22 = Sinonasal Outcome Test 22, ACQ = Asthma Control Questionnaire, FEV1 = forced expiratory volume 1 s, POSE = Perioperative Sinus Endoscopy score. The bold values were those with statistical significance and a p value of <0.05.

There were no significant complications during the ASA desensitization procedure and all patients were safely discharged from the outpatient clinic. The 10 included patients experienced variable levels of naso-ocular and respiratory symptoms during the desensitization. One patient experienced significant gastritis within the first month of ASA maintenance accompanied by transient liver enzyme elevation. This patient was discontinued from maintenance ASA therapy and the study. One patient left the study after deciding to enter an alternative asthma clinical trial. No other significant complications occurred during the study. Several patients reported an increased tendency to bruising.

Eight of the 10 desensitized patients completed follow-up after 6 months of maintenance therapy and were included in the pre- and post-desensitization analysis (Fig. 1). These patients were continuing with a maintenance dose of 650 mg twice daily. One patient was given a 5-day course of oral prednisone by their pulmonologist for an asthma exacerbation during their 6 months of follow-up but no other patients received systemic steroids during the follow-up period. All the patients continued daily saline rinses with budesonide nebulas.

The median SNOT-22 score decreased from 30.0 ± 34.5 to 18.5 ± 17.3 (±IQR) after 6 months of maintenance therapy (Table 2). This difference was statistically significant

(p = 0.025, Wilcoxon signed rank test). There was also a statistically significant reduction in SNOT-22 score compared to the pre-desensitization score at 1 month (17.5 ± 46) (p = 0.012, Wilcoxon signed rank test) and at 3 months (13.0 ± 12.8) (p = 0.017, Wilcoxon signed rank test) (Fig. 2). There were no statistically significant differences in SNOT-22 score between the 1, 3, or 6-month follow-up assessments (p > 0.05 in all cases, Wilcoxon signed rank test). Of the eight patients completing follow-up, 6 had a clinically significant reduction in their SNOT-22 score of 9 or more [19]. There was a statistically significant improvement in the individual SNOT-22 items for difficulty falling asleep, lack of a good night's sleep, wake up tired, fatigue, and reduced concentration (p < 0.05) (Table 3). Six or more patients had improvement in their responses to items for need to blow nose, post-nasal discharge, lack of a good night's sleep, wake up tired, and fatigue after 6 months of maintenance therapy in comparison to pre-desensitization (Table 3).

There was no statistically significant difference in median nasal volume on acoustic rhinometry at 6 months compared to pre-desensitization (p = 0.779, Wilcoxon signed rank test) (Table 2). Also, there were no statistically significant differences in pre-desensitization and 6-month follow-up endoscopic grading based on either the POSE scores or polyp grading scale

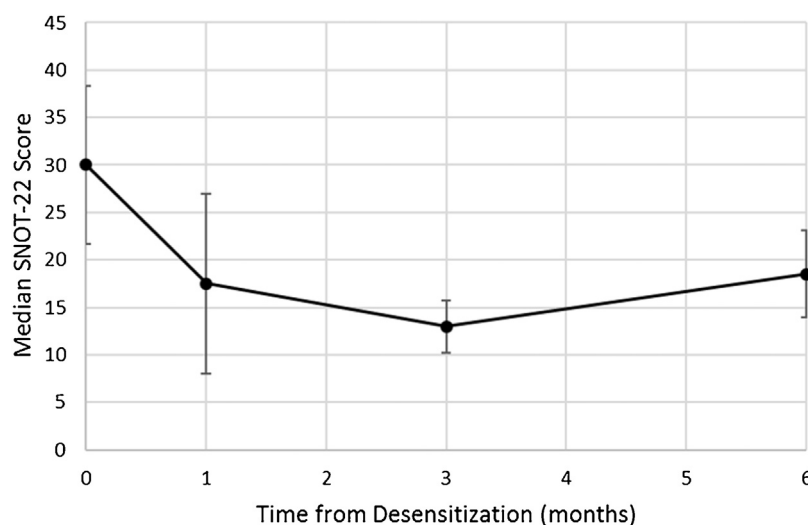


Fig. 2. Median SNOT-22 scores of patients undergoing ASA desensitization and maintenance therapy. Error bars depict standard error values. N = 8 patients completing follow-up at 6 months

Table 3

Itemization of SNOT-22 results from pre-desensitization and 6-month maintenance therapy.

SNOT-22 Item	Pre-desensitization	6 Months maintenance therapy	P value	Patients with improved score (n)	Patients with deterioration in score (n)
Need to blow nose	3.0 ± 1.5	2.0 ± 2.0	0.140	6	1
Nasal blockage	2 ± 2.8	2.0 ± 2.5	0.234	4	2
Sneezing	0.5 ± 2.0	1.0 ± 2.0	1.000	4	3
Runny nose	1.0 ± 3.0	1.0 ± 0.8	0.197	3	1
Cough	1.0 ± 2.8	0.0 ± 1.8	0.465	2	2
Post-nasal discharge	3.0 ± 2.8	1.0 ± 0.8	0.064	6	2
Thick nasal discharge	2.5 ± 3.0	1.0 ± 0.8	0.056	5	1
Ear fullness	1.0 ± 2.0	0.0 ± 2.0	0.414	2	1
Dizziness	0.0 ± 1.0	0.0 ± 0.0	0.083	3	0
Ear pain	0.0 ± 0.0	0.0 ± 0.0	1.000	1	1
Facial pain/pressure	0.5 ± 2.0	0.0 ± 1.0	0.102	3	0
Decreased sense of smell/taste	5.0 ± 4.0	3.0 ± 2.0	0.202	5	1
Difficulty falling asleep	1.5 ± 4.5	0.5 ± 2.0	0.034	5	0
Wake up at night	3.0 ± 1.5	1.0 ± 2.8	0.056	5	1
Lack of a good night's sleep	2.5 ± 4.0	1.0 ± 3.0	0.015	7	0
Wake up tired	2.0 ± 3.5	1.0 ± 2.3	0.024	6	0
Fatigue	2.0 ± 2.5	1.0 ± 2.3	0.014	7	0
Reduced productivity	1.5 ± 2.8	0.0 ± 1.0	0.066	4	0
Reduced concentration	1.0 ± 1.8	0.0 ± 1.0	0.046	4	0
Frustrated/restless/irritable	0.5 ± 2.0	0.0 ± 1.0	0.059	4	0
Sad	0.0 ± 1.8	0.0 ± 0.0	0.109	3	0
Embarrassed	0.0 ± 0.8	0.0 ± 0.0	0.157	2	0

Measures of central tendency recorded as median ± interquartile range. P value based on Wilcoxon signed rank test. N = 8 patients completing follow-up at 6 months. SNOT 22 = Sinonasal Outcome Test 22.

The bold values were those with statistical significance and a p value of <0.05.

($p = 0.483$, $p = 0.157$ respectively, Wilcoxon signed rank test) (Table 2). Individual patient SNOT-22, acoustic rhinometry, and POSE score data from pre-desensitization and after 6 months of maintenance therapy are provided in Table 4.

The median ACQ score at the time of desensitization after optimization of pulmonary status was 0.43 ± 0.32 with a median FEV1 percentage of predicted value of $111 \pm 17\%$ (Table 2). The median ACQ score was 0.21 ± 0.79 at 6 months with no statistically significant difference from the pre-desensitization score ($p = 0.833$, Wilcoxon signed rank test) (Table 2). The percent predicted FEV1 value at 6 months was $102 \pm 33\%$ with no significant difference in comparison to pre-desensitization ($p = 0.833$, Wilcoxon signed rank test).

4. Discussion

The current literature generally supports ASA desensitization as an effective adjunctive therapy for AERD patients [2,9–18]. The existing literature contains a variety of methodologies that have examined a broad spectrum of outcomes. Recent studies have aimed to characterize sinonasal outcomes using objective measures and validated, disease-specific subjective symptom scales.

Several small randomized controlled trials have been recently performed investigating ASA desensitization in patients with AERD with validated measures. Swierczynska-Krepa et al. [16] conducted a placebo-controlled randomized

Table 4

Individual patient data of pre- and post-desensitization subjective and objective sinonasal outcomes in patients completing 6 months of ASA maintenance therapy and follow up.

Patient	SNOT-22		Acoustic rhinometry volume (cm ³) ^a		POSE ^b	
	Pre-desensitization	6 Months maintenance therapy	Pre-desensitization	6 Months maintenance therapy	Pre-desensitization	6 Months maintenance therapy
1	64	27	5.35	6.49	15.5	17
2	32	30	6.85	5.94	16	26.5
3	24	15	10.30	15.48	25	27.5
4	87	51	12.88	5.74	35	32.5
5	22	11	7.86	7.20	37	34
6	11	17	11.27	9.84	6	0
7	36	20	8.44	7.82	31	29.5
8	28	7	23.05	24.23	15.5	12

SNOT 22 = Sinonasal Outcome Test 22, POSE = Perioperative Sinus Endoscopy score.

^a Volume reported as the sum of right and left side measured at a depth of 2–5 cm from the nostril.

^b POSE score reported as the average sum of the right and left sided scores by two surgeons.

trial of ASA desensitization in ASA tolerant and ASA intolerant asthmatics. They found statistically significant improvements in SNOT-20 score, ACQ and nasal peak inspiratory flow at 6 months in 8 ASA sensitive asthmatics who were desensitized and completed follow up. Objective pulmonary outcomes did not show significant differences between groups. Esmaeilzadeh et al. [17] compared 16 ASA desensitization patients to 16 controls at 6 months. They found a statistically significant improvement in SNOT-22, Lund-MacKay and FEV1 scores in patients in the desensitization arm of the study. However, they did not evaluate asthma symptoms with a validated scale or perform endoscopic scoring of nasal polyps. Mortazavi et al. [26] compared 19 patients randomized to ASA to 19 receiving placebo. A significant improvement was seen in SNOT-22 score and FEV1 score at 6 months but not in Lund MacKay score or measured interleukin levels. Fruth et al. [14] did not find statistically significant differences in endoscopic polyp scores or olfaction in 18 ASA desensitized patients compared to 13 controls at 36 months after sinus surgery. However, the desensitized patients did have improved quality of life scores on a translated version of the Rhinosinusitis Disability Index [14,27].

Several other studies have reported on significant objective sinonasal findings. Havel et al. [11] found a statistically significant improvement in asthma and sinonasal quality of life scores and objective polyp scoring at 18-month follow-up in a retrospective review of 65 patients. Rozsasi et al. [13] found significant improvements in endoscopic polyp scores, rhinomanometry, and olfaction at 12-month follow-up in a prospective cohort. Symptom scores utilized in this study were modified validated quality of life questionnaires, which showed improvement with ASA desensitization.

Our study found a statistically significant improvement in SNOT-22 scores at 1 month, 3 months, and 6 months compared to pre-desensitization scores. The improvement in SNOT-22 scores was spread over numerous questionnaire items although many did not reach statistical significance individually. Objective endoscopic scoring and acoustic rhinometry measurements were stable at 6 months. Subjective and objective asthma measures were also unchanged at 6 months. This may be expected as patients were optimized with regards to asthma management prior to desensitization. The stability of patients' endoscopic scores and acoustic rhinometry results are suggestive of effective disease management given the recalcitrant, progressive nature of these patients' nasal polyps prior to desensitization. This is the first study to utilize the POSE score as an outcome in ASA desensitization to document detailed endoscopic findings. The utilization of both clinically relevant, disease-specific, validated subjective and objective outcome measures for both chronic rhinosinusitis and asthma is a major strength of this study.

A role for ASA desensitization therapy following recovery from endoscopic sinus surgery has been advocated for in the management of AERD patients in a recent evidence-based review [9]. No studies have demonstrated the use of ASA desensitization as an alternative to surgery in patients meeting surgical indications. The patients in our study were desensitized as part of ongoing management of refractory sinonasal

symptoms despite prior surgical and ongoing conventional medical management. Many pursued ASA desensitization with a desire to avoid further surgical intervention.

ASA desensitization remains an underutilized treatment modality in patients with AERD. A recent survey of allergists and fellows in the United States showed that only 67% offer ASA desensitization and a significant number who do not perform desensitization would not refer to another allergist to perform this procedure [28]. Cited barriers to performing desensitization included nursing care logistics, poor compensation, concern for safety risks, and lack of exposure to ASA desensitization during fellowship training.

This study has several limitations. Like other prospective studies on ASA desensitization, the number of patients completing desensitization and follow-up is small. Due to the exclusion of patients who did not have a sensitivity response to ASA during the desensitization protocol and attrition during the follow up period, the study had fewer than the ad-hoc power calculation. However, statistical significance was still achieved for the primary outcome measure. There was no control group with which to compare our treatment cohort with. As such, there is a potential for a placebo effect or other aspects of their medical management to affect outcomes.

5. Conclusions

ASA desensitization may be considered as an adjunctive therapy to standard medical and surgical management of patients with AERD. Patients may experience subjective sinonasal symptom benefit at 6 months following desensitization and stable objective assessments. The performance of large, well-designed, controlled trials remains a challenge in this area of study due to numerous obstacles including low patient volumes and patient compliance with long term therapy. Long term follow-up studies utilizing validated, disease-specific outcomes in combination with objective, clinically relevant endoscopic scoring systems are needed. The management of patients with AERD is complex and involves a multidisciplinary team approach. Further discussion regarding the place of ASA desensitization in the management of CRSwNP in AERD patients and the availability of this treatment modality is needed within the otolaryngology community.

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None.

Ethics approval

Prior to commencement, health research ethics board approval was obtained.

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