Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study with 1-year follow-up

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Background: **This study evaluated 1-year outcomes in patients with chronic rhinosinusitis (CRS) who were considered surgical candidates by study criteria and elected either medical management or endoscopic sinus surgery (ESS). In addition, some patients initially enrolled in the medical treatment arm crossed over to the surgery arm during the study period and their respective outcomes are evaluated.**

Methods: **Adult subjects with CRS who failed initial medical therapy were prospectively enrolled into a nonrandomized, multi-institutional cohort. Subjects were included in 1 of 3 cohorts: medically managed, surgically managed, or crossover (from medical to surgical). The primary outcome measure was disease-specific quality-of-life (QOL). Bivariate and multivariate analyses compared QOL improvement between cohort groups.**

Results: **Baseline comorbidity, QOL, and other disease severity measures were not different between the 3 cohorts. With 1-year follow up, surgical patients (n = 65) reported significantly more improvement than medically managed patients (n = 33; Rhinosinusitis Disability Index (RSDI), $p = 0.039$; Chronic Sinusitis Survey (CSS), $p = 0.018$). Seventeen subjects who had initially elected medical management crossed over to surgery during the follow-up period. QOL in the crossover cohort was initially stagnant or worsening followed by improvement after ESS (RSDI, $p = 0.035$; CSS, $p = 0.070$). At 1-year follow-up, higher frequency of improvement was found in the surgical cohort vs medical cohort for several outcomes (total CSS: 70.8% vs 45.5%; odds ratio [OR], 3.37; 95% confidence interval [CI], 1.27-8.90; $p = 0.014$).**

Conclusion: **With 1 year of follow-up, patients electing ESS experienced significantly higher levels of improvement in outcomes compared to patients managed by medication alone. In addition, a crossover cohort who initially elected medical management experienced improvement in several outcomes after crossing over to ESS.** © 2013 ARS-AAOA, LLC.

Key Words:
sinusitis; surgery; endoscopy; medical; outcomes; comparative effectiveness

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We have previously published results of a prospective, multicenter, nonrandomized study of medical therapy vs endoscopic sinus surgery (ESS) for patients who failed initial medical management for chronic rhinosinusitis

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(CRS).[1] In that study, patients who had initially failed medical therapy and were considered surgical candidates by study criteria elected 1 of 2 treatment options: ongoing medical therapy vs ESS coupled with ongoing medical therapy. Patients electing ESS had significantly greater quality of life (QOL) improvements in addition to less exposure to oral antibiotics and oral steroids as well as fewer missed school and work days, compared to those electing ongoing medical therapy with 6 months of follow up. The objective of this study was to evaluate 1-year QOL outcomes and to examine a crossover cohort of patients who crossed over from medical therapy to ESS during the study period.

Methods

Inclusion criteria and multi-institutional data collection

Adult subjects (≥18 years) were prospectively enrolled from 4 tertiary rhinology practices including: Oregon Health and Science University (OHSU); Northwestern University (NWU); Medical University of South Carolina (MUSC); and the University of Pennsylvania (UPenn). All patients were diagnosed with CRS as defined by the 2007 Adult Sinusitis Guidelines.[2] Prior to enrollment, all subjects had previously failed medical management defined as a minimum of a 3-week course of broad spectrum or culture directed antibiotics and 3-week trial of topical steroid application. After enrollment, patients were followed prospectively at 3, 6, and 12 months following surgery or medical therapy, with the 12-month time point as the main time point of interest. Informed consent and study protocols were all monitored and approved by the Institutional Review Board at each enrollment site. Patients were assigned unique study identification numbers by the Study Coordinator to protect all health-related information.

Clinical data was collected by the enrolling physician based on patient history and clinical examination. Study variables included age, gender, race/ethnicity, history of previous sinus surgery, sinonasal polyposis, and septal deviation. Additional study information included a patient history of asthma, acetylsalicylic acid (ASA) intolerance, allergy, depression, oral steroid dependency, and tobacco use. Study patients were categorized into 1 of 3 treatment arms including a medical management cohort, surgical treatment cohort, and a crossover cohort consisting of patients originally electing medical management but altering their treatment course to include ESS at some point during the investigational period.

Baseline objective measures of disease

Baseline coronal plane computed tomography (CT) and endoscopy scores were recorded for each treatment arm utilizing the scoring systems of Lund-Mackay (score range: 0-24) and Lund-Kennedy (score range: 0–20).[3,4]

Primary outcomes: QOL measures

All study patients were asked to complete 2 disease-specific QOL surveys during the initial enrollment meeting and at subsequent follow-up visits for the 12-month duration of the study. The Rhinosinusitis Disability Index (RSDI) is a 30-question survey comprised of 3 individual subscales to measure the impact of sinus disease on the physical, functional, and emotional domains on a continuum (score range: 0-120).[5] Higher RSDI total and subscale scores represent a higher impact of disease. The Chronic Sinusitis Survey (CSS) is a 6-question survey designed to measure sinusitis-specific symptoms and medication use within the preceding 8-week period (score range: 0-100).[6] Lower total and subscale scores indicate a greater impact of CRS on each patient. The primary outcome of interest was the mean change in QOL scores as measured by the RSDI and CSS total scores (12-month follow-up score minus baseline score).

Statistical analysis

Study sample size determinations were calculated and previously reported.[1] All survey data were collected, transcribed, and manually scored after each clinic visit by a research coordinator on standardized clinical research forms. Responses were deidentified and securely stored in a relational database during the collection period (Microsoft FoxPro; Microsoft Corp., Redmond, WA.). Descriptive statistics (means, standard deviations [SDs], ranges, and frequencies) and distributions were assessed for all patient factors and outcome variables for both treatment cohorts.

Pearson's χ^2 tests or Fishers' exact tests were used to compare comorbidity frequency between treatment groups. Paired *t* tests or Wilcoxon signed-rank tests were be used to assess significant improvement between baseline and follow-up time scores within each treatment group. Independent *t* tests or Mann Whitney U tests were used to assess differences in preoperative and postoperative QOL scores between treatment groups. One-way analysis of variance (ANOVA) and the Bonferroni post hoc test for multiple comparisons was used to evaluate differences between individual treatment groups for all mean continuous variables. Repeated measures ANOVA was were used to evaluate if treatment cohort was a significant predictor of RSDI and CSS improvement while controlling for correlation between time points. Models were built using an exchangeable covariance matrix and RSDI and CSS total scores as within-subjects variables (level IV) for all patients and individual cohorts separately. Treatment cohort was evaluated as the between-subjects factor while adjusting for potential site differences.

Logistic regression models were also used to assess the association between treatment groups and dichotomized QOL improvement, after adjusting for independent predictor or potential confounding variables. The categorical treatment group variable was considered the main independent predictor and separated into binary comparisons ("dummy variables"). The dependent variable was clinically significant improvement in QOL ("Yes" vs "No") as defined by a posttreatment change of at least 0.50 SD of

TABLE 1. Baseline demographics and patient characteristics for medical treatment vs surgical treatment vs crossover cohort*

Characteristics	Medical cohort (n = 33) n (%)	Surgical cohort (n = 65) n (%)	Crossover cohort (n = 17) n (%)	p[a]
Age, years[a]	54.2 ± 16.8	47.4 ± 13.1	51.9 ± 14.3	0.133
Gender				0.203
Male	12 (36.4)	36 (55.4)	8 (47.1)	
Female	21 (63.6)	29 (44.6)	9 (52.9)	
Previous sinus surgery	15 (45.5)	22 (33.8)	2 (11.8)	0.043
Nasal polyposis	12 (36.4)	30 (46.2)	5 (29.4)	0.377
Septal deviation	5 (15.2)	14 (21.5)	4 (23.5)	0.700
Asthma	11 (33.3)	25 (38.5)	5 (29.4)	0.745
ASA intolerance	0 (0.0)	5 (7.7)	0 (0.0)	0.623
Allergy	10 (30.3)	29 (44.6)	8 (47.1)	0.338
Depression	1 (3.0)	2 (3.1)	0 (0.0)	0.765
Oral steroid dependency	2 (6.1)	3 (4.6)	1 (5.9)	0.531
Current smoker	1 (3.0)	1 (1.5)	1 (5.9)	0.706

*Values are n (%) except for age, which is mean ± SD.

[a]Values of p are reflective of global differences between all cohorts using chi-square analysis and 1-way ANOVA.

ANOVA = analysis of variance; ASA = acetylsalicylic acid; SD = standard deviation.

the baseline QOL score of the whole population.[7] Odds ratios (ORs) for treatment group were compared between unadjusted and adjusted models to check for confounding. Variables resulting in an absolute difference of 10% in the association estimate of the treatment variable were considered confounders and were kept in final models when clinically relevant. Variables with univariate regression coefficients significant at $p \leq 0.25$ were included as candidates for the multivariate regression models. Important interaction terms were considered in the model. Final models were constructed using clinical judgment and a stepwise selection method with predetermined significance levels for entry (0.05) and removal (0.10). Final models included adjustment for enrollment-site variation and "goodness-of-fit" was tested using the Hosmer-Lemeshow test statistics.[8] Statistical analyses were performed using commercially available statistical software (SPSS v.19; SPSS Inc., Chicago, IL).

Results

Baseline cohort characteristics

A total of 180 patients were enrolled between March 2009 and April 2010 (OHSU = 61; NWU = 46; MUSC = 42; and UPenn = 31). Eighty-one patients originally elected medical management and 99 patients elected sinus surgery coupled with ongoing medical therapy. A total of 115 (63.9%) patients were followed to the 1-year endpoint including 50 patients initially enrolled in the medical management cohort and 65 patients in the surgical treatment cohort. During the follow-up period, 17 patients with follow-up (34.0%) crossed over from the medical cohort to the surgical cohort creating a third "crossover cohort." The final tally in the 3 cohorts was as follows: surgery cohort (n = 65); medical cohort (n = 33); and crossover cohort (n = 17). Baseline patient characteristics for the 3 cohorts with 12-month follow-up are shown in Table 1.

At baseline, patients in the crossover cohort were less likely to have had prior sinus surgery ($p = 0.043$). No other differences in baseline comorbid factors, or clinical measures of disease severity (including baseline CT and endoscopy) were found between the 3 cohorts. Baseline QOL was not significantly different between the 3 cohorts (Table 2).

Longitudinal evaluation of outcomes

Corrected repeated-measures ANOVA determined that mean RSDI and CSS total scores improved significantly between time points ($p < 0.001$) for all 3 cohorts. Most improvement in QOL outcomes occurred within the first 6 months following baseline assessment. RSDI and CSS scores were stable for all 3 cohorts between 6 and 12 months (ie, not statistically different after adjustment for multiple comparisons, all $p > 0.999$; Figs. 1 and 2). The crossover cohort demonstrated initial worsening on the CSS and stagnation on the RSDI prior to crossover to ESS and then improvement in total QOL mean scores after 3-month follow-up (RSDI, $p = 0.035$; CSS, $p = 0.070$; Figs. 1 and 2).

Relative changes in QOL outcomes following intervention

Patients in the surgery cohort reported significant absolute improvement between baseline and 12-month follow-up for both RSDI and CSS scores (all $p \leq 0.001$). Patients in the medical cohort reported similar statistically significant

TABLE 2. Comparison of baseline quality of life and objective measures of disease between treatment cohorts

	Medical cohort (n = 33) (mean ± SD)	Surgical cohort (n = 65) (mean ± SD)	Crossover cohort (n = 17) (mean ± SD)	p^a
Primary measures				
RSDI physical	14.7 ± 8.5	16.9 ± 7.9	18.4 ± 6.4	0.243
RSDI functional	11.2 ± 7.1	13.2 ± 6.1	15.4 ± 7.0	0.088
RSDI emotional	8.9 ± 6.4	10.7 ± 6.9	11.8 ± 6.6	0.282
RSDI total	34.7 ± 19.8	41.0 ± 18.9	45.1 ± 16.9	0.142
CSS symptom	38.6 ± 28.2	29.1 ± 25.8	41.2 ± 32.2	0.135
CSS medication	58.8 ± 27.5	51.5 ± 26.2	55.4 ± 28.7	0.438
CSS total	48.7 ± 21.4	40.3 ± 21.6	48.3 ± 25.4	0.145
Disease severity measures				
Lund-Mackay CT score	11.3 ± 4.6	12.8 ± 5.5	12.4 ± 5.0	0.439
Lund-Kennedy endoscopy score	5.8 ± 3.0	6.2 ± 3.4	5.0 ± 3.5	0.444

[a]Values of *p* are reflective of global differences between all cohorts using 1-way ANOVA.

ANOVA = analysis of variance; CSS = Chronic Sinusitis Survey; CT = computed tomography; RSDI = Rhinosinusitis Disability Index; SD = standard deviation.

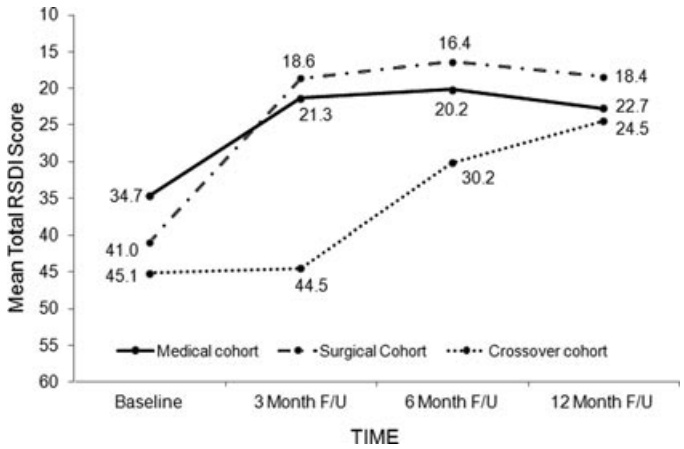

FIGURE 1. Longitudinal trends in mean RSDI total scores for the medical, surgical, and crossover cohorts. RSDI = Rhinosinusitis Disability Index.

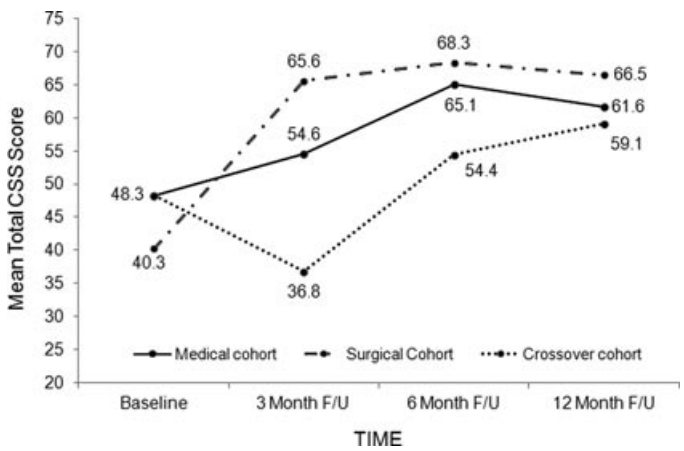

FIGURE 2. Longitudinal trends in mean CSS total scores for the medical, surgical, and crossover cohorts. CSS = Chronic Sinusitis Survey.

improvement between baseline and 12 months, with the exception of the CSS medication subscale score ($p = 0.372$), indicating that medical cohort patients required similar exposure to antibiotics, prescribed nasal sprays, and sinus medications in pill form during follow-up as compared to baseline. Patients in the crossover cohort demonstrated significant improvement over time in total RSDI scores ($p = 0.009$), as well as the CSS symptom subscale ($p = 0.048$).

Comparisons between cohorts found that the surgery and crossover cohorts experienced significantly greater improvement on the RSDI as compared to the medical cohort (Table 3). The surgery cohort reported significantly greater absolute improvement in the CSS total and medication scores as compared to the medical or crossover cohorts.

Logistic regression modeling

After adjustment for enrollment site, age, and previous sinus surgery where appropriate, patients electing sinus surgery were found to be associated with a greater odds of clinically meaningful improvement on the RSDI physical subscale ($p = 0.021$), CSS symptom subscale ($p = 0.020$), and CSS total scores ($p = 0.014$) compared to medically treated patients (Table 4). No indication of collinearity, covariate interaction, or confounding was noted, whereas goodness-of-model fit was found to be adequate for all final, adjusted models ($p \geq 0.05$).

Discussion

This study prospectively evaluated patients who failed a defined trial of medical management and were considered candidates for sinus surgery. Initially, approximately one-half of these patients elected continued medical management while the other one-half elected ESS coupled with continued

TABLE 3. Comparison of level of absolute improvement in QOL scores between treatment cohorts at 12-month follow-up

Primary measures	Medical cohort (n = 33) (mean ± SD)	Surgical cohort (n = 65) (mean ± SD)	Crossover cohort (n = 17) (mean ± SD)	*p*
RSDI physical	5.2 ± 8.3	9.2 ± 10.3	8.5 ± 8.5	0.159
RSDI functional	3.8 ± 6.7	7.4 ± 7.8	7.7 ± 11.4	0.028[a]
RSDI emotional	3.0 ± 6.1	5.6 ± 8.1	4.9 ± 10.4	0.302
RSDI total	12.1 ± 19.5	22.3 ± 24.3	20.6 ± 28.6	0.039[a]
CSS symptom	23.0 ± 35.1	35.4 ± 32.8	17.6 ± 34.0	0.075
CSS medication	3.9 ± 24.4	15.6 ± 27.0	3.9 ± 27.3	0.042[a]
CSS total	13.4 ± 21.1	25.5 ± 24.1	10.8 ± 26.8	0.018[a]

[a]Significant mean differences between the medical and surgical cohort measures. Remaining *p* values reflect a global assessment of mean scores between cohorts using 1-way ANOVA.

ANOVA = analysis of variance; CSS = Chronic Sinusitis Survey; QOL = quality of life; RSDI = Rhinosinusitis Disability Index; SD = standard deviation.

TABLE 4. Comparisons between crude and adjusted ORs for the frequency of improvement in QOL

			Crude			Adjusted		
Outcomes	Medical cohort n (%)	Surgical cohort n (%)	OR	95% CI	*p*	OR	95% CI	*p*
A. Patients originally electing medical treatment compared to surgical treatment								
RSDI physical	18 (54.5)	49 (75.4)	2.55	1.05–6.20	0.036	3.16	0.19–8.39	0.021
RSDI functional	17 (51.5)	44 (67.7)	1.97	0.84–4.65	0.118	1.78	0.59–5.34	0.306
RSDI emotional	14 (42.4)	35 (53.8)	1.58	0.68–3.69	0.285	1.32	0.46–3.80	0.605
RSDI total	18 (54.5)	47 (72.3)	2.18	0.91–5.22	0.079	2.44	0.78–7.61	0.124
CSS symptom	17 (51.5)	46 (70.8)	2.28	0.96–5.42	0.060	3.17	0.19–8.41	0.020
CSS medication	11 (33.3)	33 (50.8)	2.06	0.86–4.93	0.101	2.04	0.81–5.16	0.132
CSS total	15 (45.5)	46 (70.8)	2.91	1.22–6.92	0.015	3.37	1.27–8.90	0.014
B. Patients crossing over to surgical treatment compared to medical treatment								
RSDI physical	18 (54.5)	14 (82.4)	3.89	0.94–16.13	0.052	1.96	0.96–3.99	0.065
RSDI functional	17 (51.5)	11 (64.7)	1.73	0.52–5.77	0.373	1.17	0.58–2.35	0.668
RSDI emotional	14 (42.4)	10 (58.8)	1.94	0.59–6.36	0.272	1.37	0.76–2.50	0.296
RSDI total	18 (54.5)	12 (70.6)	2.00	0.57–6.97	0.273	1.39	0.74–2.61	0.310
CSS symptom	17 (51.5)	9 (52.9)	1.06	0.33–3.42	0.924	0.99	0.54–1.81	0.966
CSS medication	11 (33.3)	7 (41.2)	1.40	0.42–4.68	0.584	1.19	0.65–2.19	0.569
CSS total	15 (45.5)	9 (52.9)	1.35	0.42–4.36	0.616	1.12	0.57–2.24	0.738

CI = confidence interval; CSS = Chronic Sinusitis Survey; OR = odds ratio; QOL = quality-of-life; RSDI = Rhinosinusitis Disability Index.

medical therapy. Over the course of 1-year follow up, more than one-third of the patients initially electing medical therapy crossed over to ESS, allowing evaluation of a crossover cohort. Baseline QOL and objective measures of disease severity (CT and endoscopy) were not significantly different between the 3 cohorts. All 3 cohorts experienced significant and durable improvement up to 12 months, with the surgical cohort demonstrating significantly greater improvement than the medical cohort in QOL—nearly twice as much improvement in most QOL domains. The crossover cohort demonstrated initial stagnation or worsening in QOL on medical therapy followed by significant improvement in QOL after ESS. Comparisons of frequency of improvement between therapies suggests trends of more frequent improvement in the surgical and crossover cohorts relative to the medical cohort, but sample size is insufficient to draw conclusions.

In 2006, a systematic review by the Cochrane Group concluded that ESS had not been demonstrated to confer additional benefit to that obtained by medical therapy.[9] This conclusion was reached on the basis of 3 randomized trials that did not compare ESS to medical therapy in patients who had previously failed initial standard medical management. While the Cochrane systematic review standards were very scientifically rigorous, the studies included used inappropriate comparison groups, particularly when considering the standard of care through which real-world decisions are made regarding surgical patient selection.[10]

Our initial study design was developed to compare effectiveness of ongoing medical therapy vs ESS in patients who had already *failed a defined trial of initial medical management and could be considered surgical candidates*. Our sample size calculation was based on the power necessary to detect a clinically meaningful difference in outcome between these 2 cohorts. We were surprised that more than one-third of the medical cohort elected to cross over to surgery sometime during the 12-month follow-up period. This was fortuitous in that it allowed the evaluation and comparison of a crossover cohort relative to the medical and surgical cohorts.

However, this unanticipated quantity of crossover to surgery created a problem in that it significantly reduced the size of the original medical cohort so that our study theoretically lost power to determine if differences in fact existed. Despite this unforeseen reduction in sample size, significant differences in level of improvement were still observed between the medical vs surgical cohorts, with greater improvement in QOL in the surgical cohort on both disease-specific QOL instrument total scores (Table 3). Sample size does appear to become an issue when comparing frequency of improvement in QOL between the cohorts. Whereas each and every comparison demonstrated a trend of higher frequency improvement in the surgical or crossover cohorts compared to the medical cohort, this reached significance for only 1 RSDI subscale score and only 1 CSS subscale score in addition to the CSS total score (Table 4). An intention-to-treat analysis is not necessary or appropriate given that the initial cohorts were not randomized to treatment arms. Our prior report discusses the many issues preventing the current feasibility of a randomized controlled trial (RCT) design as well as the measured and unmeasured confounding and potential treatment selection bias concerns of the current observational study design.[1]

Subjects choosing to cross over from medical management to surgical management did not appear to differ to any significant degree at baseline when compared to the medical and surgical cohorts with regard to disease-severity measures, QOL, or comorbidity. It is interesting to note that disease-specific QOL appeared to initially stagnate on the RSDI (Fig. 1) and worsen on the CSS (Fig. 2) for patients in the medical cohort who ultimately crossed over to ESS, suggesting that lack of improvement or even worsening in QOL is a factor for patient decision-making.

Limitations of this study include the potential lack of generalizability of the results given the study setting in tertiary referral centers. "Failed medical management" included a course of broad-spectrum or culture-directed antibiotics and topical steroids for a minimum of 3 weeks. While most patients received more intensive medical therapy than this prior to enrollment, it can be argued that topical steroids require a longer course to have full effect.

Conclusion

This prospective, multi-institutional study with 1 year of follow-up demonstrates that patients electing ESS experience significantly higher levels of QOL improvement as compared to patients managed by medication alone. In addition, over one-third of patients who initially elected medical management experienced stagnation or worsening of disease-specific QOL followed by significant improvement in several outcomes after crossing over to ESS.

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