Surgical therapy vs continued medical therapy for medically refractory chronic rhinosinusitis: a systematic review and meta-analysis

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Background: **The currently accepted treatment paradigm of treating chronic rhinosinusitis (CRS) first with appropriate medical therapy (AMT) and then with surgery if patients are refractory to AMT, has been criticized for lack of evidence. The objective of this study was to reassess the literature and establish the highest level of evidence possible regarding further management of CRS patients refractory to AMT.**

Methods: **This study was a systematic review (SR) with meta-analysis (MA). Adult CRS patients who received AMT and then underwent either medical or surgical therapy in moderate to high level prospective studies were included. Outcomes assessed were disease-specific quality of life (QOL), nasal endoscopy, health-state utility, missed work days, change in cardinal symptoms of CRS, economic impact, and adverse events.**

Results: **A total of 970 manuscripts were identified; 6 studies were ultimately included in the SR with 5 included in the MA. Compared to continued medical therapy, endoscopic sinus surgery (ESS) significantly improved patient-based QOL scores ($p < 0.00001$) and nasal endoscopy scores ($p < 0.00001$). Difference in missed work days depended heavily on patient choice of intervention. Unpooled analysis showed improvements in olfaction, health utility scores, and cost-effectiveness.**

Conclusion: **On meta-analysis, for CRS patients refractory to AMT, ESS significantly improves objective endoscopic scoring outcomes vs continued medical therapy alone. In patients with refractory CRS who have significant reductions in baseline QOL, ESS results in significant improvements. Continued medical therapy appears to maintain outcomes in patients with less severe baseline QOL. Unpooled analysis demonstrates improvement in health utility, olfaction, and cost-effectiveness following ESS compared to continued medical therapy alone, in medically refractory CRS.**

Key Words:
sinusitis; rhinosinusitis; surgery; antibiotics; treatment; management; otolaryngology

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Chronic rhinosinusitis (CRS) is a disease of underappreciated severity, with often debilitating effects on quality of life (QOL), afflicting 5% to 11% of the world's adult populations.[1–3] Health status in several domains of those suffering from CRS are comparable to patients with diabetes mellitus, asthma, and chronic obstructive pulmonary disease, and yet many people do not consider the necessity of appropriate treatment in CRS with the same gravity as they do in these other disease states.[4] There is also a significant economic burden associated with CRS, with annual

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direct and indirect costs in the United States alone estimated at $9.9 billion and $13 billion, respectively.[5–7]

The obvious scope and impact of CRS begs for standardized and validated treatment paradigms, and yet the literature and evidence have lagged behind common practice. There is a widely held belief among the physicians treating patients with CRS that when "maximal medical therapy" has failed to cure a patient, surgery offers better outcomes than continuation of medical therapy. However, until recently, if one looked for high-level evidence supporting this management decision, there would have been a true paucity in the literature. In fact, 2 Cochrane reviews of the literature concluded that there is no difference in outcomes of surgical management compared with medical management in CRS with and without polyps.[8,9] There are 2 major issues with these reviews. First, they did not take into account the standard practice of ensuring that a patient has first failed medical management before moving on to surgical interventions. Most well-trained otolaryngologists and rhinologists would not jump first to surgical intervention for uncomplicated CRS, as a proportion of these patients can resolve or remain stable with medical management. By including studies that do not use a relevant starting point for treatment, the reviews do not offer conclusions that are necessarily applicable to real world practice. Secondly, the limitation of using only randomized controlled trials (RCTs) in these reviews excluded a number of potentially valuable studies. Of course, the admirable quest of only using the highest level of evidence for a review of the literature should be commended, but unfortunately—as noted in both the reviews and included feedback responses to those reviews—those level 1 studies either were poor quality or did not actually answer the appropriate clinical question.[8]

There are several reasons why systematic reviews to date have excluded many seemingly valid studies, resulting in conclusions that appear to be at odds with common practice. The first is an inconsistency in what authors have reported as presurgical maximal medical therapy (MMT), or appropriate medical therapy (AMT), with a wide range in duration and variability in specific types of medication. A recent review examining the literature for some consensus as to what constitutes AMT in our literature found that only 21% of studies reported specific AMT criteria. When AMT had been reported, the majority of protocols involved 8 weeks of topical intranasal corticosteroids and 3 weeks of antibiotics. A little over one-half of the studies also included 1 to 2 weeks of oral corticosteroids.[10]

A second contributing factor regarding the difficulty of performing an RCT looking at the specific question of surgical vs continued medical therapy in patients who have failed AMT, is that an RCT could pose difficulties in the feasibility of blinding surgical procedures, and call into question the ethicality of performing "sham" procedures as controls. This is due to the deep-seated belief within our field that our current treatment paradigm is best for patients and that prolonging the interval to appropriate treatment may worsen outcomes.

However, as providers constantly striving to deliver optimal care to our patients, we should not let these limitations prevent us from continually examining the best evidence available to us and using this to guide treatment decisions. In 2005, a systematic review of outcomes of surgery vs continued medical therapy identified only 1 publication with level 2 evidence and otherwise referenced over 40 publications with level 4 evidence.[11] The preponderance of that evidence did overwhelmingly point to surgery being more effective in this group of patients, but due to the low level of the evidence the authors could only give recommendations for better design and methodology for studies moving forward.

Over the last decade, an effort has indeed been made to use more rigorous methodology in prospective studies, thus offering higher levels of evidence to bring us closer to answering this important question. Therefore, the objective of this review is to use this best available evidence, published over the last decade, to answer our question of whether surgical therapy or continued medical therapy is more effective in treating medically refractory CRS.

Materials and methods

Our review followed an a priori protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The review protocol was registered on the PROSPERO website (http://www.crd.york.ac.uk/prospero) prior to data extraction (registration no: CRD42016037010).

Types of studies

This review sought to include RCTs and prospective cohort and cross-over studies with moderate-to-high rating. The quality of crossover and cohort studies was assessed using Newcastle-Ottawa Scale.[13] Moderate rating based on the Newcastle-Ottawa Scale was 5 to 6 stars with high-quality rating ranging from 7 to 9 stars.

Types of participants

Inclusion criteria:

- CRS based on national guidelines (American Academy of Otolaryngology [AAO], Canadian, European Position Paper on Rhinosinusitis and Nasal Polyps [EPOS]);
- Adult patient population (>18 years old);
- Study population to have undergone AMT defined by at least 3 weeks of antibiotics, with or without topical and/or oral corticosteroids;
- Received either medical or surgical therapy after AMT.

Exclusion criteria:

- Immunodeficiency;
- Cystic fibrosis;
- Wegener's or other autoimmune disease;
- Management of CRS with balloon sinuplasty.

Types of interventions

Patients who have failed AMT who continue to be treated with medical therapy or receive surgical intervention. Medical therapy is defined as receiving any form of topical or oral therapy based on the degree of sinus disease chosen by treating physician. Surgical intervention is known as endoscopic sinus surgery (ESS).

Outcome measures

Primary outcomes:

1. Subjective disease-specific QOL scores;
2. Subjective health utility value QOL scores;
3. Objective validated endoscopic grading scores.

Secondary outcomes:

1. Objective or subjective measures of "cardinal" sinus symptoms which include facial pain, nasal obstruction, thick discharge or olfactory dysfunction;
2. Missed days due to CRS;
3. Economic impact due to CRS;
4. Reported adverse outcomes due to medical or surgical intervention.

Search methods

We conducted the search with restrictions including only English language and years 2005 to 2016. The literature search included Ovid MEDLINE (PubMed), Excerpta Medica Database (EMBASE), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Science Citation Index, Database of Abstracts and Reviews of Effects, CAB Abstracts, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Searches were limited to journal articles published in the 10 years since the last systematic review was published on this topic (December 1, 2005 to March 31, 2016), to allow for relative consistency with what is currently generally considered AMT prior to surgical intervention.

Electronic search terms

After consultation with a librarian and search engine specialist, search terms included: ("medical therapy" [tw] OR "medical management" [tw] OR nonsurgical [tw] OR "drug therapy" [sh] OR "therapy" [Subheading:NoExp] OR "therapeutic use" [sh] OR (medical [ti] AND versus [ti]) OR (medical [ti] AND vs [ti]) OR "medical treatment" [tw]) AND (rhinosinu* [ti] OR sinusit* [ti] OR "sinusitis" [mesh] OR "rhinitis" [mesh]) AND ("surgery" [sh] OR surg* [ti] OR endoscop* [ti] OR catheter* [ti]) AND ("chronic disease" [mesh] OR chronic [tw] OR refractory [tw] OR recurrent [tw]) AND English [lang] NOT ("animals" [mesh] NOT "humans") NOT editorial [pt]".

Data collection

Two of the authors (Z.M.P. and A.T.) independently screened the titles and abstracts according to the inclusion/exclusion criteria. Titles and abstracts with insufficient information were also included for full review of the articles. Full articles were then obtained and references were then reviewed to ensure all appropriate papers were selected for final review. Any disagreement between the selections of the authors was resolved by discussion and if needed, by a third author if no resolution could be made.

Assessment of risk of bias for included studies

The 2 authors then independently assessed the quality of the papers prior to data extraction. RCTs were evaluated using scheme established by the Cochrane Handbook for Systematic Reviews of Intervention.[14] The quality of crossover and cohort studies was assessed using the Newcastle-Ottawa Scale.[13] Included crossover and cohort studies required a minimum of "moderate" rating to be included for data extraction.

Data extraction and synthesis

All studies meeting the inclusion criteria underwent data extraction. The two authors independently extracted the data and synthesized the data using a data collection form. The data extraction then underwent an iterative review process by four more authors (J.V.N., L.R., T.L.S., and P.H.H.) to complete the quality control process prior to analysis. The following data was extracted:

- Author;
- Study design;
- Quality of study;
- Demographics;
- Outcomes;
- Results.

Data analysis

Disease-specific QOL scores, health utility value scores and endoscopy scores were treated as continuous variables with the mean and standard deviation (SD) recorded where available. The overall treatment effect was measured using standardized mean difference (SMD) to combine the different measurement scales and mean difference to combine the same scales from different studies.

Meta-analysis was performed using Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2014). The fixed effects model was used to estimate the overall estimate. The fixed effect model was chosen because it is reasonable to assume that the patients included in these studies received the same level of rhinological care.

Assessment of heterogeneity was determined using the χ^2 test and a $p < 0.05$ was considered significant. The I^2 test determined the level of heterogeneity (0% no heterogeneity, 25% low, 50% moderate, 75% severe). Given the limited

number of combinable studies, funnel plots and sensitivity analysis were not performed.

Results

Our search yielded 971 manuscripts and abstracts. After duplicates were removed, we were left with 897. After initial screening, 864 records were excluded and the 33 remaining full-text articles were assessed for eligibility. Only 7 publications remained that met all inclusion and exclusion criteria, and only 6 were considered for meta-analysis because 1 study was a follow-up looking at longer outcomes in the same patient population. Of the papers included in the meta-analysis, raw data was obtained from authors when necessary to assure outcomes and follow-up period were truly standardized for analysis.

Included studies

See Table 1 for characteristics of included studies.

Data was pooled for analysis in those studies with comparable scoring mechanisms and outcome measures. Not all studies were able to be pooled for analysis.

Pooled analysis of outcomes

Disease-specific QOL scores

Smith et al.[15] used 2 disease-specific QOL surveys at enrollment and at 6-month follow-up. Patients completed the Rhinosinusitis Disability Index (RSDI) and Chronic Sinusitis Survey (CSS). These are both disease-specific QOL metrics. After failing AMT, patients self-selected into continued medical therapy or sinus surgery treatment groups and were enrolled from 4 tertiary rhinology practices: Oregon Health and Science University; Northwestern University; Medical University of South Carolina; and the University of Pennsylvania. In this cohort study, 55 patients selected continued medical management and 75 patients selected surgery, both were followed for at least 6 months. Baseline QOL scores in the surgical cohort were significantly worse by CSS ($p = 0.019$) and nonsignificant but worse based on RSDI ($p = 0.059$). Nevertheless, surgical management demonstrated better QOL outcomes compared to medical management; QOL scores for both RSDI ($p = 0.015$) and CSS ($p < 0.001$) were significantly better in the surgical cohort at 6 months follow up.

Smith et al.[16] performed a follow-up study of these same patients at 12 months. His analysis included 3 cohorts: medical, surgical and crossover (ie, switching from medical to surgical therapy) patients. During the follow-up period, 17 patients switched from medical therapy to surgical therapy. Therefore, there were 33 patients which stayed in the medical group and 65 patients in the surgical group that had 12 months of follow-up data. The mean RSDI and CSS total scores improved significantly between time points ($p < 0.001$) with the most improvement appreciated in the first 6 months and with stable scores between 6 and 12 months. Those in the surgery cohort had significantly better absolute improvement between baseline and 12-month follow-up for both the RSDI and CSS scores compared to the medical cohort ($p \leq 0.05$).

Smith et al.[17] performed a cross-over study using the 22-item Sino-Nasal Outcome Test (SNOT-22). The SNOT-22 is a scale from 0 to 110 with a higher score illustrating worse disease impact. Patients were recruited from a tertiary rhinology clinic at the University of Calgary. Because of longer wait times in the Canadian health system between the determination of medically refractory CRS and the date of surgery, this study was able to assess the impact of continued medical therapy in a cohort of patients with large reductions in their baseline QOL who made a decision for surgery. This gives additional information as opposed to only being able to assess continued medical therapy in CRS patients who made a decision to continue with medical therapy alone, as would occur in a system (such as the U.S. system) in which patients can move relatively directly to surgery if they choose to. A total of 31 patients were enrolled, with continued medical therapy of a mean of 7.1 months and mean surgical postoperative follow-up of 14.6 months. While patients were receiving continued medical therapy, their SNOT-22 scores worsened from 57.6 to 66.1 ($p = 0.006$) from their baseline to presurgery follow-up visit. After receiving sinus surgery, the SNOT-22 scores of these individuals significantly improved ($p < 0.001$) from 66.1 preoperatively to 16.0 at follow-up. Consequently, the mean $\pm$ SD change of SNOT-22 for the surgical cohort (-50.1 ± 20) vs the medical cohort (8.5 ± 15.9) was significantly better ($p < 0.001$).

Quantitative analysis was performed pooling the data between the Smith et al.[15] and Smith et al.[17] studies. The study by Smith et al.[16] was not included because the patients included in this study were the same as those in the Smith et al.[15] study. Moreover, the Smith et al.[15] was chosen to be pooled with the Smith et al.[17] study because of the comparable follow-up and acceptance that 6-month follow-up is reliable for outcomes research in the management of sinus disease. Given that Smith et al.[17] was a crossover study, original data collection forms were requested from the principal investigator to include only patients who had received at least 6 months of both medical and surgical follow-up. Consequently, 19 patients were part of the medical cohort and 31 patients in the surgical cohort. Revised mean SNOT-22 scores and SDs were derived from this new dataset. Meta-analysis was performed by using SMD to combine the different measurement scales from these 2 studies. SNOT-22 and RSDI were combined given their strong correlation to each other.[18] The overall treatment effect was significant ($p < 0.00001$), but there was a significant amount of heterogeneity ($I^2 = 97\%$) (Fig. 1).

Objective endoscopic grading scores

Smith et al.[17] used the Lund-Kennedy endoscopic scoring system to assess the sinonasal cavity. They found that endoscopy scores significantly worsened while patients

TABLE 1. Characteristics of included studies

Author	Study design	Quality of study	Demographics	Pertinent outcomes	Pertinent results	Comments
Smith et al.[15] (2011)	Cohort	Moderate	n = 130; MT = 55; ST = 75; age of MT = 51.5 (16.0); age of ST = 44.1 (13.8)	RSDI, CSS, missed work/school days at 6-month follow-up	MT cohort: RSDI total = 14.8 (19.1); CSS total = 11.8 (21.1); missed work/school days = 0.7 (2.3). ST cohort: RSDI total = 24.1 (22.1); CSS total = 27.5 (23.8); missed work/school days = 0.4 (1.1).	50 lost to follow-up; baseline ST group were younger ($p = 0.003$), septal deviation ($p = 0.050$), ASA intolerance ($p = 0.024$); 7 MT crossed over to the ST group
Smith et al.[16] (2013)	Cohort with crossover	Moderate	n = 180; MT = 33; ST = 65; CO = 17; age of MT = 54.2 (16.8); age of ST = 47.4 (13.1); age of CO = 51.9 (14.3)	RSDI, CSS at 12 month follow-up	MT cohort: RSDI total = 12.1 (19.5); CSS total = 13.4 (21.1). ST cohort: RSDI total = 22.3 (24.3); CSS total = 25.5 (24.1). CO cohort: RSDI total = 20.6 (28.6); CSS total = 10.8 (26.8).	Study lost power due to loss of MT patients to the CO cohort; same cohort of patients from Smith, 2011 (therefore NOT included in meta-analysis)
Smith et al.[17] (2014)	Crossover	Moderate	n = 31; age = 45.3 (20–65)	SNOT-22, Lund-Kennedy endoscopic grading, work/school days missed past 90 days with mean follow-up for MT and ST group at 7.1 and 14.6 months, respectively	MT cohort: SNOT-22 = 66.1 (18.4); Lund-Kennedy = 7.7 (2.9); missed work/school days = 6.1 (9.0). ST cohort: SNOT-22 = 16.0 (13.0); Lund-Kennedy = 2.4 (1.7); missed work/school days = 0.2 (0.6).	Significant improvement in SNOT-22, Lund-Kennedy scores, missed days in ST vs MT ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively)
DeConde et al.[20] (2014)	Cohort	Moderate	n = 280; MT = 58; ST = 222; age of MT = 50.3 (15.0); age of ST = 51.9 (14.6)	B-SIT with minimum 6 month follow-up	Patients with impaired olfaction, B-SIT statistically improves in both MT (2.3 (2.8)) and ST (2.1 (3.0)) with no difference between treatments	Baseline ST group report higher burden disease with SNOT-22 ($p = 0.018$) and RSDI ($p = 0.030$); limited number of patients with impaired olfaction
Luk et al.[19] (2015)	Cohort	Moderate	n = 212; MT = 40; ST = 152; CO = 20; age of MT = 54.1 (13.0); age of ST = 53.3 (14.6); age of CO = 57.0 (15.0)	SF-6D, missed work/school days with 6-month and 12-month follow-up	Mean SF-6D at baseline, 6 months and 12 months follow-up for ST (0.70, 0.79, 0.78, $p < 0.001$), MT (0.76, 0.76, 0.76, $p = 0.967$), CO (0.69, 0.73, 0.75, $p = 0.115$), respectively.	Baseline ST group significantly worse health utility ($p = 0.023$), missed days ($p = 0.009$) compared to MT; do no report data missed work/school days
Rudmik et al.[21] (2015)	Cohort	Moderate[a]	N/A	ICER per QALY	ST: cost $48,838.38; 20.50 QALYs MT: cost $28,948.98; 17.13 QALYs ICER ST vs MT = $5901.05/QALY	Probabilistic sensitivity analysis demonstrate 74% certainty that ST most cost effective if willing to pay $25,000
Scangas et al.[22] (2016)	Cohort	Moderate[a]	N/A	ICER per QALY	ST: cost $42,522.95; 18.53 QALYs MT: cost $29,225.74; 17.57 QALYs ICER ST vs MT = $13,851.26/QALY	Probabilistic sensitivity analysis demonstrate 85% certainty that ST most cost effective if willing to pay $25,000

[a]Used Smith et al.15 study patients to perform cohort-style Markov decision tree.

B-SIT = Brief Smell Identification Test; CO = crossover; CSS = Chronic Sinusitis Survey; ICER = incremental cost effectiveness ratio; MT = medical therapy; QALY = quality-adjusted life-year; RSDI = Rhinosinusitis Disability Index; SF-6D = Short Form-6D; SNOT-22 = 22-item Sino-Nasal Outcome Test; ST = surgical therapy.

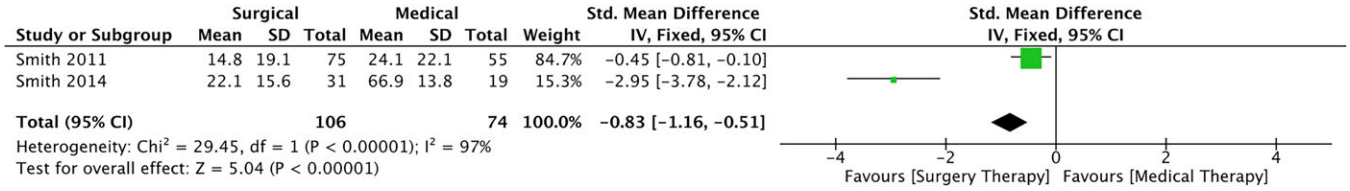

FIGURE 1. Disease-specific quality of life scores. CI = confidence interval; SD = standard deviation.

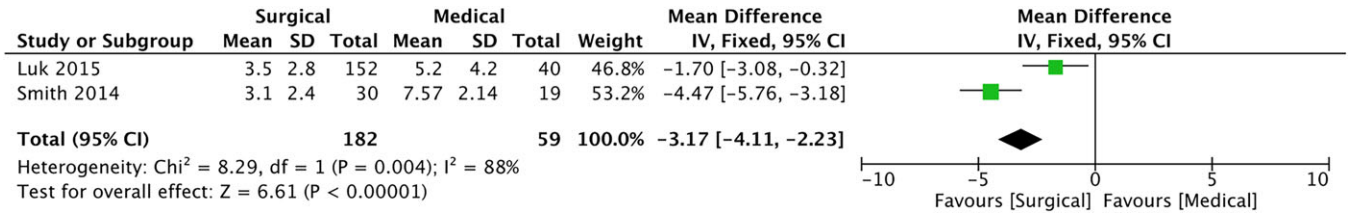

FIGURE 2. Endoscopic grading scores. CI = confidence interval; SD = standard deviation.

continued on medical therapy ($p = 0.007$). The scores increased from 6.9 ± 2.7 to 7.7 ± 2.9. These scores then significantly improved following surgical therapy ($p < 0.001$). The endoscopy score of 7.7 ± 2.9 dropped to 2.4 ± 1.7. Luk et al.[19] also recorded Lund-Kennedy scores but noted that the Lund-Kennedy scores in the medical cohort improved with 6 months of medical treatment from 6.6 ± 3.9 to 5.2 ± 4.2 (raw data was obtained from principal investigator [PI]). The surgical cohort showed a greater degree of improvement in endoscopic score, from 6.5 ± 3.7 to 3.5 ± 2.8. Quantitative analysis by pooling the data of both studies, only including patients with minimum 6 months follow-up from the Smith et al.[17] study, revealed a significantly greater improvement of the endoscopy scores for the surgical cohort compared to the medical cohort ($p < 0.00001$). However, the data was quite heterogeneous ($I^2 = 88\%$) (Fig. 2).

Missed work days due to CRS in past 90 days

Smith et al.[15] reported that patients in the surgical cohort had a significant reduction in number of missed work days over the past 90 days between baseline (1.9 ± 3.6 days) and 6-month postoperative follow-up (0.4 ± 1.1 days) ($p < 0.001$). There was also reduction in missed days over the past 90 days in the medical cohort but it was nonsignificant ($p = 0.170$). The number of missed days at baseline for the medical cohort patients was 1.6 +-5.2 days with a 6-month follow-up of 0.7 2.3 missed days.

In contrast, when using raw data provided by the PI and using just the subgroup of patients with 6 months of medical therapy in Smith et al.,[17] medical cohort patients reported 3.84 ± 4.62 missed days in the prior 90-day period. However, the surgical cohort in the study after 6 months of follow-up had 0.2 ± 0.6 missed days in the past 90 days, which was similar to the Smith et al.[15] study.

The study by Luk et al.[19] showed considerably different results. The surgical cohort had considerably more missed days over a 90-day period compared to the medical cohort. The surgical cohort had 4.4 ± 14.7 missed days compared to the medical cohort who had 0.9 ± 2.2 missed days.

Pooling all studies showed no significance ($p = 0.26$) in the the absolute number of missed days over the past 90 days. There was also a severe degree of heterogeneity among the study patient populations ($I^2 = 90\%$) (Fig. 3).

Unpooled analysis of outcomes

Objective or subjective measures of "cardinal" sinus symptoms, which include facial pain, nasal obstruction, thick discharge, or decreased olfaction

The only "cardinal" sinus symptom that has been studied which fits the aforementioned inclusion and exclusion criteria is olfaction. DeConde et al.[20] used the Brief Smell Identification Test (B-SIT), which is a validated 12-item noninvasive olfactory test with scores ranging from 0 to 12 with a score ≥9 being "normal." The majority of patients within the medical (70.7%) and surgical cohort (70.3%) had normal sense of smell. Those who had normal sense of smell prior to further medical or surgical treatment continued to have normal sense of smell. Patients who had abnormal BSIT scores (<9) had significant improvement in both the medical ($p = 0.005$) and surgical ($p < 0.001$) cohort; however, there was no significant difference in the change in improvement between the medical and surgical cohort. Multivariate analysis showed that history of prior surgery was the only predictor for least amount of olfactory improvement with either therapy.

Health utility value QOL scores

Luk et al.[19] used the Short Form-6D (SF-6D) to assess the health utility of the surgical cohort vs the medical cohort of patients. The SF-6D is a subset of questions from the

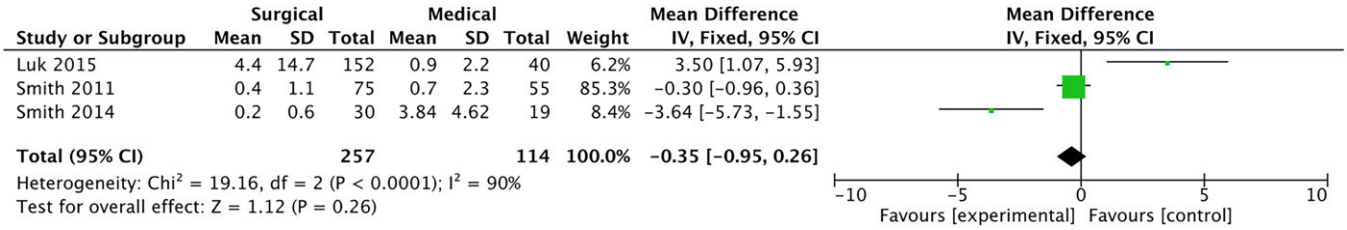

FIGURE 3. Missed work days. CI = confidence interval; SD = standard deviation.

SF-36 survey. The health utility values range from 0.3 to 1.0. Lower values represent poor health state whereas 1.0 is perfect health. There was both statistical and clinical health utility improvement for those receiving sinus surgery ($p < 0.001$), but no improvement was appreciated in the medical cohort ($p = 0.746$).

Economic impact due to CRS

Rudmik et al.[21] performed a cohort-style Markov decision tree economic evaluation of CRS patients receiving sinus surgery vs continued medical therapy. The economic perspective was the U.S. third party payer and the study demonstrated with 74% certainty that sinus surgery is the most cost-effective decision for any willingness to pay threshold greater than $25,000 per quality-adjusted life-year (QALY). The cost of sinus surgery was $48,838.38 and produced 20.50 QALYs, whereas continued medical therapy was $28,948.98 and produced 17.13 QALYs. The incremental cost effectiveness ratio (ICER) for sinus surgery vs medical therapy was $5901.90 per QALY.

Similarly, a more recent study by Scangas et al.[22] also used Markov decision tree analysis to evaluate the cost-effectiveness of ESS compared to medical therapy, and they showed an ICER for ESS vs medical therapy alone as $13,851.26 per QALY. They demonstrated that at willingness-to-pay thresholds of $25,000 and $50,000 respectively, the cost-effectiveness acceptability curve demonstrated 85.84% and 98.69% certainty that ESS was the most cost-effective option.

The major limitation of using Markov transition probabilities is the assumption of durability of improvement past the initial 5 to 7 years, as we are lacking data on more long-term outcomes. This limitation was explored in the 2016 study by performing a 1-way sensitivity analysis on rate of revision surgery. Medical therapy became the most cost-effective choice only when an annual rate of revision surgery reached 24%, a number exceeding even the highest published estimates (19.1% 5-year revision rate, published by Hopkins et al.[23] in 2009).

Reported adverse outcomes due to medical or surgical intervention

No studies fit the inclusion and exclusion criteria.

Discussion

By careful selection and inclusion of only prospective moderate-to-high rated studies, we have aimed to ensure that this systematic review (SR) and meta-analysis encapsulates the highest level of evidence possible from our current literature, in spite of persistent heterogeneity.

The results of this SR demonstrate that when considering outcomes as reflected by disease-specific QOL scores, health utility value QOL scores, nasal endoscopic scores, olfaction, and economic impact, surgery yields better results than continued medical therapy in a patient population who fails appropriate medical therapy and make a preference-based decision to undergo surgery. The patient's decision to undergo sinus surgery, as opposed to continuing with medical therapy, appears to be based on the severity of baseline disease-specific QOL.[24] In contrast, when patients with refractory CRS make a preference-based decision to continue with medical therapy, they tend to have less severe baseline disease-specific QOL and often remain stable as opposed to receiving further clinical improvements.

The outcome of missed days of work, when analyzed by our methodology, showed superiority of both medical and surgical cohorts depending on the study. When the data was pooled, there was ultimately no significant difference in missed days between the surgical and medical cohorts, but this more importantly highlights the flaw in trying to compare 2 groups who have differing baselines vs showing a true inclonclusiveness within the data. This finding likely reflects the difference in baseline productivity losses between patients who select medical therapy as opposed to those patients who select to undergo sinus surgery. A recent prospective study demonstrated that patients who selected continued medical therapy started with a baseline productivity loss of 5 days per year and were maintained at this level of productivity throughout treatment.[25] In comparison, CRS patients who selected sinus surgery started with a worse baseline productivity level (22 days of missed work per year) and received a significant improvement in productivity after surgery (3 days of missed work per year).[26]

An important point regarding this data is that AMT as established in this SR has purposefully set the bar higher (more medical therapy) than what may actually be necessary in treating some of these patients before moving to surgical intervention. In order to improve patient selection

for sinus surgery, a recent RAND appropriateness methodology study sought to define appropriate indications for sinus surgery using criteria based on Lund-Mckay computed tomography (CT) scoring, SNOT-22 scoring, and failed medical treatment for uncomplicated adult CRS.[27] Although these appropriateness criteria highlight the importance of incorporating several variables into the medical vs surgical decision-making process, clinicians must also assess the patients preference for intervention to ensure care is patient-centered.

Some of our outcome measures were unable to be studied, as there was a lack of data looking at change in cardinal symptoms of CRS other than olfaction, and lack of adverse outcomes reporting. While all therapies—whether medical or surgical—come with associated risks, the overall incidence of adverse outcomes is very low in this patient population. Looking to the existing literature regarding risks of ESS, surgical complications are rare, with an overall complication rate of 3.1%.[28] Of this percentage, 39% is related to bleeding. Orbital injury occurs in only 0.07% to 0.23% of cases, with intracranial complications occurring only 0.13% of the time in the modern era of surgery.[29] Less well known is the rate of possible olfactory disturbance of sinus surgery with one source estimating 2.5% of patients reporting this deficit.[29]

One must also compare and contrast these complication rates with the adverse events known to be associated with medical therapy. The rates of adverse events associated with antibiotic and steroid therapy given for treating CRS is difficult to approximate, as drug manufacturers do not tend to separate adverse events based on what disease process is being treated. However, some commonly seen adverse events associated with antibiotics include gastrointestinal disturbance, rash, and tendon rupture. Less common but important adverse events include QT prolongation, ototoxicity, peripheral neuropathy, thrombocytopenia, neutropenia, and even anaphylaxis. Complications associated with systemic administration of corticosteroids can also be problematic, including weight gain, hyperglycemia/diabetes, psychosis, gastrointestinal disturbances, ophthalmologic complications, hepatotoxicity, acne, striae, avascular necrosis, and adrenal suppression. The risks and benefits of any intervention, whether surgical or medical, should always be discussed thoroughly with the patient.

It is also important to note that all studies included in this SR took place in a tertiary-care, academic setting. It is very likely that this patient population has more recalcitrant disease than that seen in the setting of a general ENT community practice, and therefore these findings should be evaluated and interpreted within this context.

Similarly, it is imperative to recognize that CRS is a disease state with a vast spectrum of presentation, and there are patients with differing phenotypes and endotypes, some of which may do better when treated differently than the very generalized treatment paradigms studied here. This work in no way should prevent individualized patient care based on sound clinical judgement. Our desire is solely to present and analyze the data we currently have, understanding that this construct may be variably applicable to different subsets of the CRS patient population.

The lack of clinical RCTs to complement these prospective cohort studies remains a notable deficit in our literature and evidence base. However, it would also not be useful to our clinical practice to ignore well-done prospective studies that can help guide practice.

Conclusion

For patients with CRS who have failed to improve after AMT, outcomes demonstrate that ESS is more effective than continued medical therapy in improving disease-specific QOL scores and nasal endoscopy scores. Unpooled data analyzed within our systematic review demonstrates ESS is more effective than continued medical therapy in improving health utility value QOL scores, hyposmia, and cost-effectiveness. Without the reporting of adverse events associated with therapeutic choice in the studies included in this SR, one should use the existing literature on adverse events and clinical judgement in weighing these risks when choosing either medical or surgical therapy.

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