Clinical outcomes of functional endoscopic sinus surgery in cystic fibrosis patients - a single centre experience

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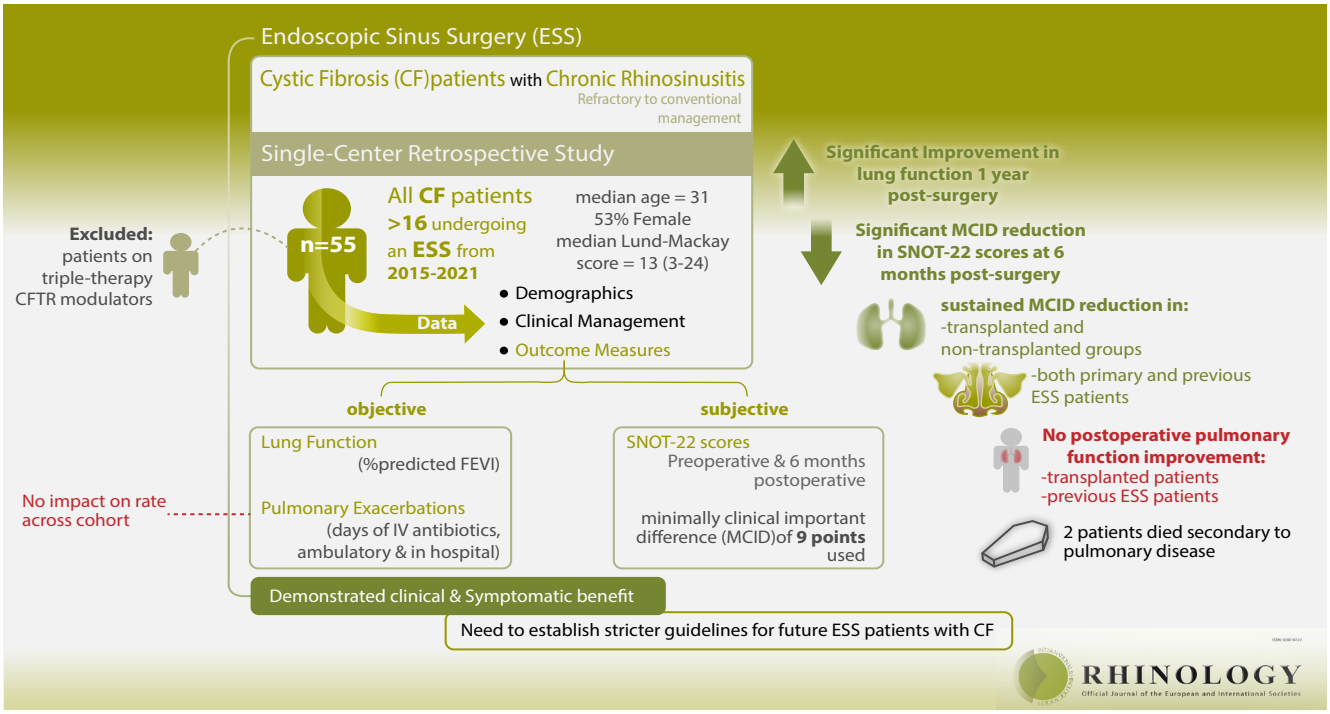

Abstract

Background: Endoscopic sinus surgery (ESS) is an established surgical option for cystic fibrosis (CF) patients with chronic rhinosinusitis that is refractory to conventional medical management. Objective and subjective evidence of benefit of ESS in this cohort of patients is currently conflicting in the literature. **Methodology**: A single center retrospective study was undertaken of all CF patients (transplanted and non-transplanted) over the age of 16 who underwent an ESS over a six-year period from 2015 to 2021. Patients on triple-therapy CFTR modulators were excluded. Data was collected on demographics, clinical management, and outcome measures. The objective outcome measures were lung function (%predicted FEV1), pulmonary exacerbations (total number of days of IV antibiotics- both ambulatory and in hospital). The subjective outcome measure was SNOT-22 scores pre- and 6 months post-operatively. A minimally clinical important difference (MCID) in SNOT-22 scores of 9 points was used. **Results**: 55 patients were included in our study, with a median age of 31 and 53% females. Median Lund-Mackay scores for the cohort was 13 (3-24). There was a significant improvement in lung function at 1-year post-surgery, and a significant MCID reduction in SNOT-22 scores at 6 months post-surgery across the cohort. Sub-group analysis revealed a sustained MCID reduction in SNOT-22 scores in both lung-transplanted and native lung groups, and in patients with primary ESS or previous ESS. However, there was no post-operative pulmonary function improvement in lung transplanted patients and patients with previous ESS. There was no impact on the rate of pulmonary exacerbations across the cohort. 2 patients in the cohort died secondary to pulmonary disease. **Conclusions**: There was a demonstrated clinical and symptomatic benefit of ESS in CF patients in this study. Stricter guidelines for indications for ESS need to be established with regards to CF patients who will undergo ESS in the future.

Key words: cystic fibrosis, paranasal sinus diseases, forced expiratory volume, patient reported outcome measure, sino-nasal outcome test

Introduction

Cystic fibrosis (CF) is a life shortening autosomal recessive condition that leads to progressive multi-organ damage. Its incidence and prevalence vary greatly by ethnicity and geography. It is most common amongst the Caucasian population with a birth prevalence of approximately 1 in 3000 [1]. It is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene resulting in dysregulation of sodium and chloride ions across epithelial membranes, resulting in impaired mucociliary clearance, chronic airway infection, pancreatic insufficiency, and digestive disorders [2, 3]. Airway and lung disease primarily results in premature death, with a median predicted survival in the UK of 53.1 years in males and 47.0 years in females [4].

Chronic rhinosinusitis (CRS) is a commonly reported feature of CF and can symptomatically affect up to half of all patients [5]; some studies have reported up to 100% of patients having radiological evidence of sinus opacification [6]. Obstruction of the paranasal sinuses from the hyperviscosity of mucus and impaired clearance can lead to repeated pulmonary exacerbations. The sinuses are thought to be a bacterial reservoir, responsible for the transmission of infections from the upper to lower airway. Management of CRS is therefore a priority to ensure improved outcomes of CF patients.

Current management of CF-related CRS is an evolving topic and is currently variable [7]. There remains a lack of high-quality randomised controlled trials to strongly support certain evidence-based treatment regimes in these patients [8]. Existing cohort studies have investigated the use of conservative management as first line management, but thus far none have been supported by high-level recommendations [2]. These include nasal saline lavage, nasal decongestants, intranasal corticosteroids, and antibiotics. Conventional medical therapy has proven difficult in managing long-term CRS-related symptoms in CF patients. New studies exploring the use of intranasal dornase alfa (a mucoactive therapy), topical tobramycin and colistin, CFTR-targeted therapies such as ivacaftor, and elexacaftor-tezacaftor-ivacaftor are now considered transformative therapies and have now demonstrated both symptomatic benefits and improved pulmonary function in these patients [2, 9, 10, 11].

Endoscopic Sinus Surgery (ESS) is currently the first line surgical option for refractory CF-related CRS. The objective and subjective benefit of endoscopic sinus surgery in CF patients in the literature is currently conflicting. Despite this, it has been reported that up to 60% of CF patients undergo ESS [12]. As the life expectancy of CF patients increase, it is necessary to establish strict indications for surgery and establish which cohort of patients will gain the most clinical and symptomatic benefit.

The aim of the current study is to present our single-centre experience of managing chronic rhinosinusitis in CF patients with endoscopic sinus surgery (ESS). Both objective and subjective clinical outcome measures were recorded for our cohort of patients, specifically lung function, pulmonary exacerbations, and SNOT-22 scores.

Materials and methods

Patients

All consecutive cystic fibrosis patients over the age of 16 who underwent functional endoscopic surgery at our centre over a six-year period from 2015 to 2021 were retrospectively included in this study. All patients were under the joint care of the adult CF team at the Royal Brompton Hospital and ENT surgeons at Charing Cross Hospital, Imperial College Healthcare Trust. All patients on triple-therapy CFTR modulators were excluded from our study.

Ethical statement

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data collection

Data were collected on demographics, clinical management and outcome measures using electronic and paper records. Lund-Mackay and Nair scores for the cohort were calculated from their pre-operative radiological images. Insufficient numbers of the cohort had post-operative imaging to be able to calculate post-operative Lund-Mackay and Nair scores.

Objective clinical outcome measures were collected for this cohort. Pulmonary function was evaluated using % predicted FEV1 (forced expiratory volume in one second). The best percentage in the year pre- and post-surgery were collected. Pre-operative lung optimisation % predicted FEV1s and % predicted FEV1s during an exacerbation were excluded. All post-operative % predicted FEV1 were collected at least three months after surgery. The total number of days requiring IV antibiotics was collected (both in hospital and at home) in the immediately preceding year pre-operatively and year post-operatively were collected for each patient. IV antibiotics days for optimisation prior to surgery was not included.

Subjective clinical outcome measures were collected. All patients completed a standardised SNOT-22 questionnaire both pre-surgery and 6 months post-op. We evaluated the minimal clinically important difference (MCID) of 9 points in the SNOT-22

Table 1. Clinicodemographic data of the cohort.

	Number of patients (%)
TOTAL	55
Gender	
Male	26 (47%)
Female	29 (53%)
Median Age	
Total	31 (16-60)
Male	29 (19-60)
Female	33 (16-48)
Mutation	
DeltaF508	42 (76%)
Homo DeltaF508	26 (47%)
Hetero DeltaF508	16 (29%)
3849+10kbC->T	2 (4%)
Others	11 (20%)
Previous ESS	21 (38%)
Nasal polyposis	42 (76%)
CFTR Modulators	24 (44%)*
Lung Transplant	19 (35%)
Lund-Mackay Score	13 (3-24)
Male	13
Female	15
Lung transplant	18
No lung transplant	13
Nair Score	16 (2-24)
Post-operative complications*	4 (7%)
Mortality	2 (4%)

*This refers to single or double CFTR modulators only. *post-operative complications included 2 post-operative sinus infections requiring oral antibitoics, and 2 re-presentations for pain.

after endoscopic sinus surgery (ESS) [13].

Statistical analysis

SPSS (version 21, IBM®) was used to perform statistical analysis. Clinicodemographical data was analysed using chi-squared testing. Paired pre- and post-operative non-parametric clinical outcome measures for the cohort were analysed using Wilcoxon Signed-Rank test. A $p<0.05$ was deemed clinically significant.

Surgical approach

Indications for sinus surgery in this cohort included:

1. Patients with severe refractory symptoms of CRS after maximal medical therapy
2. Patients symptomatic with lung transplants
3. Recurrent severe respiratory infections with significant sinus disease.

Our surgical practice involved: bilateral uncinectomies, wide middle meatal antrostomies, complete anterior and posterior ethmoidectomies, sphenoidotomies, frontal sinusotomies according to anatomy (some CF patients had no frontal sinuses) and disease severity, usually Draf I or Draf IIa, however some cases required a Draf III (endoscopic modified Lothrop procedure) [23]. All patients received a stat dose of intravenous antibitoics at induction, unless contra-indicated. Some patients required perioperative antibiotics, but this was dictated by the severity of their lung disease not their sinus disease and was directed by our respiratory physicians.

Results

55 patients with CF who underwent ESS were included in this study. The median age was 31, and 53% of the cohort was female. Table 1 displays the clinicodemographic data of the patient cohort. 38% of the cohort had undergone a previous ESS, either at our hospital trust or another site. The most common organisms to colonise the paranasal sinuses pre-operatively were *Pseudomonas aeruginosa* (40%) and *Staphylococcus aureus* (22%), whilst sputum pre- and post-operatively were colonised with *Pseudomonas aeruginosa* (45%), *Staphylococcus aureus* (17%) and *Achromobacter* species (10%). There was no significant difference in in the number of patients positive with *Pseudomonas* pre-operatively versus post-operatively.

Median Lund-Mackay scores were 13/24. Although there was a difference in Lund-Mackay scores between transplanted and non-transplanted patients, this was not statistically significant. Two patients died from the cohort, both directly due to CF pulmonary disease.

Table 2 compares the pre-operative and post-operative clinical outcome measures: Lung function (FEV1%), SNOT-22 score, unplanned days in hospital for pulmonary exacerbation. There was a statistically significant increase in lung function post-operatively ($p<0.05$). Subjectively, patients reported a significantly decreased SNOT-22 score post-operatively greater than MCID ($p<0.05$). 84% of our cohort achieved a reduction in SNOT-22 scores above the MCID of 9 points. There was no statistically significant difference in just the rhinological domain of SNOT-22 after surgery. There was a reduction in the total number of unplanned days spent in hospital due to pulmonary exacerbations, but this was not statistically significant.

Table 3 displays a subgroup analysis of the clinical outcome measures: Lung transplant vs no lung transplant, and previous ESS vs primary ESS. Lung function did not improve post-operatively in the transplanted group and the previously operated group but remained significantly increased post-op in the non-transplanted and primary operated groups. All groups reported a subjective MCID improvement in SNOT-22 scores of greater than 9 points ($p<0.05$). Furthermore, there were no significant differences in the number of unplanned days due to pulmonary exacerbations between any group.

Table 2. Clinical pre-operative and post-operative outcome measures for the group.

	Pre-operative	Post-operative	P-value
Lung Function- FEV1 %	68	72	0.009*
SNOT-22 score	47	32	0.000*
IV antibiotic days	10	6	0.134

* implies comparison is significant

Table 3. Sub-group comparison of clinical pre- and post-operative outcome measures in lung transplant patients and patients with previous ESS.

	Pre-operative	Post-operative	P-value
Lung Function- FEV1 %			
Lung Transplant	75	76	0.340
No lung transplant	63	70	**0.001***
Previous ESS	72	76	0.097
Primary ESS	62	66	**0.043***
SNOT-22 score			
Lung Transplant	44	26	**0.003***
No lung transplant	50	34	**0.000***
Previous ESS	52	37	**0.009***
Primary ESS	47	34	**0.000***
IV antibiotic days			
Lung Transplant	4	3	0.878
No lung transplant	13	9	0.181
Previous ESS	4	6	0.853
Primary ESS	12	7	0.293

* implies comparison is significant

Discussion

Indications for ESS in CF patients

The pathological and impaired function of the CFTR gene leads to hyperviscous mucous and impaired mucociliary clearance throughout the airway. This extends to the paranasal sinuses manifesting as chronic rhinosinusitis, impacting significantly on clinical symptoms and quality of life.

The reported prevalence of CRS in CF patients varies from 50-100% [3,4]. First line therapy for CRS in CF patients involves maximising medical treatment: topical nasal therapy and systemic medication [14]. Current recommendations for surgical therapy follow national guidelines for non-CF patients. The prevalence of severe and refractory CRS in CF patients is higher than the average population, with between 20-60% of CF patients with clinical CRS proceeding to sinus surgery [12]

In refractory CRS, the role of endoscopic sinus surgery in CF is twofold: to relieve sinonasal symptoms and eradicate bacteria. ESS aims to improve symptoms by opening the sinuses widely to enable douching and allow medication to treat the mucosa. Secondly, CRS and associated post-nasal drip can increase the risk of chronic pathological bacterial pulmonary colonisation and subsequent infection. Kang et al. [15] comment on the similar profile of pathogens in the sinuses and lower respiratory tract, particularly *Pseudomonas aeruginosa*. The maxillary sinuses are considered the main reservoir of pathological bacteria within the upper respiratory tract [12]. Effective clearance in the paranasal sinuses can help to preserve lung function and reduce pulmonary infective exacerbations [15].

Clinical outcome measures

A primary consideration of ESS in CF patients is the improvement in quality of life (QOL). SNOT-22 score is a subjective tool to measure the impact of CRS symptoms on patient QOL perioperatively [16]. They were evaluated as a clinical outcome measure with a minimally clinically important difference of 9 points, as established by the literature [13]. Our study importantly revealed that the significant improvement in SNOT-22 scores post-operatively was clinically important for patients, and thus advocates for a role of sinus surgery both as revision surgery and in lung transplanted patients.

CF patients complete regular spirometry to monitor pulmonary health. We utilised this to determine if there was a significant improvement in pulmonary function after ESS. Evidence is conflicting in the literature: Dadgostar et al. [6] found that FEV1 did not improve in 40 CF patients at 1- or 2-years post-ESS. With a larger patient cohort and regular spirometry, we found a statistically significant improvement in FEV1 within a year post-operatively. This improvement in lung function is likely multifactorial: improved quality of life can lead to increased activity and nutrition leading to better pulmonary outcomes; reduced inflammatory burden of sinuses and the upper airways can be propagated to the lower airways. Additionally, other studies have found a much greater improvement in lung function post-ESS in CF patients with severe and moderate disease compared to mild disease [17] and sustained improved lung infection status[18].

Radiological extent of CRS can be assessed with Lund-Mackay and Nair scores. We did not use either as outcome measures as radiological disease does not necessarily correlate with clinical symptoms [19,20], and most of our patients did not have scans post-operatively. In fact, it has been suggested that CT scans of the paranasal sinuses is not a valid indicator for sinus surgery in CF patients [21]. Other single-centre studies using only Lund-Mackay scores as a clinical outcome measure for CF patients did not find any statistically significant improvement in radiological disease post-ESS.

Lung transplant, CF and ESS

The role of ESS in CF patients post-lung transplant is considered

good practice to eradicate bacterial colonisation in the paranasal sinuses thus decreasing the likelihood of transplant infection and ultimately improving survival [22]. The leading cause of morbidity in CF patients post-transplant is *Pseudomonas aeruginosa*-associated lung infection [15]. There is suggestion that decolonisation of the paranasal sinuses post-ESS correlates with decreased incidence of infection on bronchoalveolar lavage [15], decreased recurrent pulmonary infections and improved 5-year survival [9]. Although SNOT-22 scores decreased post-ESS in the transplant cohort, there was no statistically significant improvement in lung function (FEV1). This is possible as the transplant cohort are less likely to have chronic recurrent pulmonary infections.

Surgical approach and revision rates

The purpose of endoscopic sinus surgery was primarily to eradicate disease and create a wide surgical cavity that allows effective long-term care with topical medications and sinus rinse. Most experts recommend extensive surgery to ensure that the maxillary, frontal, sphenoid, and ethmoid sinuses are all widely opened with smoothing of bony overhangs to prevent mucus retention and bacterial recolonization coupled with postoperative meticulous daily nasal irrigations [7].

In CF, a 19-28% revision rate is reported in the literature [18,24], higher than the reported revision rate of 4-15% for CRS [25,26]. Our revision rate is similar at 36%. Although our revision-ESS cohort didn't have a significant improvement in lung function, they did note a significant subjective improvement in symptoms and SNOT-22 scores.

Limitations of the study

Multiple studies suggest that symptom management with ESS may be temporary, and the symptom profile may recur or exceed the pre-operative baseline [15, 27]. The length of follow up in this patient cohort varies from one to six years, and it is essential to monitor the patients over a longer period to establish maintained improvement in QOL and FEV1. Often patients with CRS and CF require multiple sinus surgeries due to symptom recurrence. Additionally, the relatively small numbers within the subgroups raises the possibility of type 2 errors.

Our trust is a tertiary referral centre for adult patients only: no paediatric patients are in this study. The safety and efficacy of ESS for children with CF has previously been reported as equal to non-CF patients [28].

We should consider that other concurrent CF therapies and interventions could have had an impact. Triple-therapy CFTR modulators (elexacaftor/tezacaftor/ivacaftor) treat up to 90% of CF patients with statistically significant improvements in FEV1 and pulmonary exacerbations [9, 29] and lower sinus bacterial colonisation [30]. CFTR modulators can improve FEV1 in CF patients with mild, moderate and severe pulmonary disease [31]. A recent CRS prospective triple-CFTR study reported significant improvements in both SNOT-22 and CF-related quality of life scores [32]. Patient on triple-therapy CFTR modulators, licensed in the UK since 2020, were excluded from our study. The long-term effects of this medication on the CRS symptom profile and maintained improvement in SNOT-22 scores and spirometry needs to be evaluated. As the long-term outcomes of these patients is yet undetermined, and the increasing lifespan of CF patients, it is recognised that further investigation is needed to establish the optimum treatment with CFTR modulators and surgery for CRS-CF [9].

Conclusion

CF patients are a complex subgroup of CRS patients to treat. With an increasing life expectancy, current management for chronic conditions such as CRS in CF is rapidly evolving. Endoscopic sinus surgery remains a viable treatment option with established symptomatic and clinical benefit for these patients. Stricter guidelines need to be established with regards to the increasing number of CF patients who will undergo ESS in the future.

Authorship contribution

YD: acquisition, analysis, interpretation of data, writing draft; RT: acquisition, writing draft; JM: acquisition, analysis, interpretation of data; HS: supervision, final approval; CR- supervision, revisions, final approval.

Conflict of interest

No conflict of interest to declare.

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