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Outcomes of endoscopic sinus surgery in adult lung transplant patients with cystic fibrosis

Paolo Luparello[1] · Maria S. Lazio[1] · Luca Voltolini[2] · Beatrice Borchi[3] · Giovanni Taccetti[4] · Giandomenico Maggiore[1]

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Abstract

Purpose Cystic Fibrosis (CF) is the most common autosomal recessive disease in Caucasian population. Due to its pathological mechanism, chronic rhino sinusitis (CRS) associated or not with nasal polyposis usually occurs in adults and affects close to one-half of all CF patients. The goal of our work was to evaluate the impact of Endoscopic Sinus Surgery (ESS) in the quality of life (QoL) of the CF patients and demonstrate an improvement of the functional outcomes in the patients underwent the surgical procedure rather than in the not treated ones, particulary in lung transplant patients.

Methods We studied 54 adult patients affected by CF. Lund–Kennedy, Lund–Mackay scores, and SNOT-22 were analysed. 14 had lung transplant and 9 had both lung tranplant and ESS procedures.

Results 22 (40.7%) out of 54 CF patients underwent ESS. This group presented more likely complaints consistent with CRS. Lund–Kennedy and Lund–Mackay scores appeared higher in the ESS group: 10 (range of 6–12) and 15 (range of 12–20), respectively. SNOT-22 showed median values for non-ESS and ESS group of 20 (range of 3–68) and 40 (range of 10–73), respectively.

Conclusions ESS represents the best option to improve clinical QoL of CF patients who do not response to conventional medical therapy, with a stabilization of respiratory function after transplantation.

Keywords Cystic fibrosis · Endoscopic sinus surgery · Lung transplant · SNOT-22 · Quality of life

Introduction

Cystic Fibrosis (CF) is one of the most common autosomal recessive disease in Caucasian population, whose prevalence is reported to be about 0.737 per 10,000 in Europe, with a documented incidence of one case every 2500–3000 healthy new borns [1, 2]. Different mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene are responsible for the clinical manifestations of the disease, which vary from mild to severe upper and lower respiratory dysfunctions, in addition to pancreatic insufficiency, elevated sweat chloride levels, and diabetes mellitus. In this scenario, chronic rhinosinusitis (CRS), usually claimed by the 50–63% of CF patients, represents a widespread pathological condition affecting the upper respiratory tract, whose features might count the presence of nasal polyps with smell dysfunction and rhinorrhea especially in case of homozygosity for F508del [3–5].

These symptoms are often associated with a relevantly impairment of quality of life (QOL) when refractive to conventional medical therapy, and in these cases, endoscopic sinus surgery (ESS) is widely accepted as the intervention of choice [6–10].

Similarly, in case of severe respiratory function of the lower airway tract and lung failure, bilateral lung transplantation (LTx) offers true survival benefits to patients [11]. Long-term survival of lung transplant recipients is primarily limited by late allograft dysfunction and it depends on careful post-transplant management, including the prevention

✉ Paolo Luparello
luparello.paolo@yahoo.it

1 Department of Surgery and Translational Medicine, Clinic of Otolaryngology, Head and Neck Surgery, Careggi University Hospital, University of Florence, Largo Brambilla, 3-50134 Florence, Italy

2 Department of Thoracic Surgery, University Hospital Careggi, Florence, Italy

3 Infectious Disease Department, Careggi University and Hospital, Florence, Italy

4 Anna Meyer Children's University Hospital, Viale Pieraccini 23, 50139 Florence, Italy

and treatment of airways infection. Persistent post-transplant Pseudomonas airway colonisation (PAC) could be a risk factor for bronchiolitis obliterans syndrome (BOS), which might lead towards lung transplant failure in CF patients [12, 13].

Up to 100% of CF patients will have sinonasal pathology demonstrated on clinical and/or radiological examination. In addition, some two-thirds exhibit nasal polyposis (NP), which further complicates CRS management. Symptoms of CRS are debilitating and classically include headache, facial pain, nasal obstruction, congestion, and chronic nasal discharge. Moreover, sinus anatomy is often abnormal in CF patients with many exhibiting pansinus hypoplasia or aplasia, which only further contributes to CF sinus disease.

In a review by Liang et al. [14], endoscopic improvements in CF-related CRS were evident in more than 50% of studies based on assessments of polyposis, oedema, mucopurulence, crusting, and/or scarring.

Additional studies report that ESS ultimately results in reduced rates of pulmonary exacerbation by reducing the number of hospitalisations in the 6-month post-operative period [15].

Improvements in the management of CF-related lung disease have been the primary driving force behind life expectancy; however, there is evidence that CRS may affect more than just QOL, since the unified airway model suggests that it contributes to the bacterial seeding of the lower airway and the ultimate progression to pulmonary demise.

Several studies have additionally recommended ESS in patients undergoing lung transplantation due to high bacterial concordance rates between bronchoalveolar lavage and nasal cultures and the unfavourable effects associated with bacterial seeding of transplanted lungs. It is thought that chronic sinonasal bacterial colonisation results in bronchiolitis obliterans or allograft rejection. Persistent CF sinonasal pathogens despite negative BronchoAlveolar Lavage (BAL) cultures in intermittently lung-colonized patients also suggest that the sinuses represent a more permanent bacterial focus than the lungs and support the need for adequate control of upper airway disease [16].

Based on these hypotheses, few reports have carried out the hypothetical role of sinuses being the bacterial reservoir of CF patients, thus playing an important role in lung transplant recipients, because they might forward the spread of bacteria to lung, inducing allograft infection [17]. In this view, ESS in combination with routine nasal care may represent the best option for reducing or preventing this event [11, 18].

For these reasons, our purpose was to evaluate the improvement in quality of life of CF patients who had lung transplant and who underwent ESS procedure, to identify the possible adjuvant role of sinus surgery to transplanted patients. Second, we aimed at assessing the influence of ESS on long-term pulmonary function, to analyse its possible role in affecting respiratory outcomes.

Methods

Between January 2012 and December 2017, a total of 54 adult patients affected by cystic fibrosis were followed and routinely visited at the Otorhinolaryngology University Clinic of Florence.

14 patients out of 54 had lung transplant, whilst other nine patients had both lung transplant and ESS procedures; of the remaining 31 patients, 15 were submitted to ESS treatment only and 16 had no treatment. Endoscopic sinus surgery was performed in case of refractory medical treatment condition, and indications were given in case of presence of chronic and acute sinusitis, fungal sinusitis, nasal polyps, mucocele, radiological examinations, and especially in case of worsening of the respiratory function. This disease requires a multi-disciplinary management; for this reason, indications to the therapy were discussed with the Cystic Fibrosis Board (including infectious disease specialist, thoracic surgeon, and physiotherapist that follows patients in the adherents to the medical therapy and exercises in ventilation) at the Cystic Fibrosis Centre at the Meyer Children University Hospital in Florence, where these patients are routinely followed. In these patients, the principles of minimal invasively of functional endoscopic sinus surgery (FESS) were modified to a more extensive approach to clear the viscous mucus and to create larger apertures of the paranasal sinuses to achieve a better drainage. These procedures included a combination of medial maxillectomy, partial or total ethmoidectomy, frontal sinusotomy (extended from type IIb to III according to Draf, if necessary), and sphenoid sinusotomy. Nasal septoplasty and inferior turbinate reduction were also performed if important signs and symptoms of nasal obstruction were reported. We reported radiological abnormalities and the extension of ESS surgery in our nine patients in Table 1.

All of the ESS patients underwent a preoperative and post-operative systemic antibiotic prophylaxis, according to our Institution's guidelines, to prevent local and/or systemic infections. They were generally hospitalised in the infectious diseases ward 1 week before surgery to receive a complete systemic intravenous antibiotic prophylaxis before undergoing the operation. Medical therapy consisted of saline irrigation associated with serial antimicrobial lavage when required. We are used to administer steroid irrigations when CRS was associated with nasal polypoid. In the post-op, antihistamine therapy could be suggested to avoid tearing and sneezing due to the nasal packs. Systemic corticosteroids and antibiotics administrations were evaluated case by case from the Infectious Disease Department.

Table 1 Distribution of genotypes, class mutation and radiological abnormalities and the extension of ESS

Genotype	Frequency *n* (%)	Class of mutation	Hypoplasia/aplasia	ESS extension
F508del/F508del	2 (22.2)	I–III	One none One frontal	1. S-MM-ET-SP 1. S-MM-ET
F508del/N1303K	1 (11.1)	I–III	Frontal-sphenoid	MM-ET
F508del/del22-24	2 (22.2)	I–III	One frontal One sphenoid	1. MM-ET-SP 1. MM-ET-Draf IIb
F508del/UNK	1 (11.1)	I–III	Frontal-sphenoid	MM-ET
N1303K/N1303K	1 (11.1)	I–III	Frontal-sphenoid-maxillary	S-ET
G542X/G542X	1 (11.1)	I–III	None	S-MM-ET
G542X/N1303K	1 (11.1)	I–III	Maxillary	S-ET-SP

S septoplasty, *MM* medial Maxillectomy, *ET* ethmoidectomy, *SP* sphenoidectomy

Patients were given extensive information about the surgical procedures that they were about to undergo, and all the participants signed an informed consent agreement. The study was approved by the local institutional review board (IRB) committee. Patient demographic data, sinus local disease, and treatment characteristics were extracted from each patient notes. The following characteristics of patients and disease status were recorded: gender, age, body mass index (BMI), type of genetic mutations (such as homozygosity for delF508 and heterozygosis delF508/other mutations), diabetes mellitus and hepatic alterations (if present), nasal obstruction, rhinorrhea, headache, smell dysfunction, nasal polyposis, intranasal corticosteroid use, Lund–Kennedy score [19], Lund–MacKay staging [20], spirometry parameters (FEV1 and FVC), sputum bacteriology, sinuses radiology alterations, preoperative and post-operative SNOT-22 evaluation.

The SNOT-22 is a self-administered questionnaire which consists of 22 items, each with six possible answers ranging from 0 to 5 points. Higher scores indicate an increased rhinosinusitis with worst problems and is divided into different subscores to evaluate primary nasal symptoms, secondary rhinogenous symptoms, functional limitation, and emotional consequences [21].

Post-operatively clinical and functional characteristics were evaluated at 6, 12, and 24 months after surgery.

In accordance with our aims, we selected from our database only the 23 patients who underwent lung transplant, and we made a comparison between the two following groups: (1) control group: 14 patients who did not undergo ESS procedure after the lung transplant and (2) study group: nine patients who underwent had endoscopic sinus surgery after lung transplant.

Categorical variables were calculated in terms of frequencies and percentages for all of the 23 patients. Statistical comparison between groups was performed with Chi-squared test, Fisher exact test, or Mann–Whitney test when appropriate which were used to compare the characteristic of two subgroup. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to analyse the equality of functional outcomes by subgroup for the same variables.

A p value less than 0.05 was considered statistically significant.

Results

Population counted 14 (61%) males and 9 (39%) females. The median age was of 38 (range 21–55) and all patients were over 18 years. Main demographic and clinical characteristics of the study population are listed in Table 2. It came out from a preliminary comparison of the preoperative status that the study group presented a higher percentage of rhinitic symptoms than the control one; in specific, the following characteristics were registered as follows: nasal obstruction (77.8%), rhinorrhoea (100%), headache (55.6%), nasal polyps (77.8%), and rhinosinusitis (77.8%). Even the endoscopic and radiological scores were particularly higher in the ESS group ($p < 0{,}001$) by reporting a Lund–Kennedy score mean value of 10 (range of 6–12 SD ± 2.5) and a Lund–MacKay score mean value of 15 (range of 12–20 SD ± 2.8), whereas the control group reported mean values 3 (range of 0–10 SD ± 3.6) and 2 (range of 0–6 SD ± 1.8), respectively.

The SNOT-22 questionnaire showed a significant difference between the non-ESS and ESS group: 20 (range 3–68 SD ± 16.5) against 40 (range 17–58 SD ± 15.9) ($p = 0{,}007$).

FEV1 and FVC were the parameters chosen to evaluate the respiratory function, and they were recorded preoperatively and post-operatively at 6, 12, and 24 months after surgery. Despite their statistical analysis did not show any significance, the FVC at 24 months of follow-up showed an increase in its value, worthy to be pointed out because of reflecting the long-term respiratory improvement in the ESS group ($p = 0.07$) (Fig. 1).

Further analysis was carried on within the study group reported in Table 3. Single symptom improvements were recorded concerning: nasal obstruction (11.1%) ($p = 0.0412$),

Table 2 Demographic and clinical characteristics of the study participants

Variables	Non-ESS	ESS	*p* value
Patients, *n*	14	9	–
Males, *n* (%)	7 (50%)	7 (77.8%)	$p=0.23$
BMI (median)	22.8	23.2	$p=0.59$
Age (median)	40	36	$p=0.66$
Pre-operative FEV1 (median)	60.5	55	$p=1.00$
FEV1 after 6 months (median)	63.5	64.5	$p=0.39$
FEV1 after 12 months (median)	68.5	73	$p=0.72$
FEV1 after 24 months (median)	71	81.5	$p=0.92$
Pre-operative FVC pre-op. (median)	76.5	75	$p=0.87$
FVC after 6 months (median)	73	73	$p=0.56$
FVC after 12 months (median)	87	76.5	$p=0.29$
FVC after 24 months (median)	81.5	87	$p=0.68$
F508 heterozygous, *n* (%)	5 (35.7)	3 (33.3)	$p=0.32$
S. aureus, n (%)	4 (28.6)	2 (22.2)	$p=1.00$
Pseudomonas aeruginosa, n (%)	7 (50.0)	5 (55.6)	$p=1.00$
SNOT (median)	16	41	$p=0.007$*
Nasal obstruction, *n* (%)	4 (28.6)	7 (77.8)	$p=0.04$*
Rhinorrhea, *n* (%)	5 (35.7)	9 (100.0)	$p=0.002$*
Headache, *n* (%)	1 (7.1)	5 (55.6)	$p=0.02$*
Lund–Kennedy tot (median)	2	10	$p<0.001$*
Lund–Mackay (median)	1	16	$p<0.001$*
Nasal polyposis, *n* (%)	3 (25.0)	7 (77.8)	$p=0.03$*
Rhinosinusitis, *n* (%)	3 (25.0)	7 (77.8)	$p=0.03$*

*Statistical significant

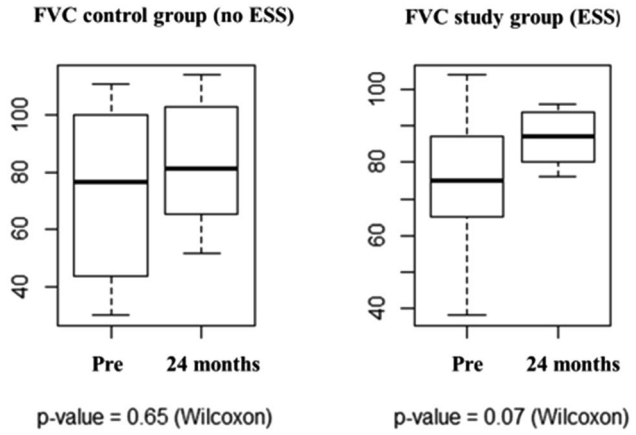

Fig. 1 FVC in subjected to ESS at 24 months post-operatively

rhinorrhoea (0%) ($p=0.0133$), headache (0%) ($p=0.0736$), smell dysfunction (55.6%) ($p=0.6171$), already at 6 months after the endoscopic procedure. Moreover, the endoscopic evaluation showed a median value of the Lund–Kennedy score of 3 (range 0–8 SD ± 2.7) and the SNOT-22 score mean value at 6 months after ESS was of 9 (range of 0–27 SD ± 8.4) showing a statistical significance ($p<0.05$), respectively (Figs. 2, 3).

Discussion

The aims of our work were to evaluate the improvement in quality of life of CF patients who had ESS procedure after lung transplant and to assess the influence of ESS on long-term pulmonary function.

Underreporting of CRS symptoms is common in this population and it represents acclimation to chronic disease.

The lack of definitive treatment consequently translate into reduction in QOL for these patients; therefore, it is especially important to use specific QOL questionnaires such as SNOT-22 for adults [22].

The presence of *Pseudomonas aeruginosa* associated with higher scores on SNOT-22 questionnaire is an important finding, since its presence is associated with worsening of lung function. This finding raises the hypothesis that the sinuses may carry chronic infection and may be a bacterial reservoir causing pulmonary exacerbations [23].

In our case series, 39% of the transplanted patients were subjected to ESS; SNOT-22 questionnaire showed pre-surgery main values for ESS group higher compared to the control group non-subjected to ESS. Six months after ESS, the SNOT-22 mean value was 7 (range of 0–44 SD ± 10.19). These values are in line with those in the literature.

After ESS, there is a statistical significant improvement in symptoms of nasal airway obstruction ($p=0.04$), sinonasal purulence ($p=0.01$), and overall activity level due to the correction of anatomical anomalies, the best ventilation of the paranasal sinuses, and the removal of nasal polyps and mucus. With regard to smell function, in three cases, there is an improvement but without statistical significant after ESS ($p=0.61$).

Lung transplantation remains an established treatment option for CF-related end-stage lung disease, and lung transplant recipients with CF have a significantly higher risk of acquiring and harbouring *Pseudomonas aeruginosa* in the lung allograft compared with non-CF recipients. This propensity to recolonise the transplanted lung is associated with inflammatory response, which may lead to graft dysfunction and rejection. Because most CF lung transplant recipients recolonise with at least one identical strain of *P. aeruginosa* cultured before lung transplantation, the sinuses and upper trachea have been proposed to serve as reservoirs for bacteria, which can seed the new lung grafts [24].

Long-term survival of lung transplant recipients is primary limited by late allograft dysfunction and depends on careful post-transplant management, including prevention and treatment of airway infections that can be a risk factor

Table 3 Demographic and clinical characteristics of the study participants after ESS

Variables	Pre-op	6 months	12 months	24 months	*p* value
FEV1	66.5	64.5	76	81.5	0.55
FVC	76	73	76.5	87	0.11
Nasal obstruction, *n* (%)	7 (77.8)	1 (11.1)	–	–	0.04*
Rhinorrhea, *n* (%)	9 (100.0)	0 (0.00)	–	–	0.01*
Headache, *n* (%)	5 (55.6)	0 (0.00)	–	–	0.07
Hyposmia/anosmia, *n* (%)	7 (77.8)	5 (55.6)	–	–	0.61
Lund–Kennedy tot (median)	10	2	–	–	0.02*
SNOT (median)	41	7	–	–	0.003*

*Statistical significant

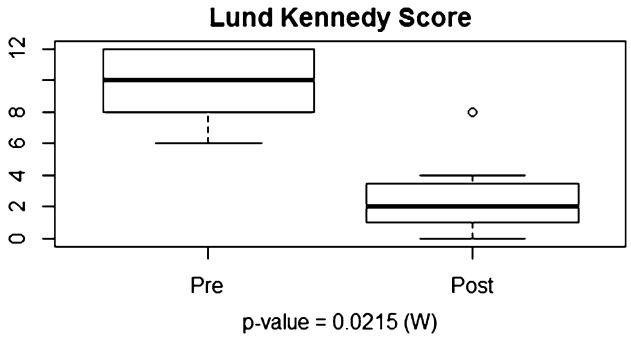

Fig. 2 Lund–Kennedy score after ESS

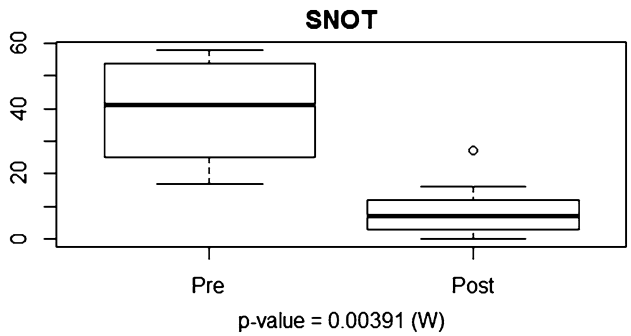

Fig. 3 SNOT-22 improvement after ESS

for bronchiolitis obliterans syndrome (BOS). Sinus surgery in combination with routine nasal care may be beneficial in this case.

In the literature, there are few studies with controversial results on the real effectiveness of ESS after transplantation. Vital et al. [25] performed sinus surgery after recovery from transplantation (mean days after LTx 36 (CI) 24–47) and daily nasal douching with results of 62% of patients with pre-transplant PAC achieved persistent PA eradication in the lower airways.

Holzmann et al. [18] performed sinus surgery after 17 ± 51 days (range 13–204) from transplantation with post-operative control of sinus infection successful in 54%, partially successful in 27% and not successful in 19%.

Instead, Leung et al. [24], followed a protocol of pre-transplant sinus surgery, observed non-significant benefit to long-term survival relative to other comparable cohorts of CF patients with no sinus surgery, but their protocol did not include daily nasal care; it showed a significant correlation between negative sinus aspirates and negative BAL cultures, suggesting that if bacterial growth in the sinuses can be controlled, lower airway colonisation and infection may be curbed.

Additional studies report that ESS ultimately results in reduce rates of pulmonary exacerbation by reducing the number of hospitalisations in the 6 months after post-operative period [15].

Next to the overmentioned improvement in sinonasal symptoms after the ESS procedure, the respiratory long-term outcomes deserve to be mentioned, especially because they represent the weak and not well-explored field of mutual influence of upper to lower respiratory tract in CF patients.

In the literature, there are very few studies concerning on how ESS can affect respiratory function after lung transplantation, and only two of these found and improvement in FVC [26].

In our series, although statistical significance is not achieved, there is a stabilization with a positive trend in respiratory function, in particular for FVC at 24-month post-operatively.

We have a relative small sample size (23 patients) in 5 years analysed in our department and cannot perform bacteriology analysis between sinuses and BAL culture; in the literature, there are studies with greater numbers but considering a longer period of time (10–20 years) and very few studies that compare the nasal bacteriology with BAL before and after surgical treatment, particularly after lung transplant. Due to the retrospective nature of our work, it was not possible to establish a precise timing of the ESS compared to the lung transplant. The wide time discrepancy between transplant and ESS can be explained by the fact that indication to the ESS was given according to the

patient's symptoms and not to the attempt to reclaim the upper airways. Although in English literature, data about precise timing in which perform ESS relating to lung transplantation are lacking; in some transplant centres, ESS intervention is a prerequisite for inclusion in the waiting list for lung transplant. Our current mean follow-up is about 44 months ± 23.51 SD (range 8–70 months), but has to be expanded in light of the longer life expectancy of these patients, allowing us to assess the need of a second ESS intervention (in literature recurrence rate from 42 to 100% after more than 24 months) and evaluate long-term respiratory function.

Conclusion

The positive impact of endoscopic surgery on the post-operative SNOT-22 score should be emphasized. ESS was well tolerated by CF patients. Although significant improvements during the entire follow-up were observed confirming the effectiveness of treatment on the QoL of CF patients and stabilization of respiratory function after transplantation. Despite the small number of patients, in the 24 months of follow-up, there was a decrease in the number of hospitalizations for pulmonary exacerbations in operated patients, although is necessary extend the number of cases to reach statistical significance.

In sight of our preliminary results, a comparative study between ESS pre- vs post-transplantation or ESS at different time points after transplantation would be useful.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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