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Functional Endoscopic Sinus Surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray*

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SUMMARY

One hundred nine patients with chronic rhinosinusitis underwent functional endoscopic sinus surgery. Seventy seven patients had polyposis. The population was studied prospectively for 5 years postoperatively. Seventy two patients attended the 5 year follow-up visit. At 1, 2, 3, 4 and 5 years of follow-up all outcome measures except olfactory detection thresholds (visual analogue scores, endoscopic findings, nasal mucociliary clearance times, total nasal volumes) were significantly improved compared to preoperative baseline values. Olfactory detection thresholds were significantly improved at 1 and 2 years postoperation. Patient symptom scores were improved in a greater percentage of patients than more objective outcome measures. Thirty eight patients required a total of 88 postoperative rescue medication courses with prednisolone and antibiotic. Twelve patients failed the study as they required at least 1 rescue medication course a month for 2 consecutive months. We demonstrated an 89% 5 year "survival" rate with regards to the risk of failure.

The patients were also entered into a randomised, stratified, prospective, double-blind, placebo controlled study of fluticasone propionate aqueous nasal spray 200mcg twice daily, commencing 6 weeks after FESS, with a 5 year follow-up. The change in overall visual analogue score was significantly better in the FPANS group at 5 years. The changes in endoscopic oedema and polyp scores and in total nasal volumes were significantly better in the FPANS group at 4 years but not 5 years. Last value carried forward analysis demonstrated that changes in endoscopic polyp score and in total nasal volume was significantly better in the FPANS group at 5 years. Significantly more prednisolone rescue medication courses were prescribed in the placebo group. Of the 12 patients who failed the study, 10 were in the placebo group. This difference nearly achieved significance.

Key words: chronic rhinosinusitis, sinonasal polyposis, functional endoscopic sinus surgery, fluticasone propionate aqueous nasal spray

INTRODUCTION

Endoscopic sinus surgery was described by Stammberger [1] in 1985 and in the same year Kennedy [2] coined the term "functional endoscopic sinus surgery" (FESS) to highlight an associated surgical philosophy. The concept of FESS embraced mucosal sparing surgery. Surgery was tailored to disease extent and concentrated on restoring mucociliary clearance and ventilation by opening the ostio-meatal complex pre-chambers of the major, dependent sinuses. FESS therefore differed from traditional, wide exenteration procedures and less physiologi-

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cal drainage procedures. Many studies subsequently described the results of FESS but frequently these papers had methodological flaws. Increasingly also the importance of generalized, respiratory tract mucosal immunopathological factors in determining disease behaviour has been considered [3-5]. This makes long-term follow-up important in assessing the influence of surgical intervention on chronic rhinosinusitis with or without polyposis.

Similarly postoperative medical intervention that influences mucosal immunology might be expected to have a significant bearing on results. Earlier studies illustrated benefit from topical nasal steroids following polyp surgery [6-10]. We therefore planned a prospective, 5 year follow-up study of FESS, performed by a single surgeon, in which postoperative oral steroid and antibiotic requirements were recorded as one of the outcome measures. Patients were also randomly allocated to fluticasone propionate aqueous nasal spray or placebo, dummy spray postoperatively to assess the impact of long-term topical steroids on outcome, irrespective of the presence of polyps. No prospective studies of this magnitude or duration have been conducted hitherto.

Furthermore we have proposed that chronic rhinosinusitis without polyposis is not always synonymous with an infective aetiology and may be part of a spectrum of eosinophilic sinusitis of which polyposis is a part [11]. Steroids might therefore be expected to influence the postoperative mucosal behaviour of rhinosinusitis whether polyps are present or absent.

MATERIALS AND METHODS

Patients

Hundred thirty two consecutive patients were assessed in a tertiary referral clinic. They had been referred for functional endoscopic sinus surgery (FESS). Patients were consecutively recruited from this population for a 5 year follow up study of the outcome of FESS including a prospective, stratified, randomised, double-blind, placebo controlled, parallel group study of postoperative, fluticasone propionate aqueous nasal spray (FPANS). This study was approved by the research and ethics committee of Charing Cross Hospital and Medical School. All patients had failed to improve with a range of prior medical treatments including nasal or systemic steroids and antibiotics prior to referral. Patients were asked to stop any topical nasal treatment, including steroids, for 2 weeks prior to being seen in our clinic.

Data collection

At their initial visit patients were assessed with regard to whether FESS was indicated and baseline data was collected. The dataset comprised 6 visual analogue scores and 5 sinonasal, endoscopic scores as described by Lund and Mackay [12]. Nasal mucociliary clearance times [13] and olfactory detection thresholds using PM – carbinol concentrations [14] were recorded. Total nasal volume (the sum of right and left sides) was measured with acoustic rhinometry.

Skin prick tests were also performed to house dust mite, cat and dog dander, 3 trees, weeds, moulds and grass pollen. Allergen avoidance measures were explained and advised to patients when necessary.

Our indications for FESS with regard to symptoms, in patients with chronic rhinosinusitis with sinonasal polyps were intolerable nasal obstruction or 2 or more of the following symptoms: i) anosmia/hyposmia; ii) nasal obstruction/congestion; iii) anterior or posterior rhinorrhoea; iv) headache/facial pain. Our indications for FESS in patients with chronic rhinosinusitis (CRSS) without polyposis were i) anosmia/hyposmia; ii) nasal blockage/congestion; iii) posterior rhinorrhoea; iv) headache/facial pain, for more than 1 hour on most days, for 2 months or more.

Following initial data collection patients received a 3 week course of fluticasone propionate, 100 microgram's (2 sprays) to each side of the nose twice daily and were reviewed. A positive steroid response was defined as a 2 cm improvement in the visual analogue score for each of 2 or more symptoms. If the patients had not improved they were considered for FESS. This ensured all patients had undergone a supervised trial of topical steroids and meant that any patient subsequently recruited for the clinical trial of postoperative fluticasone propionate had not responded to this drug preoperatively. This helped minimise the bias of choosing patients who might be expected to respond favourably if allocated to the active rather than placebo group.

Computed tomography (CT) scans were performed at completion of the 3 week course of FPANS on those patients who reported no improvement in symptoms. CT scans were not performed within 4 weeks of a coryzal illness or an acute exacerbation of CRSS. To proceed to FESS patients had to demonstrate a CT scan score [12], on the worst side, of at least 3, excluding an isolated polypoidal opacity within a sinus. Patients with 4 episodes per year of acute, recurrent rhinosinusitis of at least 10 days duration and a persistent CT scan score of at least 3, excluding an isolated polypoidal opacity within a sinus, were also included. CT scan changes had to be present at least 4 weeks after an acute infection.

The following patients were excluded from study: pregnant women; age $>$ 60 years or $<$16 years; patients taking regular oral steroids; patients taking $>$ 1500 microgram's of inhaled steroid per day; patients with antro-choanal or isolated polyps; patients requiring combined external approach and endoscopic, sinus surgery; patients requiring frontal sinus ostioplasty procedures; patients who had undergone sinus surgery within the last 12 months; patients with mucocoeles; patients with tumours.

Surgery was performed by the first author in all cases and involved removal of polyps and diseased mucosa and opening of the next anatomical compartment as described by Stammberger [1] and Kennedy [2]. Microdebriders and image navigation were not available in our unit at the time of the study.

All patients received a 3 week course of oral prednisolone (30mg for 7 days, 20 mg for 7 days, 10 mg for 7 days) and a two week course of co-amoxiclav, 625mg t.d.s. after FESS. Patients allergic to penicillin received a two week course of vibramycin (200mg for day 1 and 100mg per day subsequently) postoperatively. Local postoperative, out-patient surgical procedures on the sinuses, such as small polyp recurrence removal was not permitted, other than for the initial endoscopic care and toilet 7 – 10 days following surgery. Patients were then seen again at 6 weeks post operation.

At this time patients were stratified by their preoperative Lund & Mackay [12] CT scan score to ensure matched distribution of disease extent between treatment groups and were randomly allocated by computer generated number to FPANS or placebo postoperatively for five years. The dose of FPANS was 200 microgram's b.d. Placebo spray comprised all the constituents of the standard FPANS spray, excluding fluticasone propionate. Data was collected postoperatively at 6 weeks, 3, 6, 9 and 12 months and then 6 monthly for the subsequent 4 years. Patients returned their empty spray bottles at each visit at which time they also received the sprays for the next time period. If polyp recurrence post-operatively was not controlled or tolerated by the patient and / or if CRSS persisted or was acutely exacerbated, then a 7 day course "rescue medication" comprising prednisolone (30mg, 30mg, 25mg, 20mg, 15mg, 10mg and 5mg) and co-amoxiclav 625mg t.d.s. was prescribed. Patients allergic to penicillin received a 7 day course of vibramycin (200mg for day 1 and 100mg per day subsequently). If a patient required a monthly rescue course for 2 consecutive months they were defined as having "failed". Topical nasal medication other than FPANS or placebo was prohibited.

We chose as outcome measures the visual analogue score related to how they felt overall, the total sum of all 6 visual analogue scores, the sum of right and left endoscopic polyp scores; the sum of right and left oedema scores; the sum of right and left discharge scores, nasal mucociliary clearance time, olfactory detection threshold values and the sum of right and left nasal volumes. Rescue medication requirements and the number of "failures" were also recorded.

Hundred seventeen patients underwent FESS. One patient failed to attend for postoperative follow-up and 7 patients did not consent to participate in the study. Hundred nine patients were therefore entered into the study.

Statistical analysis

Sample size was calculated using Wilcoxon's 2 sample test, 2 sided at the 5% level of significance. To have a power of 80% in detecting a 20% visual analogue score difference between the 2 groups a sample size of 66 was required.

Hundred five patients commenced the clinical trial with treatment group randomisation 6 weeks after surgery and 4 others who had not attended at 6 weeks post surgery did attend to commence the trial with treatment group allocation 12 weeks after surgery. Post-operatively, for the 5 year duration of the study 55 patients were allocated FPANS and 54 placebo spray. At the preoperative baseline visit all 109 patients completed visual analogue scores, and had endoscopic examination and nasal mucociliary clearance times recorded. Hundred four had acoustic rhinometry performed and 96 had olfactory detection thresholds determined. The demographics overall and by treatment group are illustrated in Table 1. Of the 109 patients 51 (46.8%) had a systemic diagnosis, as described by Lund & Mackay [12], affecting the upper respiratory tract. The commonest of these diagnoses was asthma which was present in 39 (36%) patients. Five of these asthmatic patients had aspirin sensitivity.

Table 1. Demographics, nasal diagnoses and systemic diagnoses by treatment group. ASA = aspirin sensitive asthma, Ig = immunoglobulin.

	FPANS	Placebo	Total	%
AVERAGE AGE (years)	40	42		
MALE	32	34	66	61
SMOKER	13	16	29	26
ATOPIC	26	27	53	49
CT score ≤ 5 on worst side	18	16	34	31
CT score ≥ 6 on worst side	37	38	75	69
CHRONIC RHINOSINUSITIS	16	16	32	29
GRADE 1 POLYPS	13	16	29	26
GRADE 2 POLYPS	16	11	27	25
GRADE 3 POLYPS	10	11	21	19
ASTHMA	18	16	34	31
ASA	5	0	5	5
IDIOPATHIC BRONCHIECTASIS	2	0	2	2
CYSTIC FIBROSIS	2	0	2	2
MAJOR Ig DEFICIENCY	2	0	2	2
PRIMARY CILIARY DYSKINESIA	1	2	3	3
SJOGREN'S SYNDROME	1	0	1	1
YOUNG'S SYNDROME	1	0	1	1
PREVIOUS FESS	7	4	11	10

When assessing the results of FESS, regardless of whether they received post-operative FPANS each outcome measure value at 6 weeks, 1, 2, 3, 4 and 5 years post operatively was compared with the paired, preoperative baseline visit value using Wilcoxon's signed rank test. A Kaplan-Meier plot was produced using failure as the end-point.

When assessing the effects of postoperative FPANS, the outcome measure values at 1, 2, 3, 4 and 5 years for each subject were subtracted from the value for the same subject recorded at 6 weeks postoperation. The calculated values in the FPANS group were then compared with those similarly calculated in the placebo group using Mann-Whitney U tests. Two analyses were performed. The first analysis used data provided by all patients attending for follow-up at each time period. The second analysis excluded any data provided by a patient who had failed, after their point of failure. The values recorded at their time of failure were brought forward for inclusion in each subsequent postoperative time period analysis. This last value carried forward analysis also included the last data from patients

were lost to follow-up over the study but who had not failed. Rescue medication requirements and the number of failures in each treatment group were compared using chi-squared tests. Kaplan-Meier plots for each group were also compared. Interim analysis was performed at 1 year post FESS by the first author after code breaking. The other investigators and all patients remained blinded to their treatment group until 5 years of follow-up was completed on all patients. The first author did not record outcome measures after the first year of follow-up.

RESULTS

Overall results of FESS

Hundred patients attended for follow up at year 1, 79 at year 2, 67 at year 3, 72 at year 4 and 72 at year 5. The patient flow is seen in Figure 1. The mean overall results at pre-operative baseline, 6 weeks and 5 years post-operation, regardless of treatment arm are recorded in Table 2. Data was analysed to determine whether outcome measures were better, the same or worse at 5 years for the 72 patients with 5 year follow-up. These are recorded in Table 3.

During year 1, 15 (14%) of the 109 patients starting the year required rescue medication, during year 2, 12 (12%) of the 100 patients still in the study at the beginning of the year required rescue medication, during year 3, 8 (10%) of 79, year 4, 7 (9%) of 75 and year 5, 12 (17%) of 72. Of the 109 patients starting the study, over the 5 years 38 patients (35%) required rescue medication. Seventeen patients required 1 course, 8 patients 2 courses, 4 patients 3 courses, 4 patients 4 courses, 3 patients 5 courses and 2 patients 6 courses. Of the 72 patients attending for 5 year follow up 26 (36%) required rescue, 12 required 1 course, 5 required 2 courses, 1 required 3 courses, 3 required 4 courses, 3 required 5 courses and 2 required 6 courses.

Twelve patients failed during the 5 year follow-up, 1 at 3 months postoperatively, 1 at 6 months, 5 at 18 months, 2 at 2.5 years, 1 at 3.5 years, 1 at 4 years and 1 at 4.5 years. After failing, 3 had further surgery (18 months after the first procedure) and were then followed up for the 5 years. Neither required surgery

Figure 1. Flow chart showing the number of patients who attended for follow-up, were lost to follow-up or who missed a follow-up but attended their next appointment, per year post-operation. Numbers in parentheses are those who received active FPANS.

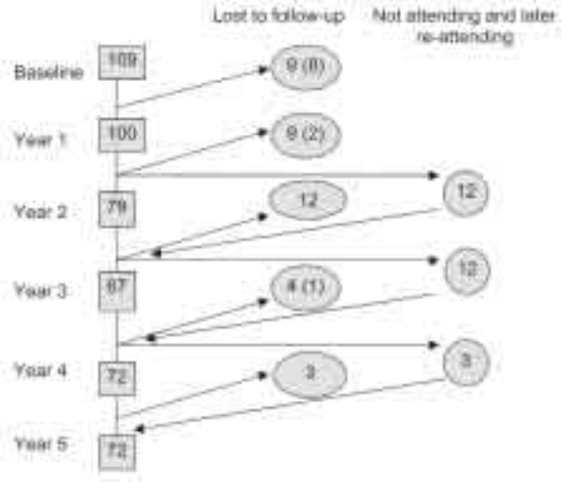


Table 2. Means for each outcome measure recorded 6 weeks and 5 years post-operation and the means of the matched pre-operative baseline values. Figures in parentheses = number of patients attending at that time. Wilcoxon signed rank analysis: * p=0; † p=0.003; ^ p=0.44. NMCC = nasal mucociliary clearance time in minutes. ODT = olfactory detection threshold in decismells. Total nasal volume is measured in millilitres using acoustic rhinometry.

Outcome measure	baseline	6 weeks post FESS	baseline	5 years post FESS
"how do you feel overall?" VAS	6.9	2.5 (105)*	7.2	2.7 (72)*
total VAS	33.9	13.7 (105)*	34.8	14.7 (72)*
endoscopic polyp score	2	0.2 (105)*	2.2	0.6 (72)*
endoscopic oedema score	3.4	2.1 (105)*	3.5	1 (72)*
endoscopic discharge score	2.6	1.6 (105)*	2.6	0.8 (72)*
NMCC	30.4	24.1 (105)†	29.7	20.6 (72)*
ODT	36.9	29.6 (92)*	37.5	34.9 (64)^
total nasal volume	20.8	29.2 (92)*	20.5	26.8 (70)*

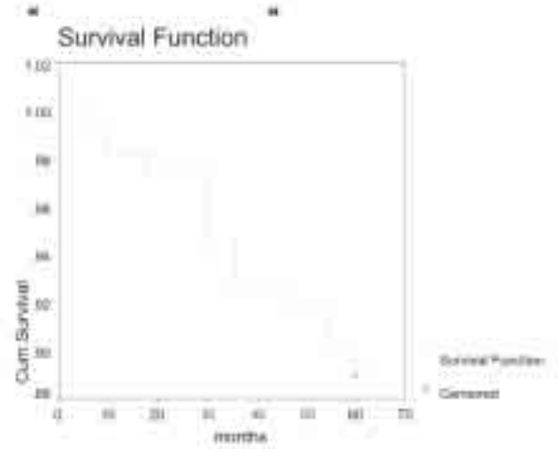
Table 3. Patients attending at 5 years with an analysis of whether each outcome measure was better, the same or worse than at their preoperative visit. n = the number of patients providing data for each outcome measure at 5 years.

Outcome measure at 5 years	n	better	%	same	%	worse	%
"how do you feel overall?" VAS	72	64	89	6	8	2	3
total VAS	72	69	96	2	3	1	1
endoscopic polyp score	72	46	64	25	35	1	1
endoscopic oedema score	72	67	93	5	7	0	0
endoscopic discharge score	72	63	88	8	11	1	1
NMCC	70	46	66	24	34	0	0
ODT	64	19	30	28	44	17	26
total nasal volume	69	56	81	0	0	13	19

again or failed with rescue medication during this time. 7 of the failed patients were treated with unblinded FPANS (all were found to have been in the placebo group when the code was broken). Five of these patients were followed to 5 years without failing again. One was lost to further follow-up at the time of failure and 1 was followed for a further year and was then lost to follow-up. Figure 3 illustrates the Kaplan-Meier survival curve using failure as an end-point and those patients lost to follow-up as censored data.

Nine patients were prescribed prednisolone by their chest physician for asthma exacerbations during the study. None of these courses amounted to the dosage required for our definition of sinonasal failure. One of these patients failed our study because of rescue medication prescribed by us for sinonasal symptoms. Six patients required antibiotics for chest disease related to host defence deficiency. None of these patients failed. Sixteen patients were prescribed antibiotics by their general practitioners for sinusitis without attending our clinic for conformation of this diagnosis. Three of these patients later failed our study having also been prescribed the requisite rescue medication by us.

Figure 2. Kaplan-Meier plot for all 109 patients starting the study. The end point was defined as the requirement of at least 1 rescue medication course a month for 2 consecutive months. Censored values were patients lost to follow-up. Cum survival = cumulative survival.



Results related to post-operative treatment

We analysed the effects of FESS in the placebo group alone and the results are shown in Table 4 for the 34 patients who attended at 5 years.

Subsequently the data in both treatment groups was compared to assess any additional effects of post-operative FPANS versus placebo. Of the 37 patients lost to follow-up 20 were in the placebo group and 17 in the FPANS group (Figure 1). The average time at which this occurred was 18 months in the FPANS group and 24 months in the placebo group.

Over the 5 years 6 patients did not start using their sprays and all were lost to follow-up. Eight patients (5 placebo, 3 FPANS) stopped using their sprays at an average of 18 months considering them ineffective, 6 were non-compliant (all in placebo group), 2 patients in the placebo group perceived non-specific side-effects and one patient (in the placebo group) complained of epistaxes. These continued despite stopping the spray.

We subtracted the value recorded for each outcome measure 1 and 5 years postoperatively from its paired value recorded 6 weeks after surgery. This gave us a value for the change in that outcome measure over each time period. The means of each calculated value for each treatment group are seen in Table 5. A higher visual analogue score, as described by Lund and Mackay [12], equates with greater symptom severity. If subtracting the 5 year visual analogue score from the 6 week visual analogue score produces a negative value then the 5 year visual analogue score must be greater and therefore worse than the 6 week visual analogue score. With regard to nasal volume however a greater value at 5 years than 6 weeks equates to an improvement in airway. This improvement would be demonstrated by a negative value when calculated by subtracting the 5 year from the 6 week value. All patients attending at 1 and 5 years post-operation had their data for that time period included regardless of whether they had previously failed. The last value carried forward analysis is also tabulated. The Mann-Whitney U analysis p values comparing results in the post-operative placebo and FPANS groups are shown. Graphs of the mean outcome measures for the "how do you feel overall" visual analogue score, endoscopic polyp score and total nasal volume recorded at each post-operative time period are illustrated in Figures 3-5.

Table 4. Mean values for each outcome measure recorded at pre-operative baseline visit and 5 years post-operation for patients receiving placebo spray after surgery. WSR = Wilcoxon signed rank; n = number of patients attending at that follow-up time period; NMCC = nasal mucociliary clearance time in minutes; ODT = olfactory detection threshold in decismells; Total nasal volume is measured in milliliters using acoustic rhinometry.

Outcome measure - placebo group only	n	baseline	5 years post FESS	WSR p value
"how do you feel overall?" VAS	34	7	2.9	0
total VAS	34	34.3	15.7	0
endoscopic polyp score	34	2	0.8	0
endoscopic oedema score	34	3.4	1.2	0
endoscopic discharge score	34	2.6	0.9	0
NMCC	34	31	19.4	0
ODT	32	36	33	0.36
total nasal volume	32	20	24.7	0

Table 5. Results of Mann-Whitney U (MWU) analysis comparing post-operative placebo and FPANS groups for each outcome measure at 1 and 5 years follow-up. The values tabulated are the means of those produced by subtracting the value recorded from each patient at year 1 and 5 of follow-up from their matched value recorded at the 6 week postoperative visit. LVCF = last value carried forward.

Outcome measure by year	Placebo	FPANS	MWU p	Placebo (LVCF)	FPANS (LVCF)	MWU p
"How do you feel overall" VAS						
year 1	-0.2	0.7	0.054	-0.3	0.5	0.065
year 5	-0.4	0.1	0.044	-0.6	0.1	0.233
Total VAS						
year 1	0.8	2.5	0.28	-0.1	1.9	0.311
year 5	-1.3	-0.2	0.168	-2.1	-0.2	0.391
Endoscopic polyp score						
year 1	-0.2	0.2	0.043	-0.2	0.1	0.027
year 5	-0.6	-0.2	0.157	-0.7	-0.2	0.023
Endoscopic oedema score						
year 1	0.8	1.1	0.525	0.8	-0.8	0.964
year 5	1.2	1.2	0.197	1	1.2	0.564
Endoscopic discharge score						
year 1	0.9	1.1	0.943	0.7	0.9	0.897
year 5	0.7	1	0.244	0.5	0.9	0.292
NMCC						
year 1	5.1	6.4	0.851	3.9	5.4	0.917
year 5	4	1.9	0.061	5.1	2.3	0.021
ODT						
year 1	3.6	2.3	0.303	3.3	-0.9	0.276
year 5	-4.8	-7.3	0.881	-4.2	-7.6	0.718
Total nasal volume						
year 1	2.7	-0.5	0.019	3	-0.2	0.008
year 5	3.7	1.4	0.181	3.8	1.1	0.027

Thirteen patients in the FPANS and 25 in the placebo group received rescue medication p=0.038 (Pearson chi square = 4.327 with 1 d.f. Of the 12 patients who failed the study 2 were receiving FPANS and 10 placebo (p=0.06 chi square). The Kaplan-Meier curves are plotted in Figure 6. The average failure time in the FPANS group was 12 months and in the placebo group 30 months.

Of the 9 patients prescribed prednisolone for asthma 4 were in the FPANS group. Of the 6 patients who took antibiotics for chest disease 5 were in the FPANS group. Of the 16 patients prescribed antibiotics by their general practioner for sinusitis 7 were in the FPANS group.

DISCUSSION

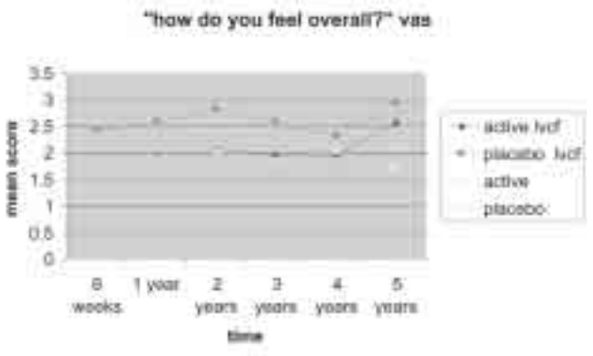
In 2001 Lund [15] critically reviewed outcomes of surgery for chronic rhinosinusitis and assessed the levels of evidence available at that time. Eighteen studies on the outcome of endoscopic sinus surgery were analysed. A mean of 89% of patients reported surgery as successful. These studies provided level 3 evidence. Five papers quoted a mean of 11% of patients feeling unchanged or worse after surgery. However these papers represent a range of endoscopic procedures. FESS has been used by some authors as a term representing more extensive marsupialisation and exenteration of all involved sinuses [16-17] which differs from the surgical philosophy and approach of Stammberger [1] and Kennedy [2].

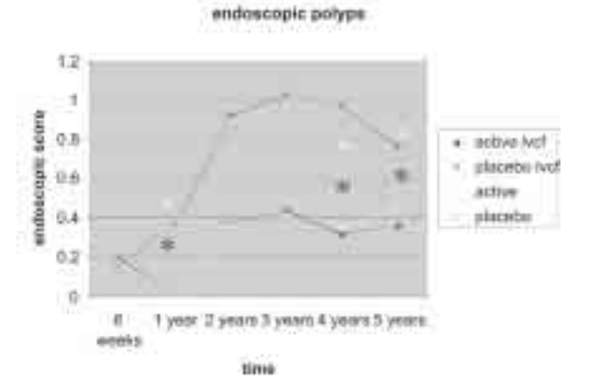
The pathological case-mix may vary widely inter and intra study and may be poorly described. As yet no clear classification based on aetiology, immunology, molecular biology or natural history exists to help provide a system for unified reporting of results. Similarly no prognostic staging system exists to help describe and classify disease. Co-existent systemic disease such as asthma may influence prognosis [5] but the prevalence of such diseases is not always included in study population descriptions.

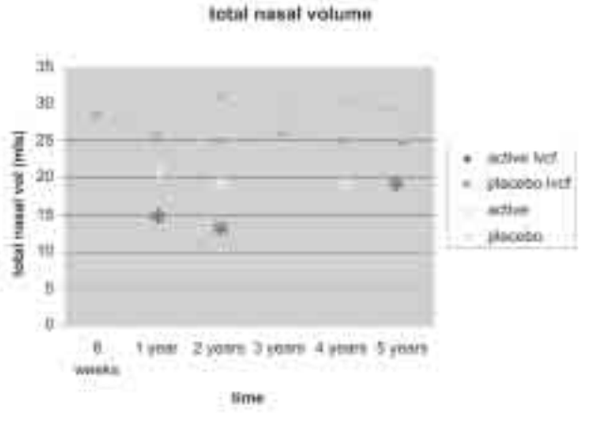
As with any surgical procedure there can be no true placebo for control. Many studies are retrospective with varying follow-up times, some as short as 3 months.

Significantly postoperative treatment details whether medical or surgical may also be absent. Postoperative protocols vary amongst studies [18], amongst patients within the same study [19] or may not be described at all. Long-term outcomes of index FESS procedures have been published without reference as to whether patients had required medication or further surgery during the follow-up period [20]. The results may therefore be erroneously attributed to the initial surgery alone.

Figure 3, 4 & 5. Plots of the mean values for outcomes: "how do you feel overall" visual analogue score (VAS), endoscopic polyp score and total nasal volume recorded at each post-operative time period from 6 weeks to 5 years. Each treatment group is plotted with separate curves for the means of all patients attending for data collection regardless of whether or not they had previously "failed" and for the last value carried forward (lvcf) analysis. Active = FPANS group .* = significant difference, Mann Whitney U analysis.

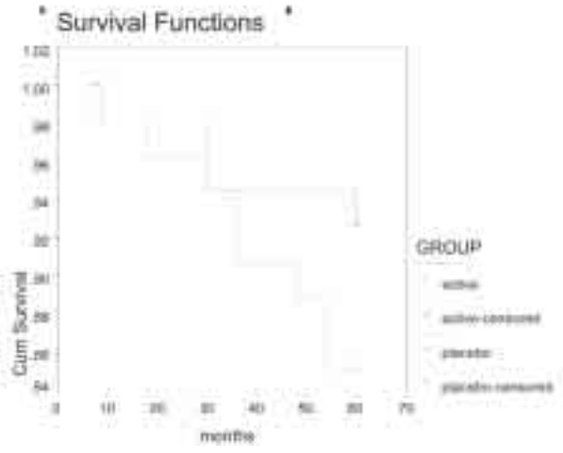






Furthermore outcome measures are not standardised. The results may also be solely judged by the operating surgeons rather than patients, potentially leading to bias related to a vested interest in recording favourable results. Postoperative endoscopic findings, determined by the operating surgeon have been proposed as objective outcome measures [21] but these are open to individual interpretation and bias. In an attempt to overcome some of these problems, an objective assessment was conducted by Lund & Scadding [22] on 200 patients with chronic rhinosinusitis, with an average of 2.3 years' follow up providing level 2b evidence. Symptoms were assessed after FESS by visual analogue scoring (VAS) and objective tests included ciliary beat frequency (CBF), quantitative and threshold olfaction with University of Pennsylvania Smell Identification Testing and pm-carbinol concentrations, nasal forced inspiratory peak flow, anterior rhinomanometry, and in selected cases acoustic rhinometry. No details of postoperative medication requirements however were included.

Figure 6. Kaplan-Meier plot for all 109 patients starting the study. The end point was defined as the requirement of at least 1 rescue medication course a month for 2 consecutive months. Censored values were patients lost to follow-up. Cum survival = cumulative survival. Curves for placebo and FPANS groups are plotted separately.



Since Lund's evidence based review in 2001 [15], 10 clinical trials on the outcome of endoscopic sinus surgery have been published, excluding 6 papers on surgical techniques for frontal sinusitis, 1 on the treatment of maxillary sinus lesions and 1 on children with cystic fibrosis and polyps. 2 of the 10 papers provide level 2 evidence. Kuehnemund et al. [23] in a multi-centre study compared extended approach with limited approach endoscopic sinus surgery involving 65 patients. Surgical results and symptomatology were similar in both groups of patients. Venkatachalam & Jain [24] compared functional endoscopic sinus surgery with conventional surgery and described 92% of patients improved in the former group and 76% in the latter group.

Of the remaining 8 studies, 2 used quality of life scores and both found significant score improvements following endoscopic sinus surgery [25,26]. Ramadan [27,28] in 2 papers described a mean of 81% success in relation to symptom questionnaire scores in children undergoing endoscopic sinus surgery and Jiang & Hsu [29] found no difference in outcome related to age whether child, adult or adult over 65 years. The Glasgow benefit inventory has also found significant improvement in quality of life following endoscopic sinus surgery with

a minimum 12 month follow-up in a retrospective postal questionnaire study [30].
Our study was performed prospectively on a well documented population undergoing FESS as originally described. Outcome measures included patient rated symptom scores, the recording of which was supervised by a nurse rather than the operating surgeon. Endoscopic scores were recorded and objective measures also collected. We also standardised postoperative medication prescribing and recorded steroid and antibiotic requirements. We have used the concept of failure after surgery, originally described by us in relation to endoscopic sinus surgery for patients with cystic fibrosis [31] as a useful comparative outcome statistic.

FESS is associated with a high level of symptom, mucosal pathology and nasal function improvement at 5 years of follow-up. At all time periods all outcome measures were significantly improved compared to preoperative baseline values except olfactory detection thresholds at 3, 4 and 5 years. This measure however was improved at 6 weeks [32], 1 and 2 years post FESS. Patient symptom scores tended to be improved in a greater percentage of patients than were the range of more objective outcome measures, particularly with regard to polyposis. The discrepancy between patient reported improvement and the endoscopic findings has been illustrated by others [3,20].
Table 2 shows all outcome measures with the exception of olfactory detection thresholds to be significantly improved at 5 years post FESS even if topical nasal steroids are not used, so implying beneficial effects of FESS alone. However, it must be recognised that this would be to ignore the need for prednisolone in 25 of the patients using placebo spray and 38 patients in the study overall. Furthermore 3 patients providing 5 year follow-up data had also undergone further surgery after their initial FESS. Their results could not therefore be attributed to the index procedure alone. The results of FESS should therefore be judged in the context of ongoing, combined medical and surgical therapy over given time periods. The concept of defining failure related to steroid requirements and using this as an end point for Kaplan-Meier analysis recognises the contribution to overall results of further surgery and of postoperative medical treatments. Using our definition of failure which was recorded as an end point when a course of prednisolone was required once a month for two consecutive months, we achieved a 5 year "survival" rate after FESS of 89%.
Our study has also shown additional benefit from regular postoperative FPANS, up to 5 years following FESS. This is an additional effect over and above that of surgery as in the analysis the yearly follow-up results were compared with the values recorded 6 weeks following FESS. FPANS has previously been shown to be effective in treating the symptoms of nasal polyps with a trend towards a faster onset of action than intranasal beclomethasone dipropionate aqueous nasal spray [33,34]. Holmberg et al.'s [33] paper states that endoscopic polyp size was recorded but the data on this outcome measure was not presented in the paper. Loratadine was used as a rescue medication by Holmberg [33]. The study found significantly fewer days of loratadine use in the FPANS group compared with placebo spray. Fluticasone propionate nasal drops at a dose of 400mcg twice daily have been shown to reduce polyp size [35,36].
Previous studies, with shorter follow-up times ranging from 3 months to 2.5 years, using flunisolide [7,9], beclomethasone dipropionate [8] and budesonide [10] sprays have shown them to be beneficial after polypectomy. Budesonide was only beneficial in those patients who stated they had undergone previous polyp surgery before the study. Beclomethasone dipropionate spray has also been associated with benefit after ethmoidectomy for polyposis [6]. No mention was made in these studies as to whether other postoperative medications were required at any time. Only one study described whether or not subjects underwent further surgery during the follow-up period [7].

The statistically significant improvements present in our study 5 years after FESS in the placebo group demonstrates that surgery without postoperative topical medication provides a marked improvement. It might therefore be difficult to demonstrate further benefit from postoperative topical medical therapy. However using data recorded from all patients still attending at 5 years whether or not they had previously failed or had undergone further surgery, we found the overall visual analogue score changes were significantly better in the FPANS group. The changes in endoscopic oedema and polyp scores and in total nasal volumes were significantly better in the FPANS group at 4 years but not 5 years. Including patients who faired the worst and failed and not having data from those patients lost to follow-up however may bias the comparison. Therefore we performed a last value carried forward analysis which demonstrated that the changes in endoscopic polyp score and in total nasal volume was significantly better in the FPANS group. Interestingly patients in the placebo group had significantly better nasal mucociliary clearance time changes than the FPANS group, although no difference in the changes in endoscopic discharge scores were noted. The beneficial effects of FPANS were further demonstrated by the requirement for significantly more prednisolone rescue medication courses in the placebo group. The greater number of failing patients in the placebo group nearly achieved significance.
Finally we found no evidence of infection associated with FPANS use after polypectomy [37] as described by Mostafa [38].

CONCLUSION

In conclusion patients who have undergone FESS for rhinosinusitis with or without polyposis continue to demonstrate subjective and objective benefit 5 years postoperatively but approximately 36% will have required additional medical treat-

ment with steroids and antibiotics. Our patients demonstrated an 89% 5 year "survival" with FESS and postoperative rescue medication as necessary, such that they had not deteriorated to persistently remain with symptoms as severe as they had suffered pre-operatively. The cohort of patients receiving FPANS required significantly less rescue medication and had significantly less polyp recurrence over the 5 year period.

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