ORIGINAL CONTRIBUTION

Rhinosinusitis, symptomatology & absence of polyposis in children with primary ciliary dyskinesia*

M. Rollin, K. Seymour, M. Hariri, J. Harcourt

Department of Otolaryngology / Head & Neck Surgery, Charing Cross and Royal Brompton Hospitals, London, United Kingdom

SUMMARY

Introduction: Primary Ciliary Dyskinesia (PCD) describes a group of inherited disorders which result in functional ciliary defects leading to mucous stasis. Clinical manifestations include otitis media with effusion and chronic rhinosinusitis. Nasal polyposis has previously been thought to be linked to PCD, and current theories of 'polypogenesis' suggest that early and severe polyp formation could be expected among sufferers of this condition.
Methods: Cross-sectional observational review of all children attending the multi-disciplinary clinic at a national tertiary-referral centre for PCD across a 3-month period. Careful examination was undertaken, and the SNOT-20 questionnaire administered.
Results: Thirty patients were included. No nasal polyps were found, despite children clearly suffering rhinosinusitis and being debilitated by their symptoms. The rhinologically orientated questions of the SNOT-20 produced the most positive responses; however some other questions were found not to be useful in a paediatric population.
Conclusions: Nasal polyps do not occur in children with PCD, despite the presence of rhinosinusitis. Given that many current theories of polyp pathogenesis hinge on prolongation of pro-inflammatory stimuli, further investigations are needed into why this should not occur in the situation of chronic mucous stasis which is the hallmark of PCD.

Key words: Rhinosinusitis, nasal polyposis, Primary Ciliary Dyskinesia, Kartagener Syndrome

INTRODUCTION

Primary ciliary dyskinesia (PCD) describes a group of inherited disorders of ciliary structure or function. Clinical manifestations include neonatal respiratory distress, otitis media with effusion, rhinosinusitis and subfertility. Fifty percent of those with PCD may also demonstrate *situs inversus*, in which case the term used is Kartagener's Syndrome (the triad described by Kartagener in 1933 [1] was that of *situs inversus*, bronchiectasis and chronic sinusitis; it is now considered a subtype of PCD). Several ciliary ultrastructural defects have been identified to date, and in some cases specific genetic loci have been identified [2,3]. The great majority of cases are inherited as an autosomal recessive condition [3-5].

The incidence is approximately one in 15000, and there are estimated to be 3000 affected individuals in the UK, with approximately 70 new cases each year, although the condition is generally accepted to be somewhat under-diagnosed [3,5-7]. Diagnosis is via a cascade of investigations, culminating in mucosal biopsy for ciliary examination [2,3,5,7].

Chronic rhinosinusitis, the most common chronic disease, is an inflammatory disorder of the upper airways with a multifactorial and incompletely understood causation. It exists along a spectrum of severity, and in its more severe forms is noted to be a significantly debilitating condition, with adult patients demonstrating poorer "quality of life" scores than sufferers of many other chronic cardiorespiratory diseases such as angina or congestive cardiac failure [8]. Nasal polyps are benign protrusions of chronically-inflamed and oedematous nasal mucosa into the upper airway. Originally thought to be a separate clinical entity, this condition is now considered, by some, to represent part of the continuum of chronic rhinosinusitis [9-13].

The prevalence of chronic rhinosinusitis has been estimated as 14% of the (USA-based) population [14]. Other studies have estimated the prevalence of polypoid rhinosinusitis as lying between 0.2 and 4.3% of the general population [12], and much higher in the immunosuppressed [14].
There is a well-documented link between polypoid rhinosinusitis and host-defence disorders such as cystic fibrosis

[10,12,15]. Decreased mucociliary clearance has also been demonstrated in studies of otherwise-healthy adults with chronic rhinosinusitis [8,16].

The consensus view now points towards a strictly localised inflammatory process as being responsible for the genesis of polypoid rhinosinusitis [9,12,17,20,21]. Current theories regarding this inflammatory state [9,11,13,15,17,18,22-24] universally rely on a spectrum of mediators released in response to an initial inflammatory stimulus [9,11-15,17,18,22-26].

It follows that a state of permanent mucous stasis would result in persistence of initial pro-inflammatory stimuli, supporting and accelerating general progress towards a state of chronic inflammation. Logically, this implies that patients with primary ciliary dyskinesia could be expected to show signs of chronic rhinosinusitis, leading to early and marked polyp formation.

Correspondingly, chronic rhinosinusitis is an accepted manifestation of PCD, appearing on most lists of childhood signs & symptoms suggestive of the condition [2,4,7,27], and whilst polypoid disease has been considered to be similarly linked [7,28,29], the prevalence has not been reported.

The 20-question Sino-Nasal Outcome Test (SNOT-20), which arose as a modification of the 31-question Rhinosinusitis Outcome Measure (RSOM-31), is a validated patient-reported subjective measure of symptomatology in sino-nasal disorders[30], which has also recently begun to gain popularity as a research tool [30,31]. 20 factors related to nasal function (and its impact on overall function) are subjectively scored from 0 to 5 depending on the impact each has on the subject's daily life (Table 1). Results can be given as a mean score (0 to 5) or a total (0 to 100). The SNOT-20 has not been validated for use with paediatric patients.

METHODS
Setting
The Royal Brompton Hospital multidisciplinary paediatric PCD clinic (an internationally-recognised centre for this condition). The baseline entry criterion for the study was an existing firm diagnosis of PCD, made following observation of a functional ciliary defect on light microscopy of nasal brushings, with or without a structural ciliary defect demonstrated on Transmission Electron Microscopy. A cross-sectional observational review of all such children attending the clinic was performed across a three-month period, from mid-July to mid-September 2007.

Examination
Careful bilateral examination of the nasal cavity was performed without anaesthesia by a single senior clinician, using either a 5mm or 3mm endoscope. Detailed examination was made of the lateral nasal wall, middle and superior meati. Tympanic membranes were also carefully examined.

Questionnaire
The SNOT-20 questionnaire was administered to the attending parent, with age-appropriate input from the child, in order to determine symptom load. One question was modified from the official SNOT-20 in order to be more relevant to a paediatric population: "reduced productivity" was changed to "difficulty with schoolwork". Details of demographics, diagnosis and specialist investigations were obtained from the notes.

RESULTS
Thirty patients were included in the study. Twelve had ciliary dyskinesia with situs inversus, two had ciliary dyskinesia with dextrocardia, and 16 had ciliary dyskinesia alone.

Seventeen patients were male, 13 were female, and in the case of both Kartagener's Syndrome and simple PCD, the distribution of male and female patients was broadly equal. Patients' ages ranged from 1 to 14 years, the mean age of PCD patients (9 years) being slightly higher in this sample than the mean age of Kartagener's Syndrome patients (6 years).

Two patients regularly used nasal steroid inhalers (one fluticasone, one mometasone), and in addition one of these patients used Stérimar daily. Nineteen patients took oral antibiotics regularly; 11 patients used an oral steroid inhaler daily; and 8 used an oral salbutamol inhaler daily. None of the patients had recently been prescribed oral steroids, and none had had any form of nasal or sinus surgery.

No nasal polyps were found on examination in any of the patients. Two patients (identical twins aged 6 years) were suffering with acute upper respiratory tract infections at the time of examination, and were noted to have congested nasal

Table 1. The SNOT-20 scoring system.

Question	
1	Need to blow nose
2	Sneezing
3	Runny nose
4	Cough
5	Postnasal drip
6	Thick nasal discharge
7	Ear fullness
8	Dizziness
9	Ear pain
10	Facial pain / pressure
11	Difficulty falling asleep
12	Waking up in the night
13	Lack of a good night's sleep
14	Waking up tired
15	Fatigue
16	Reduced productivity
17	Reduced concentration
18	Frustration / restlessness / irritability
19	Sadness
20	Embarrassment

mucosa and mucopus. Moderate to severe rhinitis without polyposis was noted in two patients (aged 8 and 12 years) and bilateral hypertrophy of the inferior turbinates in one (aged 4). Eight patients (27%) were found to have mild to moderate rhinitis with significant buildup of secretions; 16 patients (53%) were mildly rhinitic with pooling of secretions (Figure 1). No correlation was found between clinical findings and age.

Eighteen patients were found to have healed chronic otitis media, and 10 showed evidence of otitis media with effusion. One patient had bilateral perforations, and another was suffering with wax impaction which precluded examination of the membrane (Figure 2). Age was correlated negatively with severity of clinical findings, in line with previous work [32] (R = 0.392; R2 = 0.153; t = -2.257; p = 0.032). Across the cohort as a whole, no correlation was found between these findings and those on nasal examination.

Mean total SNOT score was 14.7 (SD 9.37, range 0-44). Scores of zero in every patient were recorded for questions 16 (difficulty with schoolwork) and 19 (sadness related to symptomatology).
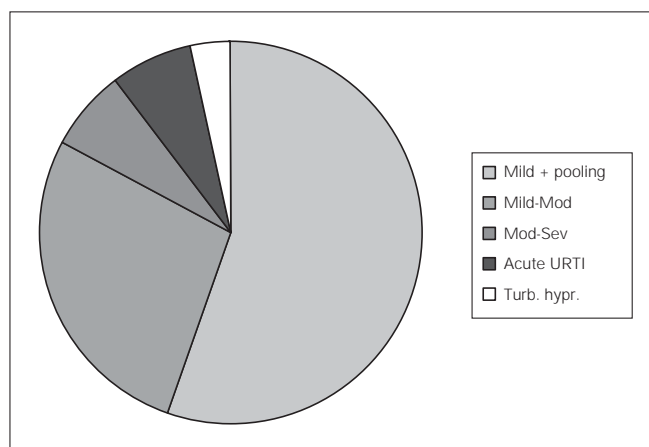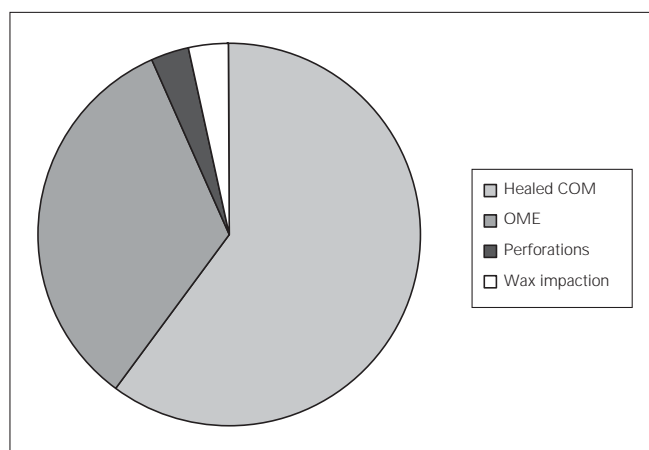

Figure 1. Rhinological symptoms.

Figure 2. Otological symptoms.

Table 2. Highest-scoring responses to the SNOT-20 questions.

Question	Mean score
Need to blow nose	3.07
Thick nasal discharge	2.13
Cough	2.07
Watery nasal discharge	1.73
Waking up feeling tired	1.13
Post-nasal discharge	0.8
Lack of a good night's sleep	0.77
Fatigue	0.63
Waking up in the night	0.53
Difficulty falling asleep	0.37

The results of two questions correlated negatively with age: questions 12 (waking in the night, R = 0.437; R^2 = 0.191; t = −2.572; p = 0.015) and 15 (feeling tired in the day, R = 0.421; R^2 = 0.177; t = −2.458; p = 0.020). Responses to all other questions did not show a relationship to age.

Questions producing the highest response scores in this cohort tended to be rhinological in nature, with three of the highest four scores relating to nasal symptoms. The next-highest-scoring group tended towards sleep function (Table 2).

Only the highest-scoring five questions of the 20 showed a mean score above 1.0. Overall mean score per question was 0.735 (SD 0.0468).

DISCUSSION

These results show that, whilst polypoid rhinosinusitis is considered to be amongst the sequelae of PCD [7,28,29], the true prevalence may be far lower than previously thought. Indeed, in our sample, no evidence of nasal polyposis was seen in any patient.

This occurred despite the fact that clinical signs consistent with some degree of rhinitis were noted in virtually all patients in this cohort. Nasal symptoms clearly trouble these patients: symptoms attributable to rhinitis formed the mainstay of the positive SNOT responses, and symptoms which were scored as significantly impacting on patients' lives were exclusively rhinological in nature.

Current theories of polyp pathogenesis hinge on prolongation of an initial pro-inflammatory stimulus; and invite the conclusion that relative mucous stasis within the upper airway should lead to persistence of such a stimulus, and relative perpetuation of upper airway inflammation. It follows that patients with PCD should show signs both of significant rhinosinusitis, and of early (possibly extensive) polyp formation. This group of patients, however, despite clearly suffering from a chronic rhinitic process, universally showed no sign of polyp formation.

This suggests that part of the pathophysiological process of polyp formation is not explicable by current theories.

No symptom-scoring system was available that had been validated for use with children. The SNOT-20 has been validated for use in adults, and was therefore chosen as an evidence-based alternative, in the knowledge that it would be unlikely to provide a perfect solution. This assumption was confirmed, and it is also acknowledged that use of a control group for the SNOT questionnaire might have enhanced the reliability of this symptom-scoring data. The use of a subjective symptom scale with a young child is naturally coloured by the fact that the majority of the responses are given by a parent or carer. Certain questions in the SNOT-20 are highly age-dependent: questions 10 (facial pain/pressure), 12 (waking in the night) and 15 (daytime tiredness) are examples. No child or parent admitted to any sadness related to their symptoms.

These findings suggest that, contrary to the popular general perception, nasal polyposis does not occur in children with PCD. Further work is needed in order to arrive at a full understanding of the pathophysiology of polyp formation in the upper airways. We suggest that the SNOT-20 should be used with great caution in a paediatric population, and the development of a new instrument should be considered.

REFERENCES

1. Kartagener M. Zur Pathogenese der Bronchiektasien bei Situs viscerum inversus. Klin Tuberk 1933; 83: 489-501.
2. Pifferi M, Caramella D, Cangiotti A et al. Nasal nitric oxide in atypical primary ciliary dyskinesia. Chest 2007; 131: 870-873.
3. Roomans GM, Ivanovs A, Shebani EB, Johannesson M. Transmission electron microscopy in the diagnosis of primary ciliary dyskinesia. Upsala J Med Sci 2006; 111: 155-168.
4. Chodhari R, Mitchison HM, Meeks M. Cilia, primary ciliary dyskinesia and molecular genetics. Paediatr Respir Rev 2004; 5: 69-76.
5. Meeks M, Bush A. Primary ciliary dyskinesia (PCD). Paediatr Pulmonol 2000; 29: 307-316.
6. Geremek M, Witt M. Primary ciliary dyskinesia: genes, candidate genes and chromosomal regions. J Appl Genet 2004; 45: 347-361.
7. Bush A, Cole P, Hariri M, Mackay I et al. Primary ciliary dyskinesia: diagnosis and standards of care. Eur Respir J 1998; 12: 982-988.
8. Antunes MB, Cohen NA. Mucociliary clearance – a critical upper airway hose defense mechanism and methods of assessment. Curr Opin Allergy Clin Immunol 2007; 7: 5-10.
9. Meltzer EO et al. Rhinosinusitis: establishing definitions for research and patient care. J Allergy Clin Immunol. 2004 Dec; 114(6) suppl: 155-212.
10. Rowe-Jones JM, Mackay IS. Management of nasal polyps. Curr Opin Otolaryngol Head Neck Surg. 1998; 6: 41-46.
11. Bryson JM, Tasca RA, Rowe-Jones JM. Local and systemic eosinophilia in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis with and without polyposis. Clin Otolaryngol 2003; 28: 55-58.
12. Bateman ND, Fahy C, Woolford TJ. Nasal polyps: still more questions than answers. Laryngol Otol 2003; 117: 1-9.
13. Pawankar R, Nonaka M. Inflammatory mechanisms and remodelling in chronic rhinosinusitis and nasal polyps. Curr Allergy Asthma Rep 2007; 7: 202-208.
14. Gosepath J, Mann WJ. Current concepts in therapy of chronic rhinosinusitis and nasal polyposis. ORL 2005; 67: 125-136.
15. Rowe-Jones JM, Trendell-Smith N, Shembekar M, Mackay IS. Polypoid rhinosinusitis in patients with host defence deficiencies: cellular infiltration and disease severity. Rhinology 1997; 35: 113-117.
16. Broody FM. Mucociliary transport in chronic rhinosinusitis. Clin Allergy Immunol 2007; 20: 103-119.
17. Hirshberg A, Jokuti A, Darvas Z et al. The pathogenesis of nasal polyposis by Immunoglobulin E and Interleukin-5 is completed by Transforming Growth Factor b1. Laryngoscope 2003; 113: 120-124.
18. Pawankar R. Mast cells in allergic airway disease and chronic rhinosinusitis. Chem Immunol Allergy 2005; 87: 111-129.
19. Norlander T, Bronnegard M, Stierna P. The relationship of nasal polyps, infection and inflammation. Am J Rhinol 1999; 13: 349-355.
20. Bachert C, Gevaert P, Zhang N, et al. Role of staphylococcal superantigens in airway disease. Chem Immunol Allergy 2007; 93: 214-36
21. Kirtreesakul V. Update on nasal polyps: etiopathogenesis. J Med Assoc Thai 2005; 88: 1966-1972.
22. Hamilos DL, Lund VJ. Etiology of chronic rhinosinusitis: the role of fungus. Ann Otol Rhinol Laryngol 2004; 113: 27-31.
23. Pawliczak R, Lewandowska PA, Kowalski ML. Pathogenesis of nasal polyps: an update. Curr Allergy Asthma Rep 2005; 5: 463-471.
24. Pawankar R. Nasal polyposis: an update: editorial review. Curr Opin Allergy Clin Immunol 2003; 3: 1-6.
25. Bernstein JM. The molecular biology of nasal polyposis. Curr Allergy Asthma Rep 2001; 1: 262-267.
26. Bernstein JM. Update on the molecular biology of nasal polyposis. Otolaryngol Clin North Am 2005; 38: 1243-1255.
27. Greenstone M, Rutman A, Dewar A et al. Primary ciliary dyskinesia: cytological and clinical features. Q J Med 1988; 67: 405-430.
28. Holzmann D, Ott PM, Felix H. Diagnostic approach to primary ciliary dyskinesia: a review. Eur J Paediatr 2000; 159: 95-98.
29. Drake-Lee AB. Medical treatment of nasal polyps. Rhinology 1994; 32: 1-4.
30. Piccirillo JF, Merritt BA, Richards ML. Psychometric and clinimetric validity of the 20-item sino-nasal outcome test (SNOT-20). Otolaryngol Head Neck Surg 2002; 126: 41-47.
31. Deal RT, Kountakis SE. Significance of nasal polyps in chronic rhinosinusitis: symptoms and surgical outcomes. Laryngoscope 2004; 114: 1932-1935.
32. Majithia A, Fong J, Hariri M, Harcourt J. Hearing outcomes in children with primary ciliary dyskinesia – a longitudinal study. Int J Paediatr Otorhinolaryngol 2005; 69: 1061-1064.

Mr Matthew Rollin
"Jacques", Back Street
Garboldisham
Diss, Norfolk IP22 2SD
United Kingdom

ORIGINAL CONTRIBUTION

Postoperative maxillary sinus mucocoele: risk factors for restenosis after surgery and preventive effects of mytomycin-C*

Hyo Yeol Kim, Hun-Jong Dhong, Jin-Young Min, Young Gi Jung, Shin Hong Park, Seung-Kyu Chung

Department of Otorhinolaryngology - Head and Neck Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

SUMMARY

Objective: To evaluate the clinical factors associated with restenosis after the surgery for treating postoperative maxillary sinus mucocoele and the preventive effect of topically applied mytomycin-C (MMC) on the restenosis.

Methods: This double-blinded randomized controlled prospective study included 38 cases of postoperative maxillary sinus mucocoeles. The patients underwent inferior meatal antrostomy with or without Caldwell-Luc operation, and cotton-pledgets soaked with MMC or normal saline were applied to the antrostomy sites for 5 minutes.

The degree of narrowing of the opening and its correlation with the preoperative characteristics, including age, gender, allergy, presence of polyps, interval between previous surgery and computed tomography findings were evaluated.

Results: Three months after the surgery, the openings were patent in 24 cases, narrowed in 5 cases and stenotic in 9 cases. MMC application, septation of mucocoele and concurrent inflammation at the lesion side all had a significant effect on stenosis of the antrostomy site at 3 months after the surgery (p < 0.05, Chi-square test).

Conclusions: MMC has a favorable effect in preventing narrowing of the opening after surgery for maxillary sinus mucocoeles. The presence of septa in the mucocoeles or concurrent inflammation in the ipsilateral sinuses has an effect to promote restenosis.

Key words: maxillary sinus, mucocoele, stenosis, mitomycin C, antrostomy

INTRODUCTION

Mucocoeles are benign and locally expansile cysts of the paranasal sinus lined by respiratory mucosa with pseudostratified columnar epithelium and filled with mucus. Mucocoeles are most common in the frontal sinus followed by the ethmoid and sphenoid sinus [1]. Maxillary sinus mucocoeles are relatively rare in western countries, accounting for 10% or less of all paranasal sinus mucocoeles. However, one type of the maxillary sinus mucocoeles, the postoperative maxillary sinus mucocoele, is more commonly reported in Korea and Japan, and they are usually a long-term sequel of a Caldwell-Luc operation [2]. The exact pathophysiological mechanisms responsible for paranasal sinus mucocoeles are still under debate. However mucocoeles are believed to result from obstruction of the sinus ostia, with associated accumulation of fluid. The mucocoele gradually expands as mucus continues to be produced within it. This results in remodeling and/or erosion of the surrounding bone. Secondary infection can make the mucocoele to expand rapidly and increase the risk of complications [3]. The treatment for mucocoeles is surgical, and the endoscopic endonasal approach results in excellent outcomes, albeit dependent on the location and characteristics of the mucocoeles [4].

Marsupialization and antrostomy of the sinus by the intranasal endoscopic approach has been advocated as an initial treatment modality [1,5].

However, stenosis or narrowing of the marsupialization site after surgery is not infrequent and can potentially lead to recurrent disease [6]. The patency of the antrostomy site is an important factor in defining the success rate. Therefore, many attempts to reduce the incidence of adhesions and stenosis after surgery, including using the use of silicon tubes, stents and splints have been tried, with controversial effects [7,8].

Mytomycin C (MMC) has recently been used to reduce the stenosis and scar formation after surgery; many ophthalmologic and otorhinolaryngolgic studies have showed its favorable effect [9,10]. MMC was initially isolated from the *Streptomyces caespitosus* strain of actinomyces for its antibacterial properties

and this drug has been used as a chemotherapeutic agent due to its ability to cross-link DNA and inhibit mitosis. Furthermore, it also has antiproliferative perperties [9,10]. This antiproliferative effect results from suppression of fibroblast activity; the studies of MMC on cultured fibroblasts have demonstrated an antiproliferative effect at concentrations of 0.04 mg/ml and a cytocidal effect at higher concentrations [11,12].

In this study, we tried to identify the significant factors associated with stenosis of the antrostomy site for maxillary sinus mucocoeles, and evaluated the efficacy of MMC for preventing narrowing of the antrostomy site after surgery.

MATERIALS AND METHODS
Patients
This prospective study was approved by the Investigational Review Board of the Samsung Medical Center. We included fifty consecutive patients presenting with postoperative maxillary sinus mucocels who underwent inferior meatal antrostomy with or without a Caldwell-Luc operation from January to December 2006. Mucocoele was defined in this study as a completely opacified maxillary sinus with evidence of expansion. The diagnosis was based on medical history and physical examination, including nasal endoscopy, computed tomography (CT).

These patients were randomly divided into the MMC-applied group (MMC group) and the control group by a double-blinded method. However, 38 of the patients were followed up for more than 3 months after their surgery.

At the initiation of the study, the medical records of the enrolled cases were reviewed and parameters, including age, gender, allergy, the presence of polyps and the interval between the previous surgery and marsupialization were evaluated. In addition, the preoperative radiological findings were evaluated with CT scans. The mean area of the antrostomy site with the greatest dimension of the mucocoele in the axial section was measured. The thickness of the thinnest portion of the medial wall of the mucocoele was measured and the severity of concurrent inflammation in the ipsilateral sinuses was evaluated using the Lund-Mackay (LM) score (low score group less than 6, and the high score group equal to or more than 6) [13].

Surgery
Surgery usually started with endoscopic inferior medial antrostomy and the medial walls of the mucocoeles were opened with such instruments as an osteotome, through-cutting forceps, etc. The pathologic mucosa and inflammation tissue was removed and in cases for which wide marsupialization was impossible with using an endonasal approach due to its location or the thick medial wall, the Caldwell-Luc approach was used to open the mucocoele. Redundant mucosal tissues were then trimmed with a microdebrider and the size of the opening was measured with a ruler or a bayonet type forceps under visualization with a 30° endoscope. In the MMC group, a pledget soaked in MMC (1 ml of 0.5-mg/mL topical solution; Kyowa hakko Kogyo Co Ltd, Tokyo, Japan) was placed on the antrostomy site for 5 minutes following completion of the surgery. For the control group, a pledget soaked in normal saline was placed with the same method.

The size of the opening was followed up and evaluated with the same method at 1 and 3 months after the surgery. The patients were divided into 3 groups: the patent group (100 ~ 75% sized opening compared with the initial measurement), the narrow group (75%~25%), and the stenotic group (25%~0%; Figure 1).
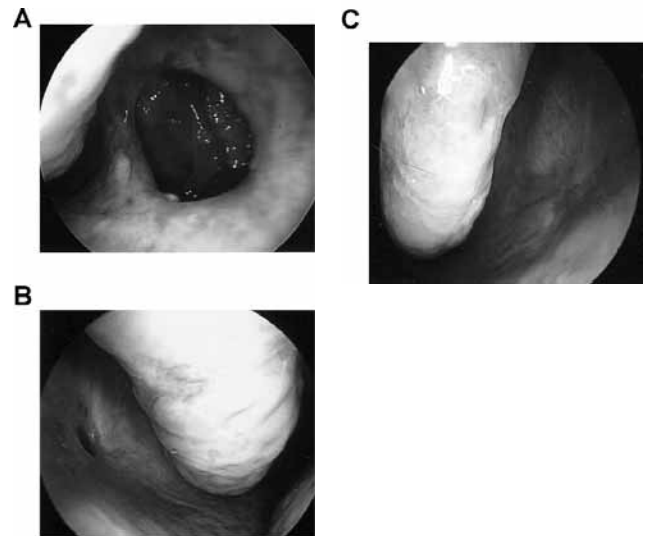

Figure 1. Patency of the antrostomy site via a 30° endoscope. (A) patent group; (B) narrow group; (C) stenotic group.

Statistics
Statistical analysis was performed with SPSS (SPSS Inc., Chicago, IL, USA), and a p-value less than 0.05 was accepted as significant. Pearson's $\chi2$-test was performed to determine correlation between patency of the opening of the mucocoeles and MMC application, gender, the presence of allergy, the grade of polyps, the surgical method, the thickness of the medial wall of the maxillary sinus, the presence of inflammation in the ipsilateral sinuses and the presence of multiple mucocoeles. Kruskal-Wallis test was performed to evaluate the differences of the size of the mucocoeles, the interval between the marsupialization and the previous surgery among the three groups.

RESULTS
Thirty-eight patients (18 males and 20 females) who underwent marsupialization and were followed up for more than 3 months were enrolled in this study. Their ages ranged from 30 to 66 years with a mean age of 46.5 years (Table 1). One month after the surgery, 30 cases had patent openings (the patent group), 4 cases had narrow openings (the narrow group) and 4 cases had stenosis of openings (the stenotic group).

Table 1. Characteristics of the patients and the clinical parameters.

Parameters	MMC application group (n= 22)	Control group (n=16)
Age(yr)	46.3±17.1	52.7±21.7
Gender		
Male	8	10
Female	14	6
Allergy		
Allergy(+)	21	13
Allergy(-)	1	3
Polyp		
Polyp(+)	12	9
Polyp(-)	10	7
Previous surgery		
Caldwell-Luc operation only	20	12
Caldwell-Luc operation with middle meatal antrostomy	2	4
Interval between previous surgery and revision (Yrs)	20.9±11.8	23.3±11.9
Surgical method		
Endoscopic approach	13	5
Combine with Caldwell-Luc operation	9	11
Mucocoele size (cm^2)	4.1±1.9	3.9±1.6
Maxillary sinus medial wall thickness		
Thick ≥ 2mm	2	1
Moderate 1~2mm	10	6
Thin < 1mm	10	9
Inflammation of ipsilateral sinus		
low Lund Mackay score <6	14	8
high Lund Mackay score ≥6	8	8
Septated or multiple mucocoele		
Septation or multiple Mucocoele(-)	14	11
Septation or multiple Mucocoele(+)	8	5
Immediate postoperative antrostomy size(cm^2)	1.9±1.9	2.3±1.2

Three months after the surgery, 24 cases could be categorized as the patent group, 9 cases as the narrow group and 4 cases as the stenotic group.

Allergic rhinitis was diagnosed in 34 cases (89.5%), and 21 cases (55.3%) had polyps in the ipsilateral nasal cavity or sinuses. All the cases had a previous history of a Caldwell-Luc operation, and the mean duration of recurrence was 21 years after the primary surgery. Marsupialization was performed endoscopically in eighteen cases (47.4%), and 20 cases (52.6%) underwent a combined endoscopic - Caldwell-Luc approach. The mean area of the mucocoeles was 4.0 ± 2.1 cm^2. When the thicknesses of the thinnest portion in the medial wall of the mucocoeles were categorized into 3 groups, including the thick group (more than 2 mm), the moderate group (less than 2 mm and more than 1 mm), and the thin group (less than 1 mm), 3 cases (7.9%) belonged to the thick group, 16 cases (42.1%) to the moderate group and 19 cases (50.0%) to the thin group. The mean size of the surgical antrostomy, as measured intraoperatively, was 2.0 ± 1.1 cm^2 (Table 1). Age, gender, allergy, polyp, the interval between previous surgery and the revision

surgery, the size of the immediate postoperative antrostomy and the surgical method did not have any significant effect on the patency of the antrostomy openings at 1 month or 3 months after the surgery ($p > 0.05$, Chi-square test and Kruskal-Wallis test, Table 1, 2).

MMC was applied to 22 cases and normal saline had been applied to the remaining 16 cases. Patent ostia were observed in 86.4%, narrow ostia in 4.5% and stenotic ostia in 9.1% of the MMC group at 1 month after the surgery. In the control group, however, patent ostia were observed in 68.8%, narrow ostia in 18.8%, and stenotic ostia in 12.5% of the MMC group at 1 month after the surgery. The differences were not statistically significant ($p = 0.326$, Chi-square test). However, at 3 months after the surgery, statistical significance was observed between the MMC and control groups ($p = 0.042$, Chi-square test). The MMC group showed patent ostia in 77.3%, narrow ostia in 9.1% and stenotic ostia in the remaining 13.6% at 3 months after the surgery. The control group, however, showed a much lower percentage of cases in the patent group (43.8%) at 3 months after the surgery compared with 68.8% at 1 month after the surgery (Table 2).

An association between the preoperative LM score for the ipsilateral sinuses and the surgical outcome was also evaluated. Sixteen patients (42.1%) had an LM score in the ipsilateral sinuses equal to or more than 6, and 22 patients (57.9%) had a low LM score less than 6. The difference of LM scores didn't reach statistical significance at 1 month after the surgery ($p = 0.878$, Chi-square test). However, statistical significance was observed at 3 months after surgery ($p = 0.042$, Chi-square test). In patients with a high LM score, the incidence of patent ostia decreased dramatically at 3 months after the surgery compared with that at 1 month after the surgery (Table 2).

Concerning the presence of septations or multiple mucocoeles, statistical significance was also found for patency of the opening at 3 months after the surgery. Patients with multiple mucocoeles showed a significantly decreased size of the openings at 3 months after the surgery compared with the patients with only one or non-septated mucocoeles ($p = 0.018$, Chi-square test, Table 2). However, the presence of septations or multiple mucocoeles didn't affect the patency of the openings at 1 month after the surgery ($p = 0.182$, Chi-square test).

DISCUSSION
Mucocoeles are locally expansile, benign, paranasal sinus cystic lesions [14], and they have an osteolytic potential and a mass effect [15]. The mainstay treatment for mucocoeles is surgery, and endoscopic drainage appears to be a reasonable approach [1,14,15]; open approaches may be required for more complicated cases [1].

In this study, we analyzed 38 cases of maxillary sinus mucocoeles that developed after Caldwell-Luc operations; these mucocoeles are also called postoperative maxillary sinus mucocoele or postoperative cheek cyst. The maxillary sinus bony

Table 2. Statistical analysis of the parameters that were associated with the patency of antrostomy.

Parameters	1 month		3 month	
	Percentage*	p-value	Percentage*	p-value
Age(yr)		0.073[†]		0.056[†]
Gender				
Male	72 /17/11	0.362[‡]	50/39/11	0.578[‡]
Female	85/5/10		75/10/15	
Allergy				
Allergy(+)	50/25/25	0.324[‡]	25/50/25	0.245[‡]
Allergy(-)	82/9/9		68/21/11	
Polyp				
Polyp(+)	77/12/11	0.945[‡]	47/41/12	0.071[‡]
Polyp(-)	81/10/9		76/10/14	
Interval between				
prev. surgery and revision(Yrs)		0.127[†]		0.175[†]
Surgical method				
Endoscopic approach	48/25/27	0.489[‡]	25/50/25	0.289[‡]
Combine with Caldwell-Luc approach	83/9/8		67/20/13	
Mucocoele size(cm^2)		0.756[†]		0.221[†]
Maxillary sinus medial wall thickness				
Thick $\geq$ 2mm	75/25/0		50/50/0	
Moderate 1~2mm	64/7/29	0.256[‡]	64/0/36	0.518[‡]
Thin <1mm	100/0/0		75/25/0	
Inflammation of ipsilateral sinus				
low Lund Mackay score <6	82/9/9	0.638[‡]	77/9/14	0.042[‡ §]
high Lund Mackay score $\geq$6	75/13/12		44/44/12	
Septated or multiple mucocoele				
Septation or multiple Mucocoele(-)	88/8/4	0.182[‡]	79/17/4	0.018[‡ §]
Septation or multiple Mucocoele(+)	64/14/22		36/36/28	
Immediate postoperative antrostomy size(cm^2)		0.838[†]		0.433†
MMC application				
MMC(+)	86/5/9	0.326[†]	77/9/14	0.042[‡ §]
MMC(-)	69/19/12		44/44/12	

*   Variables are expressed as the percentage of the patent group/narrowing group/stenotic group.

†   Statistical analyses were performed using the Kruskal-Wallis test

‡   Statistical analyses were performed using Chi-square tests

§   p-value < 0.05

wall was retracted medially and this narrowed the pathway to the middle meatus in the postoperative maxillary sinus mucocoeles. So, we performed surgery that included inferior meatal antrostomy with or without the Caldwell-Luc approach, according to the location and extent of the mucocoeles.

After endoscopic drainage, the antrostomy site is sometimes obstructed, and this causes the recurrent mucocoeles and complications of the surrounding structures. Although the predisposing factors for mucocoele formation have been well identified [15], the risk factors for restenosis of the antrostomy site are still unknown. There are few reports about this phenomenon, and various measures aimed at decreasing the incidence of postoperative stenosis have been tried, including a silicone tube and stent, but these efforts have met with limited success [6,16].

We investigated the clinical factors, including the patients' characteristics and the preoperative CT findings that are associated with stenosis of the antrostomy site for maxillary sinus mucocoeles. In addition, we determined the role of MMC in preventing restenosis of the antrostomy site.

The use of MMC to prevent postoperative scarring has been the focus of several recent studies. MMC, a natural antibiotic derived from *Streptomyces caespitosus*, has been shown to have both antineoplastic and antiproliferative properties. Chung et al. [10] showed that topical MMC applied to the middle meatus for 4 minutes at a concentration of 0.4 mg/mL resulted in fewer adhesions than the control side and it caused no adverse effects. Multiple studies have indicated the efficacy of using MMC in ophthalmologic disorders, and this resulted in minimal postoperative scarring [17,18]. Within otolaryngology, MMC application in endoscopic sinus surgery (ESS) and reconstructive laryngeal surgery has shown decreased adhesion and scar formation, but this remains controversial [9,10,19,20]. MMC has

been shown to maintain the patency of maxillary antrostomies in rabbits while preserving the mucociliary function at 1 month after application of MMC [21]. In another human study, the effect of MMC application after ESS for treating sinusitis was effective at short-term in maintaining the patency of the antrostomy [19].

Postoperative maxillary sinus mucocoele has a different pathophysiology from sinusitis and there is no literature to prove the effectiveness of MMC in the surgical management of mucocoeles. We applied MMC in the study group at a concentration of 0.4 mg/mL for 5 minutes. Our study found no adverse effect from a single topical application. We did not find any correlation between MMC application and antrostomy patency at 1 month after surgery. However, patients who underwent MMC (as opposed to normal saline) application were more likely to have patent antrostomies 3 months after surgery.

In the control group just 43.8% of patients had a patent antrostomy at 3 months compared with 68.8% at 1 month after the surgery. However, in the MMC group, 77.3% of patients, had patent ostia at 3 months, compared with 86% at 1 month after the surgery.

In addition, we could suggest that for the cases with a tendency to develop narrow antrostomy, it is necessary to combine additional procedure such as repeated application of MMC at the antrostomy site during visits to the outpatient clinic. More studies about this procedure need to be done.

Other risk factors were identified in this study. The severity of paranasal sinusitis, which was determined by the preoperative LM score, affected the patency of the antrostomy site. Mucosal swelling and inflammation may prompt bony remodeling and mucosal fibrosis. In addition, septation or multiplicity of maxillary sinus mucocoeles has significant correlation with stenosis of the antrostomy. One possible reason for this result is that the tendency for new bone formation can cause septation and multiple mucocoeles; further, it can cause bony obstruction of the antrostomy site. Nakanishi et al. reported similar results on the CT findings of frontal sinus mucocoeles [6]. Although there was no statistic significance, they found a tendency for a better outcome in the cases of solitary mucocoele with the membranous type of obstruction, but not the bony type [6].

As stated Weber et al. [7], a wide opening of the antrostomy site does not guarantee the patency after surgery, and there was no significant correlation between the immediate opening size and the postoperative patency in the present study.

There were some limitations to the study. One was the small sample size we employed to evaluate the effect of MMC. As shown in this study, however, we were able to demonstrate the pilot results concerning the efficacy of MMC and additional studies are required to confirm this. The other limitation of this study was the short-term follow-up period. The postoperative maxillary sinus mucocoeles were generally reported as long-term sequels of more than 10 years after a

Caldwell-Luc operation. Therefore, long-term follow-up is needed to completely elucidate the effect of MMC and the other parameters.

In conclusion, we analyzed the clinical factors that were associated with stenosis of the antrostomy site for maxillary sinus mucocoeles. MMC application may have a favorable effect on the maintenance of ostia patency after inferior meatal antrostomy for treating postoperative maxillary mucocoeles. In addition, the patients with concurrent inflammation in the ipsilateral sinuses or septation of mucocoeles should be managed more aggresively intra- and / or postoperatively, as they have a higher chance of restenosis and / or recurrence of the mucocoele.

REFERENCES

1. Caylakli F, Yavuz H, Cagici AC, Ozluoglu LN. Endoscopic sinus surgery for maxillary sinus mucocoeles. Head Face Med 2006; 2: 29.
2. Hasegawa M, Saito Y, Watanabe I, Kern EB. Postoperative mucocoeles of the maxillary sinus. Rhinology 1979; 17: 253-256.
3. Stiernberg CM, Bailey BJ, Calhoun KH, Quinn FB. Management of invasive frontoethmoidal sinus mucocoeles. Arch Otolaryngol Head Neck Surg 1986; 112: 1060-1063.
4. Saito T, Ikeda T, Kono Y, Ohtsubo T, Noda I, Saito H. Implications of endoscopic endonasal surgery for the treatment of postoperative maxillary mucocoeles. ORL J Otorhinolaryngol Relat Spec 2000; 62: 43-48.
5. Ikeda K, Takahashi C, Oshima T, et al. Endonasal endoscopic marsupialization of paranasal sinus mucocoeles. Am J Rhinol 2000; 14: 107-111.
6. Nakanishi M, Haruna S, Wada K, Otori N, Moriyama H. Outcomes of frontal mucocoele marsupialization: endonasal and external approaches. Am J Rhinol 2004; 18: 247-252.
7. Weber R, Keerl R, Draf W. [Endonasal endoscopic surgery of maxillary sinus mucocoeles after Caldwell-Luc operation]. Laryngorhinootologie 2000; 79: 532-535.
8. Yoshizaki T, Watanabe A. [Endoscopic endonasal sinus surgery for post-operative maxillary cysts]. Nippon Jibiinkoka Gakkai Kaiho 2002; 105: 931-936.
9. Anand VK, Tabaee A, Kacker A, Newman JG, Huang C. The role of mitomycin C in preventing synechia and stenosis after endoscopic sinus surgery. Am J Rhinol 2004; 18: 311-314.
10. Chung JH, Cosenza MJ, Rahbar R, Metson RB. Mitomycin C for the prevention of adhesion formation after endoscopic sinus surgery: a randomized, controlled study. Otolaryngol Head Neck Surg 2002; 126: 468-474.
11. Hu D, Sires BS, Tong DC, Royack GA, Oda D. Effect of brief exposure to mitomycin C on cultured human nasal mucosa fibroblasts. Ophthal Plast Reconstr Surg 2000; 16: 119-125.
12. Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz G, McGorray S. Prolonged localized tissue effects from 5-minute exposures to fluorouracil and mitomycin C. Arch Ophthalmol 1993; 111: 263-267.
13. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngol Head Neck Surg 1997; 117: S35-40.
14. Marks SC, Latoni JD, Mathog RH. Mucocoeles of the maxillary sinus. Otolaryngol Head Neck Surg 1997; 117: 18-21.
15. Serrano E, Klossek JM, Percodani J, Yardeni E, Dufour X. Surgical management of paranasal sinus mucocoeles: a long-term study of 60 cases. Otolaryngol Head Neck Surg 2004; 131: 133-140.
16. Orlandi RR, Kennedy DW. Revision endoscopic frontal sinus surgery. Otolaryngol Clin North Am 2001; 34: 77-90.
17. Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. Ophthalmology 1991; 98: 317-321.

18. Caliskan S, Orhan M, Irkec M. Intraoperative and postoperative use of mitomycin-C in the treatment of primary pterygium. Ophthalmic Surg Lasers 1996; 27: 600-604.
19. Kim ST, Gang IG, Cha HE, Ha JS, Chung YS. Effect of mitomycin C on the size of antrostomy after endoscopic sinus surgery. Ann Otol Rhinol Laryngol 2006; 115: 673-678.
20. Chan KO, Gervais M, Tsaparas Y, Genoway KA, Manarey C, Javer AR. Effectiveness of intraoperative mitomycin C in maintaining the patency of a frontal sinusotomy: a preliminary report of a double-blind randomized placebo-controlled trial. Am J Rhinol 2006; 20: 295-299.
21. Rahal A, Peloquin L, Ahmarani C. Mitomycin C in sinus surgery: preliminary results in a rabbit model. J Otolaryngol 2001; 30: 1-5.

Hun-Jong Dhong, MD, PhD.
Department of Otorhinolaryngology -
Head and Neck Surgery Samsung Medical
Center, Sungkyunkwan University School of
Medicine
50 Irwon-dong, Gangnam-gu
Seoul
Korea 135-710

Tel: +82-2-3410-3573
Fax: +82-2-3410-3879
E-mail: hjdhong@smc.samsung.co.kr