

## 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<sup>(1)</sup>. 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<sup>(2)</sup>. 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<sup>(3)</sup>. 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<sup>(4)</sup>.

Marsupialization and antrostomy of the sinus by the intranasal endoscopic approach has been advocated as an initial treatment modality<sup>(1,5)</sup>.

However, stenosis or narrowing of the marsupialization site after surgery is not infrequent and can potentially lead to recurrent disease<sup>(6)</sup>. 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<sup>(7,8)</sup>.

Mytomycin C (MMC) has recently been used to reduce the stenosis and scar formation after surgery; many ophthalmologic and otorhinolaryngologic studies have showed its favorable effect<sup>(9,10)</sup>. MMC was initially isolated from the *Streptomyces caespitosus* strain of actinomycetes 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 properties<sup>(9,10)</sup>. 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 cytotoxic effect at higher concentrations<sup>(11,12)</sup>.

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 mucocoeles 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)<sup>(13)</sup>.

### 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 pled-

get 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).

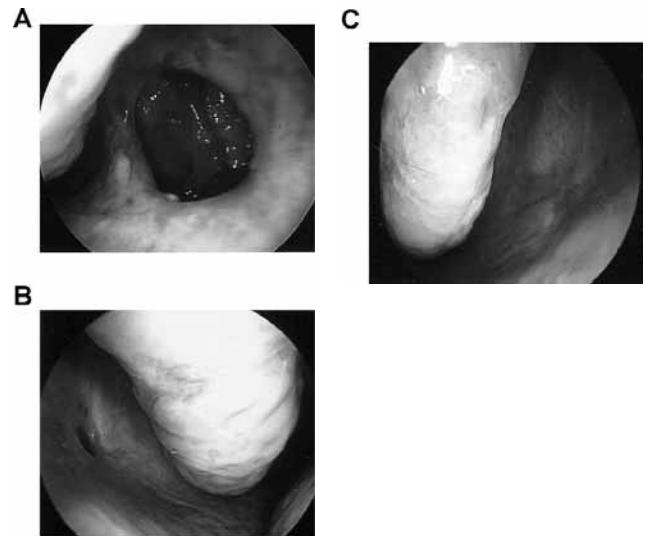


Figure 1. Patency of the antrostomy site via a 30° endoscope. (A) patent group; (B) narrow group; (C) stenotic group.

### 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  $\chi^2$ -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 <sup>2</sup> )	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 <sup>2</sup> )	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  $4.0 \pm 2.1$  cm<sup>2</sup>. 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 intra operatively, was  $2.0 \pm 1.1$  cm<sup>2</sup> (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<sup>(14)</sup>, and they have an osteolytic potential and a mass effect<sup>(15)</sup>. The mainstay treatment for mucocoeles is surgery, and endoscopic drainage appears to be a reasonable approach<sup>(1,14,15)</sup>; open approaches may be required for more complicated cases<sup>(1)</sup>.

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

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

<sup>†</sup> Statistical analyses were performed using the Kruskal-Wallis test

<sup>‡</sup> Statistical analyses were performed using Chi-square tests

<sup>§</sup> 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<sup>(15)</sup>, 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<sup>(6,16)</sup>.

We investigated the clinical factors, including the patients' characteristics and the preoperative CT findings that are associ-

ated 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.<sup>(10)</sup> 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<sup>(17,18)</sup>. Within otolaryngology, MMC application in endoscopic sinus surgery (ESS) and reconstructive laryngeal surgery has shown decreased adhesion and scar formation, but this remains controversial<sup>(9,10,19,20)</sup>. MMC has

been shown to maintain the patency of maxillary anrostomies in rabbits while preserving the mucociliary function at 1 month after application of MMC<sup>(21)</sup>. 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 anrostomy<sup>(19)</sup>.

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 anrostomy patency at 1 month after surgery. However, patients who underwent MMC (as opposed to normal saline) application were more likely to have patent anrostomies 3 months after surgery.

In the control group just 43.8% of patients had a patent anrostomy 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 anrostomy, it is necessary to combine additional procedure such as repeated application of MMC at the anrostomy 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 anrostomy 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 anrostomy. 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 anrostomy site. Nakanishi et al. reported similar results on the CT findings of frontal sinus mucocoeles<sup>(6)</sup>. 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<sup>(6)</sup>.

As stated Weber et al.<sup>(7)</sup>, a wide opening of the anrostomy 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 anrostomy site for maxillary sinus mucocoeles. MMC application may have a favorable effect on the maintenance of ostia patency after inferior meatal anrostomy for treating postoperative maxillary mucocoeles. In addition, the patients with concurrent inflammation in the ipsilateral sinuses or septation of mucocoeles should be managed more aggressively intra- and / or postoperatively, as they have a higher chance of restenosis and / or recurrence of the mucocoele.

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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](mailto:hjdhong@smc.samsung.co.kr)