Mitomycin C for the prevention of adhesion formation after endoscopic sinus surgery: A randomized, controlled study

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OBJECTIVE: **Mitomycin C (MMC) is an antineoplastic agent that has been shown to decrease scar tissue after ophthalmologic surgery. Our goal was to determine whether the application of MMC at the conclusion of sinus surgery decreases the incidence of postoperative adhesion formation.**

METHODS: **At the completion of endoscopic sinus surgery in 55 patients, a cotton pledget saturated with 1 mL of 0.4 mg/mL MMC was placed for 4 minutes in the right or left middle meatus and a similar saline-soaked pledget was placed on the opposite side. Patients were examined postoperatively by a masked observer for the presence of synechiae and mucosal changes.**

RESULTS: **Postoperative adhesions were observed in 16 patients (29%) with a mean follow-up of 4.1 months. These adhesions were bilateral in 6 patients (10.9%) and unilateral in 10 patients (18%). Unilateral adhesions were observed on only 2 sides (3.6%) treated with MMC and 8 controls (14.5%) (*P* = 0.058). No adverse effects were observed.**

CONCLUSIONS: **MMC was found to be safe to use during sinus surgery, and it may reduce the incidence of postoperative adhesions at the dosage used in this study.**

SIGNIFICANCE: **Because of the observed trend toward decreased synechiae formation with MMC application, further trials using higher concentrations and application times are warranted.** (Otolaryngol Head Neck Surg 2002;126:468-74.)

Despite the established efficacy of endoscopic sinus surgery for the treatment of chronic rhinosinusitis, recurrent symptoms develop in 7.6% to 38% of patients, necessitating revision surgery.[1,2] Recurrent mucosal disease and anatomic obstruction are 2 commonly cited causes of failed endoscopic sinus surgery.[3] Among the anatomic causes, ostial stenosis and adhesion formation appear to be most frequent.[3,4] Ramadan[3] noted that 56% of patients undergoing revision endoscopic sinus surgery had adhesions, 27% had maxillary sinus ostium stenosis, and 25% had frontal sinus ostium stenosis. Furthermore, in a review of 182 patients who underwent endoscopic sinus surgery, scarring of the maxillary antrostomy and ethmoid region was the only endoscopic finding found to correspond to poor symptoms outcome.[4]

Mitomycin C (MMC) is a topical agent that has demonstrated clinical efficacy in the reduction of clinical scar formation.[5] Initially isolated from the *Streptomyces caespitosus* strain of actinomyces for its antibacterial properties, MMC was used as a chemotherapeutic agent because of its ability to cross-link DNA and inhibit cellular mitosis. Studies of MMC on cultured fibroblasts have demonstrated an antiproliferative effect at concentrations of 0.04 mg/mL and cytocidal effects at higher concentrations.[6,7] A single 5-minute topical application has a measurable effect on cell proliferation and cellular morphology for up to 36 hours.[6] Recently, Hu et al[7] examined the effect of MMC on cultured human nasal mucosa and found that brief exposure to MMC inhibits fibroblast proliferation and increases fibroblast apoptosis.

MMC has been used extensively to reduce scar formation associated with ophthalmologic surgery.

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Table 1. Incidence of adhesion formation and characteristics in 55 patients who underwent endoscopic sinus surgery

Variable	Patients (n (%))	Adhesions (n)	No adhesions(n)	*P* value
Female	28 (51)	11	17	0.14
Asthma	19 (34.5)	6	13	0.99
Allergy	23 (41.8)	7	16	0.99
Aspirin triad	3 (5.5)	0	3	0.54
Smoking	5 (9.1)	2	3	0.64
Polyps	31 (56.4)	10	21	0.99
Prior surgery	29 (52.7)	8	21	0.76

Table 2. Operative procedures performed and the occurrence of adhesions in 55 patients

Procedure	Adhesions (No. of sides)	No Adhesions (No. of sides)	Total	*P* value
Maxillary antrostomy	21	73	94	0.34
Ethmoidectomy	22	80	102	0.99
Sphenoidotomy	15	57	72	0.81
Frontal sinusotomy	15	64	79	0.30
Septoplasty*	7	24	31	0.10
Middle turbinate reduction	9	28	37	0.33
Total	89	326	415	

*The side of septoplasty is listed as the side on which the mucosal incision was made.

Topical MMC has reduced the recurrence rate after ptyergium surgery from 89% to 2.3%.[8] It is commonly applied during glaucoma surgery, where its use has resulted in a greater than 90% patency rate for the trabeculectomy drainage site.[9] The success of MMC at reducing scar formation during these procedures has been attributed to its ability to suppress fibrosis and vascular ingrowth.[5] Ophthalmologists have also reported the use of MMC during strabismus surgery,[10] optic nerve decompression,[11] and dacryocystorhinostomy.[5]

Recent studies have also examined the efficacy of topical MMC for otolaryngologic procedures. Topical application of MMC inhibited laryngotracheal stenosis in the canine model[12,13] and may be useful in the prevention and treatment of similar stenosis in patients.[14] Other studies have shown that topical MMC use prolonged the patency of laser myringotomies in chicks[15] and rats[16] and maxillary antrostomies in rabbits.[17] In a study on the effect of MMC on sinus mucosa, Ingrams et al[17] found that a 5-minute application of 0.4 mg/mL to rabbit maxillary antrostomies delayed their closure from 1 to 4 weeks. At higher concentrations of 1.0 mg/mL, ciliary appearance and function returned to normal within 2 weeks and mucosal surfaces were able to reepithelialize normally.

The purpose of this study was to examine the clinical effects of MMC applied to sinonasal mucosa at the conclusion of sinus surgery and to determine whether such an application alters the incidence of postoperative adhesion formation.

PATIENTS AND METHODS

The study population consisted of 55 patients (28 women and 27 men) ranging in age from 21 to 75 years (mean 44.5 years) who underwent endoscopic sinus surgery for chronic rhinosinusitis (Table 1). The extent of sinus disease was determined with a previously described sinus computed tomography (CT) staging system.[18] A total of 415 separate sinus procedures were performed (Table 2). All surgeries were performed under general anesthesia by the senior author (R.M.) at the Massachusetts Eye and Ear Infirmary during a 1-year period (March 1, 2000, through February 28, 2001). Thirty-one patients had undergone prior endoscopic sinus surgery.

Table 3. Location of postoperative adhesions in 55 patients treated with mitomycin C at the conclusion of sinus surgery

		Side of adhesion		
Location of adhesions	Patients (n (%))	MMC-treated side (n (%))	Control side (n (%))	*P* value
Unilateral	10 (18)	2 (3.6)	8 (14.5)	0.058
Bilateral	6 (11)			
None	39 (71)			
Total	55 (100)			

Table 4. Cross-sectional analysis of mitomycin C application on sinonasal mucosal appearance

	Mean*			
Parameter	1 wk	2 wk	1 mo	2 mo
Mucosal hypertrophy	–0.36 ± 0.79 (P = 0.043)	0.10 ± 0.88 (P=0.726)	–0.18 ± 0.98 (P = 0.553)	–1.0 ± 1.41 (P = 0.500)
Polypoid changes	–0.50 ± 0.79 (P = 0.0152)	–0.18 ±1.08 (P = 0.588)	0 ± 1.35 (P = 1.0)	–0.025 ± 0.5 (P = 0.391)

The mean (*) differences between treatment side and control side were calculated as treatment minus control; therefore, a negative value indicates better outcome in the treatment side. *P* values were calculated using the Student's *t* test.

Table 5. Side of 22 adhesions observed after endoscopic sinus surgery

	Presence of adhesions (n)			
Side	Mitomycin C	Control	Total	*P* value
Right	4	7	11	0.083
Left	4	7	11	0.257
Total	8	14	22	0.058

At the start of surgery, the nasal cavities were sprayed with a topical decongestant (0.05% oxymetazoline hydrochloride) and packed with neurosurgical cottonoid soaked in 4 mL of 4% cocaine solution. Submucosal injections of 1% lidocaine with 1:100,000 epinephrine were administered to the surgical site. The amount and location of sinus disease present determined the extent of sinus surgery performed for each patient. When septal deformity or spur limited access to the osteomeatal complex, an endoscopic septoplasty was performed.

At the completion of the procedure, a neurosurgical cottonoid saturated with 1 mL of MMC in a concentration of 0.4 mg/mL was placed in either the right or left middle meatus (Fig 1) according to a randomized schedule. After a period of 4 minutes, the cottonoid was removed and the nasal cavity was irrigated with 60 mL of sterile normal saline. Each patient served as his or her own control with a similar saline-soaked cottonoid placed on the corresponding opposite side for 4 minutes.

At the conclusion of the procedure, the nasal cavities were packed with a finger cot made from the finger of a surgical glove filled with gauze and coated with bacitracin ointment. This packing was removed the morning after surgery. All patients were discharged with a 10-day course of antistaphylococcal antibiotic and instructions for

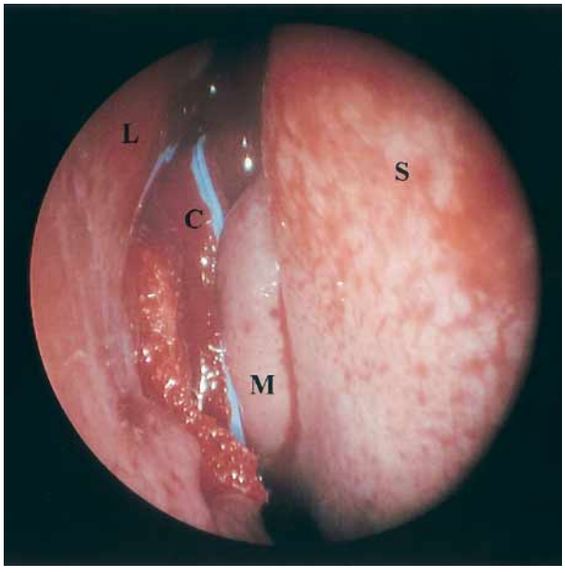

Fig 1. Intraoperative view of mitomycin C application. A neurosurgical cottonoid (C) saturated with mitomycin C is placed in the middle meatus (S, septum; L, lateral nasal wall; M, middle turbinate).

twice-a-day nasal irrigations with warm saline using a bulb syringe. No oral or topical nasal steroids were administered.

Patients were examined at 1 week and at least 1 month after surgery by one of the authors (J.C. or M.C.), who were blinded to the side of MMC application and served as a masked observer. Additional examinations occurred at 2 weeks, 2 months, and/or 6 months after surgery depending on the need to clean debris and the extent of the patient's disease. In each case, the nasal cavities were examined with an endoscope after the application of 0.5% lidocaine hydrochloride and 0.5% phenylephrine hydrochloride spray. Both sides of the nasal cavity were examined for synechiae and graded for the presence of mucosal hypertrophy and polypoid changes on a scale of 0 to 3 (0, none; 1, minimal; 2, moderate; 3, severe).

Statistical analysis was performed using the Student's *t* test and McNemar's test. All patients gave informed consent according to a protocol approved by the Human Studies Committee of the Massachusetts Eye and Ear Infirmary.

RESULTS

A total of 22 adhesions were identified in 16 of 55 operated patients, for an occurrence rate of 29%. All adhesions occurred within 2 months of surgery. Ten patients had unilateral adhesions and 6 patients had bilateral adhesions (Table 3). Of the 10 unilateral adhesions, 2 developed on the MMC-treated side and 8 developed on the control side ($P = 0.058$). One week after surgery, a decrease in mucosal hypertrophy ($P = 0.0152$) and polypoid mucosal changes ($P = 0.043$) was observed on the MMC-treated side (Table 4). However, these differences did not maintain their statistical significance at subsequent postoperative visits.

All adhesions were noted to occur within 2 months of surgery. Five (23%) of 22 adhesions were extensive enough to be rated as "severe." Three of these adhesions occurred on the control side, and 2 occurred bilaterally in the same patient. The latter patient was the only one of the 5 to develop recurrent symptoms of rhinosinusitis that required antibiotic therapy. Four adhesions (18%) were rated as "moderate," and 13 (59%) were rated as "mild."

Recurrent symptoms of rhinosinusitis requiring antibiotic therapy occurred in 5 (31%) of 16 patients who developed postoperative adhesions and 12 (31%) of the 39 patients who had no adhesions. No patients have required further sinus surgery, with a mean follow-up of 4.1 months (range 1 to 15.4 months). Neither the occurrence of adhesions nor the incidence of recurrent sinus infections was found to correlate with the extent of disease determined by preoperative CT stage: stage I, 3 patients; stage II, 12 patients; stage III, 18 patients; and stage IV, 22 patients.

Patient comorbidities, including asthma, environmental allergy, and smoking, were not found to be independent predictors of postoperative adhesion formation (Table 1). The presence of adhesions also did not correlate with patient gender, the presence of nasal polyps, or a history of previous sinus surgery. Adhesions occurred with equal prevalence on the right and left side (Table 5) and were not related to the surgical procedure performed on each side (Table 2).

No systemic or local adverse effects from topical intranasal MMC application were observed. Four patients (7.3%) developed postoperative epis-

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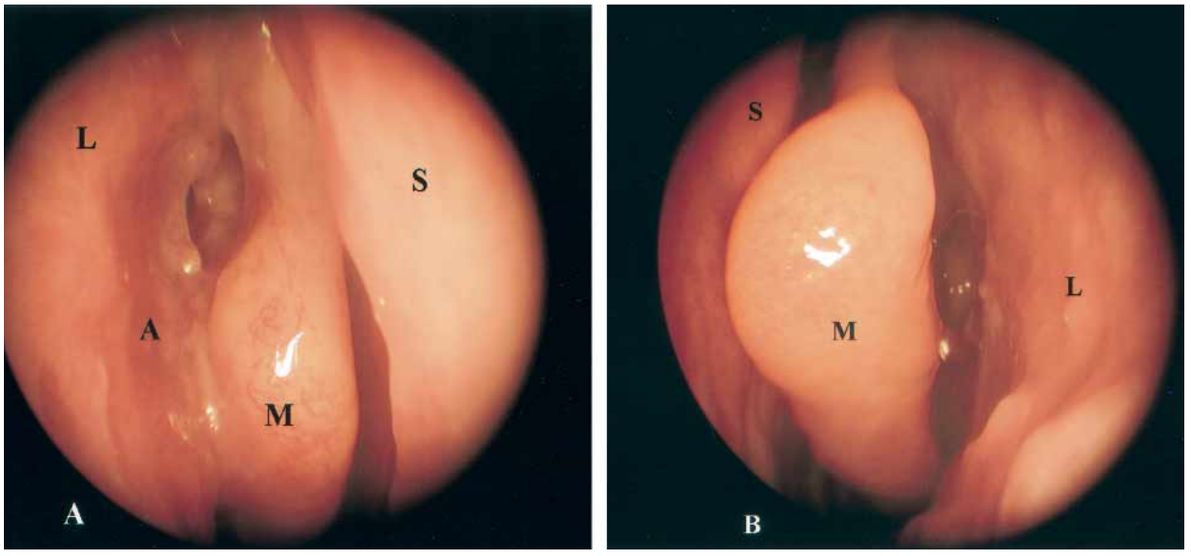

Fig 2. Endoscopic view of the control, right side **(A)** and the mitomycin C–treated, left side **(B)** 2 months after sinus surgery. An adhesion (A) is noted in the right middle meatus (L, lateral nasal wall; S, septum; M, middle turbinate).

taxis within 1 week of surgery. In 2 patients, bleeding occurred on the side of MMC application. The precise site of bleeding was not observed, and the epistaxis was controlled with anterior nasal packing. The 2 additional patients developed bleeding from the control side. The site of bleeding was thought to be the remnant of a resected middle turbinate. In both cases, the bleeding did not respond to nasal packing and required endoscopic control in the operating room.

DISCUSSION

When injured mucosal surfaces are in close proximity at the completion of sinonasal surgery, regenerating epithelium and fibrous tissue may grow between these surfaces to create an adhesion. If the adhesion is of sufficient size and proper location, it can lead to reobstruction of an adjacent sinus ostium and recurrent sinus infection. Attempts to limit such adhesion formation with anatomic barriers have been met with limited success.[19] Because of the known antifibroblastic properties of MMC, a study was designed to measure the effects of this agent on adhesion formation associated with sinus surgery.

The results of this study suggest that topical application of MMC to the middle meatus region at the conclusion of sinus surgery may decrease the incidence of postoperative adhesions. Among the 16 patients who developed adhesions, only 2 patients developed them solely on the MMC-treated site. Any difference in synechiae formation between the MMC-treated and control sides is likely attributable to the MMC application, because each patient served as his or her own control. The side of MMC application was randomized, and the operative procedures performed on each side were statistically comparable. Furthermore, the postoperative results were assessed by a clinician who was blinded as to the side of MMC application.

The sides treated with MMC had significantly less mucosal hypertrophy and polypoid changes at 1 week than did the control sides. The clinical significance of these findings is not known; however, they may reflect the ability of MMC to affect wound healing by inhibiting fibroblasts that play an active role in the early stages of inflammation. In any event, these mucosal changes were not observed at subsequent postoperative examinations.

The recurrence rate of rhinosinusitis was similar among those patients who developed adhesions and those who did not, suggesting that the observed adhesions may not have been extensive enough to produce ostial obstruction. This possibility is supported by the fact that less than one third of the adhesions was rated as "severe" by the masked observer. In addition, no patients in the study population required additional sinus surgery.

Although the initial results of this study are promising, there may be several reasons why the efficacy of MMC at decreasing adhesion formation never reached clinical significance. First, the size of the study population and the incidence of postoperative adhesions may be too small to reveal a definitive treatment effect. Second, short-term exposure to MMC has been shown to inhibit the growth of fibroblasts, yet they are still capable of contributing to other critical aspects of wound healing.[20] Furthermore, one study showed that 70% of fibroblasts were still alive after a 5-minute exposure in 0.4 mg/mL MMC and exhibited evidence of regrowth within 2 to 3 days.[7] Adhesions spanning mucosal surfaces within the middle meatus typically develop over a 1- to 2-week period and may take as long as 2 months.

The technique of MMC delivery during nasal surgery may also have an important impact on its clinical efficacy. Ophthalmologists have traditionally applied MMC to the ocular surface at the conclusion of glaucoma filtration surgery (trabeculectomy) in a dosage of 0.4 mg/mL for 4 minutes.[13,17] A similar concentration and application time was used in this study; however, it is possible that the actual concentration of MMC was diluted because of bleeding from the adjacent mucosal surfaces and that a concentration greater than 0.4 mg/mL would be more effective for sinonasal surgery. Some ophthalmologists have also suggested that the increased vascularity of nasal mucosa may reduce the efficacy of MMC application during dacryocystorhinostomy compared with trabeculectomy.[7]

Our study found no adverse effects from a one-time topical application of MMC. Nevertheless, complications with adjunctive MMC application have been reported in the ophthalmology literature and included glaucoma, corneal ulcers and perforation, cataracts, scleral calcifications, and endophthalmitis.[5] It should be noted, however, that these complications have occurred from cumulative use in patients taking MMC as eye drops for several days. No complications have been reported with one-time topical intraoperative use.

CONCLUSION

Adhesions remain one of the most common causes of recurrent symptoms necessitating revision sinus surgery. The application of MMC to exposed mucosal surfaces at the conclusion of sinus surgery may reduce the incidence of postoperative adhesion formation. Further investigation into different MMC dosages and application techniques is warranted.

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REFERENCES

1. Smith LF, Brindley PC. Indications, evaluation, complications, and results of functional endoscopic sinus surgery in 200 patients. Otolaryngol Head Neck Surg 1993; 108:688-96.
2. Matthews BL, Smith LE, Jones RJ, et al. Endoscopic sinus surgery: outcome in 155 cases. Otolaryngol Head Neck Surg 1991;104:244-6.
3. Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. Laryngoscope 1999;109:27-9.
4. Chambers DW, Davis WE, Cook PR, et al. Long-term outcome analysis of functional endoscopic sinus surgery: correlation of symptoms with endoscopic examination findings and potential prognostic variables. Laryngoscope 1997;107:504-10.
5. Kao SCS, Liao CL, Tseng JHS, et al. Dacryocystorhinostomy with intraoperative mitomycin C. Ophthalmology 1996;104:86-91.
6. Khaw PT, Doyle JW, Sherwood MB, et al. Prolonged localized tissue effects from 5-minute exposures to fluorouracil and mitomycin C. Arch Ophthalmol 1993; 111:263-7.
7. Hu D, Sires BS, Tong DC, et al. Effect of brief exposure to mitomycin C on cultured human nasal mucosa fibroblasts. Ophthal Plast Reconstr Surg 2000;16:119-25.
8. Singh G, Wilson MR, Foster CS. Mitomycin eye drops as treatment for pterygium. Ophthalmology 1988;95: 813-21.
9. Chen CW, Huang HT, Blair JS, et al. Trabeculectomy with simultaneous topical application of mitomycin C in refractory glaucoma. J Ocul Pharmacol 1990;6:175-82.
10. Urban RC Jr, Kayfman LM. Mitomycin in the treatment of hypertrophic conjunctival scars after strabismus surgery. J Pediatr Ophthalmol Strabismus 1994;31:96-8.
11. Spoor TC, McHenry JG, Shin DH, et al. Long-term results using adjunctive mitomycin C in optic nerve

sheath decompression for pseudotumor cerebri. Ophthalmology 1995;102:2024-8.
12. Eliasher R, Eliachar I, Esclamado R, et al. Can topical mitomycin prevent laryngotracheal stenosis? Laryngoscope 1999;109:1594-600.
13. Spector JE, Werkhaven JA, Spector NC, et al. Preservation of function and histologic appearance in the injured glottis with topical mitomycin C. Laryngoscope 1999;109(7 Pt 1):1125-9.
14. Rahbar R, Shapshay SM, Healy GB. Mitomycin: effects on laryngeal and tracheal stenosis, benefits, and complications. Ann Otol Rhinol Laryngol 2001;110:1-6.
15. Estrem SA, VanLeeuwen RN. Use of mitomycin C for maintaining myringotomy patency. Otolaryngol Head Neck Surg 2000;122:8-10.
16. Estrem SA, Batra PS. Preventing myringotomy closure with topical mitomycin C in rats. Otolaryngol Head Neck Surg 1999;120:794-8.
17. Ingrams DR, Volk MS, Biesman BS, et al. Sinus surgery: does mitomycin C reduce stenosis? Laryngoscope 1998;108:883-6.
18. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otlaryngol Head Neck Surg 1997;117(Pt 2):S35-40.
19. Tom LWC, Palasti S, Potsic WP, et al. The effects of gelatin film stents in the middle meatus. Am J Rhinol 1997;?:229-32.
20. Occleston NL, Daniels JT, Tarnuzzer RW, et al. Single exposures to antiproliferatives: long-term effects on ocular fibroblast wound-healing behavior. Invest Ophthalmol Vis Sci 1997;38:1998-2007.