Effectiveness of intraoperative mitomycin C in maintaining the patency of a frontal sinusotomy: A preliminary report of a double-blind randomized placebo-controlled trial

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ABSTRACT

Background: *Postoperative scarring in the frontal recess is the most common cause of iatrogenic frontal sinusitis. Topical mitomycin-C (MMC) is an antifibroblastic agent that has been shown to reduce clinical scarring. This is a preliminary report of a double-blind, randomized, placebo-controlled trial using MMC to determine its effectiveness in reducing frontal recess stenosis after frontal sinusotomy.*

Methods: *All patients with chronic rhinosinusitis undergoing primary or revision bilateral image-guided endoscopic sinus surgery were enrolled. Patients requiring frontal sinus stents and those with allergic fungal sinusitis were excluded. After completion of the frontal sinusotomy, dimensions of the frontal recess were measured using curved Frazer suction diameters. A neuropattie soaked in 0.5 mg/mL of MMC was then placed into one frontal recess for 4 minutes in a randomized manner. A saline control was used for the other side. The primary surgeon was blinded to the medicated side intraoperatively and throughout the follow-up period. Measurements of the frontal recess were repeated at 1, 3, and 6 months.*

Results: *There was no difference in the degree of frontal recess stenosis between the MMC and control sides at 1, 3, and 6 months postoperatively for both primary and revision cases.*

Conclusion: *One-time intraoperative topical MMC is not effective in reducing postoperative frontal recess stenosis in both primary and revision cases.*

(Am J Rhinol 20, 295–299, 2006; doi: 10.2500/ajr.2006.20.2860)

Functional endoscopic sinus surgery (FESS) has been shown to be effective in treating chronic sinusitis in 98.4% of patients.[1] However, failure of FESS is not uncommon and Ramadan et al.[2] have shown that 56% of patients requiring revision surgery had adhesions and 25% had frontal recess stenosis. The complex anatomy and narrow dimensions of the frontal recess make endoscopic frontal sinusotomy (FS) the most difficult aspect of FESS. Even after apparently successful endoscopic FSs using mucosal preservation techniques, postoperative scarring in the frontal recess still can occur and lead to delayed failure.

Mitomycin C (MMC) is an antineoplastic-aminoglycoside antibiotic isolated from *Streptomyces caespitosus*. It causes cross-linking of DNA and inhibits cellular mitosis and has been shown to have antiproliferative effects on cultured fibroblasts. Clinically, it has been shown to reduce scar formation.[3] Topical MMC has been shown to reduce postoperative scarring after pterygium[4] and glaucoma surgery.[5] It has been shown to reduce laryngotracheal restenosis in both the canine model as well as in humans.[6,7] Within the field of rhinology, it has been shown to maintain the patency of maxillary antrostomies in rabbits while preserving mucociliary function.[8,9] Chung *et al.* 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 caused no adverse effects.[10] This is a preliminary report of a double-blind randomized placebo-controlled trial using MMC to determine its effectiveness in keeping FSs patent.

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METHODS

Patients were diagnosed to have chronic rhinosinusitis based on the guidelines from the AAO Taskforce.[11] A three-dimensional Instatrak CT scan of the sinuses was obtained in all patients. The demographics of patients with chronic rhinosinusitis who had failed maximal medical therapy undergoing primary or revision bilateral image-guided endoscopic FSs were collected. Exclusion criteria included cases with allergic fungal sinusitis and patients who required the placement of frontal sinus stents intraoperatively. It was felt that postoperative measurements of the FSs in these cases would be unreliable and sometimes impossible.

All surgeries were performed under general anesthesia. The nasal cavities first were packed with neuropatties soaked in 0.05% oxymetazoline hydrochloride for 10 minutes. The anterior buttress region was injected with 1% lidocaine with 1:100,000 epinephrine. The extent of surgery was based on the CT scans and the intraoperative findings. Surgery was performed using the Messerklinger technique. Maxillary antrostomies, followed by anterior and posterior ethmoidectomies, were performed first. If there was CT or endoscopic evidence of sphenoid disease, a transethmoid sphenoidotomy was performed. The skull base was then followed anteriorly until the frontal recess was reached. The frontal recess was dissected with mucosal preservation techniques as described by Kuhn and Javer.[12] Meticulous removal of all bony shelves, scar bands, and agger nasi cells was performed until a clean frontal recess was obtained. None of the bony shelves or cell caps were pushed aside or left intact in the frontal recess. Skull base bone exposure was minimal to nonexistent with metic-

ulous removal of all obstructive cell caps and preservation of mucous membrane. In all cases the internal frontal sinus ostium was visualized with a 70° endoscope. All patients that had a frontal ostium that was scarred and required drilling or extensive dissection with loss of a significant amount of mucous membrane were stented either with silastic sheets rolled into a stent or with appropriately sized pediatric biliary t-tubes. Because the frontal sinus ostium in these patients would not be visualized postoperatively, they were excluded from the study.

After completion of both FSs, dimensions of the frontal ostium were measured using a curved Frazer 8 suction with direct visualization using a reverse 70° endoscope (Fig. 1). The anterior–posterior diameter (D_{AP}) and transverse diameters (D_T) were noted in terms of suction diameters. Neuropatties soaked in 0.5 mg/mL of MMC were then placed into one frontal recess for 4 minutes in a randomized manner (coin flip; Fig. 2). A saline control was used for the other side. All measurements were done by the senior surgeon (A.R.J.) intraoperatively and throughout the follow-up period. Both the primary surgeon (A.R.J.) and the patients were blinded. Follow-up visits were scheduled at 1, 3, and 6 months. At each visit, nasal debridement was performed meticulously and measurements of the frontal ostium were taken. If the internal frontal ostium was not visualized, measurements of the narrowest aspect of the frontal sinus outflow tract were taken. A pediatric or adult 70° endoscope was used to visualize the frontal recess in the office. The D_{AP} and D_T of the frontal ostium were measured using a variety of suctions depending on patient comfort (Fig. 3). The suctions used were a size 8 Frazer (diameter, 2.67 mm), a size 5 Frazer (diameter, 1.67 mm), and a Van Alyea canula (diameter, 2 mm). The cross-sectional area (CSA) of the frontal sinus ostia was calculated using the formula for an ellipse ($\pi \times D_{AP}/2 \times D_T/2$). A

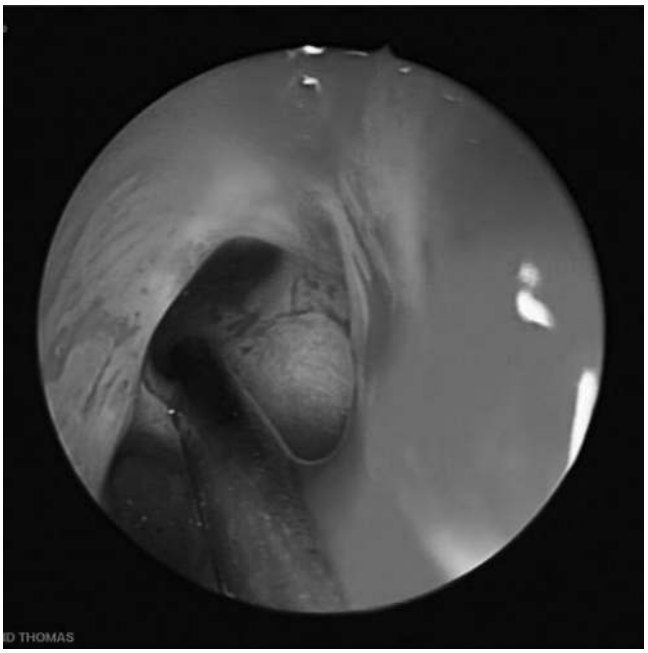

Figure 1. *Intraoperative measurement of the frontal ostium with the curved Frazer 8 suction.*

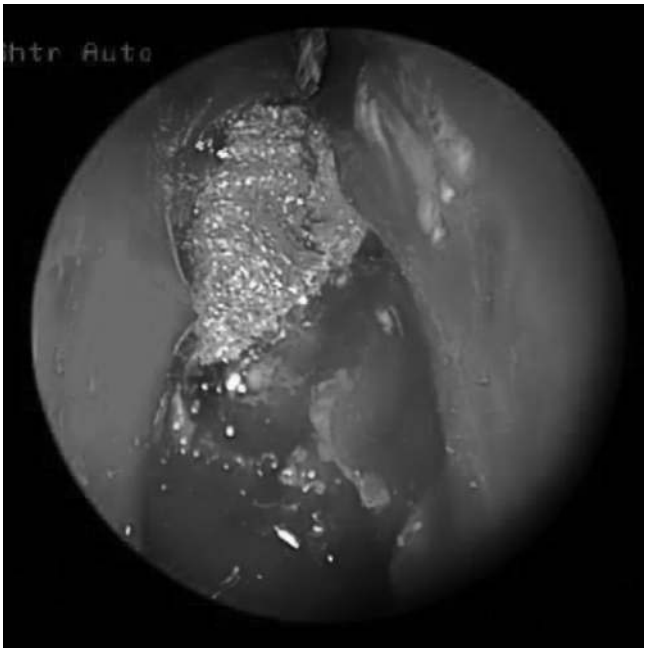

Figure 2. *Intraoperative placement of a MMC-soaked neuropattie in the frontal recess.*

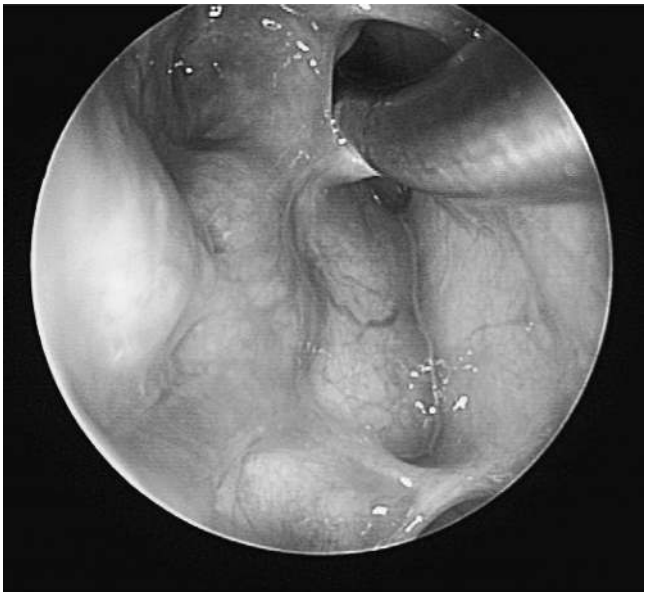

Figure 3. *Three-month postoperative measurement of the frontal ostium with a curved Frazer 8 suction.*

one-way analysis of variance test with Instat 3.0 was used to determine statistical significance.

A Lund-Mackay score analysis of the preoperative CT scans was performed to ensure that the two sides were not significantly different from each other. Total mean score analysis showed a score of 5.59 ± 3.1 for the left side and 5.40 ± 3.0 for the right side with a correlation coefficient of 0.82. Frontal sinus score analysis showed a mean left score of 0.76 ± 0.74 and a mean right score of 0.71 ± 0.73 with a correlation coefficient of 0.67. A matched pair Wilcoxon test

Table 1 **Changes in frontal ostium dimensions for all cases (n = 38)**

	MMC (intraoperatively)	MMC (1 mon)	MMC (3 mon)	MMC (6 mon)	Control (intraoperatively)	Control (1 mon)	Control (3 mon)	Control (6 mon)
D_{AP} (mm)	7.4 ± 2.5	6.5 ± 2.9	5.8 ± 2.8	6.2 ± 2.4	7.3 ± 2.1	6.2 ± 2.3	5.3 ± 2.4	5.7 ± 2.8
D_T (mm)	6.1 ± 1.7	4.9 ± 2.4	4.5 ± 2.2	5.4 ± 2.3	6.3 ± 2.7	5.5 ± 2.7	4.7 ± 2.6	4.7 ± 2.3
CSA (mm^2)	36.7 ± 18.1	28.7 ± 23.1	23.5 ± 18.1	28.8 ± 18.9	37.9 ± 21.7	30.4 ± 25.4	23.4 ± 22.3	24.5 ± 19.7

Table 2 **Changes in frontal ostium dimensions for primary cases (n = 25)**

	MMC (intraoperatvely)	MMC (1 mon)	MMC (3 mon)	MMC (6 mon)	Control (intraoperatively)	Control (1 mon)	Control (3 mon)	Control (6 mon)
D_{AP} (mm)	7.3 ± 3.1	7.3 ± 3.1	5.9 ± 2.7	6.4 ± 2.3	6.9 ± 2.3	6.6 ± 2.0	5.6 ± 2.3	6.0 ± 3.2
D_T (mm)	6.1 ± 1.9	5.1 ± 2.6	4.7 ± 2.3	5.8 ± 2.4	6.1 ± 2.6	5.6 ± 3.0	4.4 ± 2.6	4.3 ± 2.0
CSA (mm^2)	37.3 ± 21.0	33.7 ± 26.5	25.0 ± 20.4	32.1 ± 21.9	35.2 ± 23.7	32.3 ± 28.6	22.9 ± 24.8	24.2 ± 22.9

Table 3 **Changes in frontal ostium dimensions for revision cases (n = 20)**

	MMC (intraoperatively)	MMC (1 mon)	MMC (3 mon)	MMC (6 mon)	Control (intraoperatively)	Control (1 mon)	Control (3 mon)	Control (6 mon)
D_{AP} (mm)	7.4 ± 2.5	5.7 ± 2.5	5.6 ± 3.0	6.0 ± 2.7	7.9 ± 2.4	5.8 ± 2.6	4.9 ± 2.6	5.2 ± 2.3
D_T (mm)	6.2 ± 1.8	4.9 ± 2.2	4.1 ± 2.0	4.7 ± 2.1	6.3 ± 2.4	5.4 ± 2.4	4.7 ± 2.9	5.2 ± 2.8
CSA (mm^2)	36.4 ± 15.9	24.6 ± 18.3	20.7 ± 14.7	23.4 ± 13.5	39.8 ± 18.3	28.3 ± 22.3	21.8 ± 18.6	25.0 ± 15.6

showed no significant difference between the two sides at α = 0.05. This study was approved by the University of British Columbia/Providence Health Care Research Ethics Board and informed consent was obtained.

RESULTS

Forty-five patients were recruited into the study. Their ages ranged from 15 to 81 years with a mean of 49 years (Table 1). There were 27 men and 18 women. Thirty-five patients had bilateral complete frontosphenoethmoidectomies, nine patients had frontoethmoidectomies, and one patient had just FS. There were 25 primary cases (Table 2) and 20 revision cases (Table 3). MMC was used on the right side in 21 cases and on the left side in 24 cases. No adverse reactions to MMC were noted.

Of the 45 patients, one had bilateral lateralization of the middle turbinates and three had persistent chronic rhinosinusitis. In these four cases, objective measurements of the frontal recess could not be performed. In one patient, the frontal recess was visualized to be open but could not be measured because the patient could not tolerate the examination. Two patients were lost to follow-up. The following results are based on the remaining 38 patients who have completed 6 months of follow-up.

At 1, 3, and 6 months, there were no significant differences in the amount of frontal recess narrowing between the MMC and control sides (Table 1).

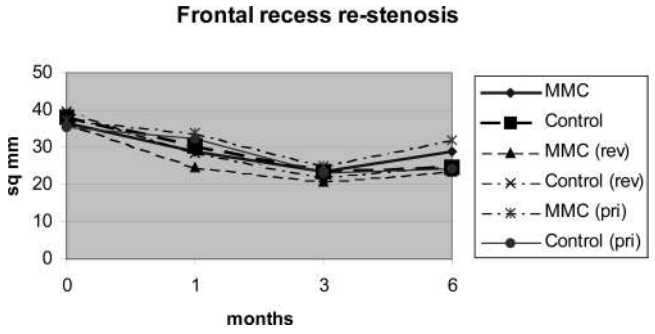

Figure 4. *Percentage of decrease in frontal recess CSA over time for the different groups.*

Primary cases also were compared with revision cases. Once again, we were unable to detect any differences between the MMC and control sides (Tables 2 and 3).

We noted a slight increase in the CSAs for the groups from 3 to 6 months. This could be caused by postoperative frontal recess edema settling down, thereby giving a larger end-stage frontal ostium size (Tables 2 and 3).

Figure 4 and Table 4 summarize the percentage decrease in the CSA of the frontal recess over time for the different groups analyzed. Even though there appears to be a trend toward reduced contracture in the MMC group, this is not significant.

Table 4 **Percent contracture of frontal ostium CSA between the treated and untreated sides for the different groups**

	Contracture (%)		
	Overall (n = 45)	**Primary Cases (n = 25)**	**Revision Cases (n = 20)**
Control group	35.5%	31.3%	37.1%
MMC group	21.5%	13.9%	35.7%

We note that all groups show a similar degree of stenosis over time.

DISCUSSION

The most common location for failure in endoscopic sinus surgery is the frontal recess. The narrow and complex anatomy of the frontal recess results in a greater tendency for exposed and traumatized mucosa in the frontal recess. Circumferential mucosal injury and bone exposure can lead to significant osteoneogenesis and contracture in the frontal recess and internal frontal ostium. Hosemann *et al.*[13] have shown that the minimum diameter of the frontal sinus ostia would on average decrease from 5.6 to 3.5 mm (a 37.5% decease) and ostia >5 mm had a much higher chance of staying patent. The greatest challenge, therefore, for the sinus surgeon is to keep the frontal sinus ostia patent, especially where the surgical diameter is <5 mm. Our results show that for the control group, frontal recess CSA decreased from 37.9 to 24.5 mm^2 (a 35.5% decrease). This is consistent with the findings from Hosemann *et al.*[13] For the MMC group, the frontal recess CSA decreased from 36.7 to 28.8 mm^2, a 21.5% decrease. Even though there appears to be a trend toward reduced contracture of the frontal recess in the MMC group, this was not significant (Table 4).

Chung e*t al.*[10] had reported on the use of MMC for the prevention of adhesions in the middle meatus. They reported a trend toward lesser adhesions on the MMC side but this did not reach statistical significance. This is the first double-blinded, randomized, placebo-controlled study investigating the use of MMC in the frontal recess to prevent restenosis. We were unable to find any statistical difference between the MMC and control sides. Even though MMC has shown to be useful in preventing scarring in glaucoma surgery, its usefulness in otolaryngology is still not well proven. Ribeiro *et al.*[14] showed that MMC applied to surgical wounds had the same degree of fibrosis at 12 weeks as untreated wounds.

A few possible reasons why we were not able to show a difference include a small sample size, the large SDs, and, possibly, the technique used for MMC delivery. Despite using vasoconstrictive agents before application of the MMC neuropathy, there still was bleeding in the frontal recess, which could wash away or dilute the MMC concentration. It is possible that a higher concentration may be required in the sinuses. Another possible reason is good surgical technique with meticulous handling of tissue in the frontal recess. With the use of mucosa-preserving techniques using through-cut instrumentation, minimal use of powered instrumentation and careful removal of all loose bone chips, scarring in the frontal recess is kept to a minimum on both sides and small differences secondary to use of mitomycin would be difficult to detect.

There were some limitations to the study. One was the exclusion of patients with osteoneogenesis or extreme scarring in the frontal recess. These patients had silastic or rubber frontal sinus stents placed intraoperatively. With the stent in place, it would have been impossible to measure the diameter of the frontal recess postoperatively. It is likely that these patients are the ones who would have benefited the most from mitomycin use. We recognize that this may add a degree of selection bias to our groups.

We used a slightly higher concentration of MMC (0.5 mg/mL) than what has been used in the literature for airway disease (0.4 mg/mL). Our reasoning was based on previous experience in ophthalmologic surgery, where the higher concentration has become an acceptable, safe, and effective concentration to reduce scarring. Also, previous use of the lower concentration has not shown a statistical decrease in scar formation in the middle meatus.[10] Therefore, a slightly higher concentration was felt to be more desirable.

As shown in this study, MMC may not be effective or necessary when a meticulously opened frontal ostium with good mucosal membrane preservation is accomplished surgically. MMC may be more effective in patients with extensively scarred frontal ostia with osteoneogenesis, significant loss of mucus membrane, and bone exposure. Additional controlled studies are required to address this.

CONCLUSION

Topical application of MMC within the frontal recess at the end of a properly performed FS does not reduce postoperative scarring and contracture in both primary and revision cases in the postoperative period.

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