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Intra- and postoperative application of Mitomycin C in the middle meatus reduces adhesions and antrostomy stenosis after FESS*

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SUMMARY

Aim: *Obstruction of the osteomeatal complex is the commonest anatomic finding in revision endoscopic sinus surgery. This study assesses the efficacy of topical mitomycin C in the middle meatus, intra- and postoperatively in the prevention of adhesion formation and restenosis of the maxillary sinus antrostomy.*

Materials and methods: *At the end of endoscopic surgery for chronic rhinosinusitis and four weeks postoperatively 30 patients received a pledget soaked with 1ml of mitomycin C (0.5 mg/ml) in the middle meatus for 5 minutes while a pledget soaked in saline was placed in the contralateral side. Patients were assessed at least 6 months postoperatively by a blinded observer for the presence of synechiae and antrostomy stenosis. Medical records were reviewed for episodes of recurrent sinusitis.*

Results: *Adhesions were observed in 8 patients. All adhesions rated as moderate to severe (4 patients) were observed in the control side ($p = 0.043$). Restenosis was observed in 2 sides treated with mitomycin C and in 9 control sides ($p = 0.032$). Recurrent symptoms of sinusitis occurred in three patients on the saline side.*

Conclusion: *Mitomycin C is safe and effective in the prevention of severe adhesions and antrostomy stenosis when applied twice, during surgery and the early postoperative period.*

Key words: Mitomycin C, antrostomy, stenosis, adhesion, sinus surgery.

INTRODUCTION

The patency and the size of the antrostomy site and the presence of adhesions in the middle meatus are two significant factors in the evaluation of a successful endoscopic sinus surgery [(1)]. Adhesion and stenosis after surgery are usually due to scar tissue or granulation formation during the tissue recovery process.

Mitomycin C (MMC) is an antibiotic isolated from the broth of *Streptomyces caespitosus*, which acts as an alkylating agent able to inhibit DNA synthesis [(2)]. It has also been shown to inhibit fibroblast proliferation and activity, which can reduce scar formation [(3)]. Topical MMC has been used in ophthalmologic surgery for glaucoma, pterygia, strabismus, and nasolacrimal duct obstruction [(2)]. Recently, MMC has also been used in otolaryngological surgery to prevent early closure of myringotomy [(4)] or stenosis after laryngeal or tracheal surgery [(5)] or choanal atresia surgery [(6)] or adhesion and ostia stenosis after endoscopic sinus surgery [(7-9)]. Although there are studies about the topical effect of MMC use in endoscopic sinus surgery, their results are still controversial [(7,8,10,11)]. However the vast majority of these studies assessed a single application of MMC [(7,8,11)]. Preliminary results from a study regarding the frontal ostium patency presented encouraging results and suggested additional applications of MMC [(9)].

The purpose of this study is to examine the clinical effects of MMC applied to sinonasal mucosa twice (intra- and postoperatively) and to determine whether such an application alters significantly the incidence of postoperative adhesion formation and maxillary ostium stenosis.

MATERIALS AND METHODS

Patients

A total of 30 patients (14 female / 16 male) ranging in age from 18 to 71 years (mean 39.5 years) who underwent endoscopic sinus surgery for chronic rhinosinusitis without polyps were included in this study. All patients provided written informed consent according to a protocol approved by the Ethic Committee of the Hospital.

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In the preoperative computed tomography scan (CT) all patients had total opacification of both middle meati and maxillary sinuses and various extent of disease in the other sinuses. However, we selected patients with similar grades of paranasal sinuses opacification in the CT scan in both sides. In order to have similar grades of the disease in both sides we used the Lund – Mackay system score for the CT scan assessment as it is a well validated staging system in CRS [12]. Each sinus is graded between 0 and 2 (0 no abnormality, 1 partial opacification, 2 total opacification), whereby the maximum score for each side is 12. Patients with a difference between sides of more than two grades in the Lund – Mackay score were excluded from the study. We also excluded patients with prior nasal endoscopic surgery, allergic rhinitis and nasal polyposis. All procedures were performed under general anesthesia by the same surgeon during a 2-year period.

Surgery

The amount and location of sinus disease determined the extent of sinus surgery performed for each patient; however, every patient in the study group underwent middle meatal antrostomy and anterior ethmoidectomy. When septal deviation limited access to the middle meatus, an endoscopic septoplasty was performed. The opening of the maxillary sinus was performed with conventional instrumentation (through cut forceps, back-biting forceps). In all cases we preserved the middle turbinate keeping its mucosa as intact as possible.

At the completion of the procedure, a neurosurgical cottonoid saturated with 1 ml of MMC in a concentration of 0.5 mg/ml was placed in either the right or left middle meatus randomly and a pledget soaked in saline was placed in the contralateral side. After a period of 5 minutes, the cottonoid was removed and the nasal cavity was irrigated with 30 ml of sterile normal saline. This methodology was useful to avoid bias as each patient served as his or her own control.

At the end of the procedure, both nasal cavities were tamponaded with Merocel packing. This packing was removed the morning after surgery. All patients were discharged with a 10-days course of oral antibiotics, nasal steroids for 4 weeks and instructions for saline irrigation of the nose for up to 2 months.

Postoperative care

The MMC application was repeated in the same side of the nose four weeks postoperatively under local anaesthesia and with the use of an endoscope (Figure 1). The contralateral side received again a cottonoid soaked with normal saline. Postoperative removal of clots and crusts was performed in a weekly basis for a period of 4 to 8 weeks if required. The final follow up appointment was at least 6 months postoperatively. At this examination an observer blinded regarding the MMC application side, performed nasal endoscopy with the same 300 degree rigid nasal endoscope for the assessment of synechiae presence and antrostomy stenosis. Both sides of the nasal cavity were examined for synechiae and graded on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe).

Figure 1. Postoperative mitomycin C application. A neurosurgical cottonoid saturated with mitomycin C is placed in the middle meatus.

Figure 2. Endoscopic view of a mitomycin C–treated, left nasal cavity. A ruler with a diameter of 5mm is placed in front of a large antrostomy with obvious patency for endoscopic evaluation of its size. (The asterisk indicates the middle turbinate).

Measurements

Antrostomy size was assessed with the use of a ruler. Specifically we used a circular probe (ear curette) of 5 mm diameter. This diameter was chosen because we considered an antrostomy as stenosed when its diameter was less than 5 mm. Although an appropriate size for the antrostomy is not determined, this diameter is suggested by many authors assessing

antrostomy size as adequate [13,14]. We placed the probe in the same plane as the antrostomy and close to the center of the endoscope's field of view in order to minimize visuospatial distortion (Figure 2). Assessment of stenosis was performed when the endoscopic image of the probe resembled a circle as closely as possible. In borderline cases the probe should occupy more than 40% of the total endoscopic field of view for precise measurements [14]. By taking a photograph under these conditions, the antrostomy could be measured accurately and reproducibly [14]. Medical records of the patients were reviewed for episodes of recurrent sinusitis during the follow-up period.

Statistics

Results were analyzed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented within the body of the text as mean values ± standard deviation. Data were analyzed with a paired t-test, and Pearson correlation. The minimum a-level was set at 0.05.

RESULTS

In the final postoperative follow-up appointment (mean time 7.2 months) 9 nasal cavities with adhesions were observed in 8 of 30 operated patients (26.6 %). The presence of adhesions did not correlate with patient's gender, age and side (right/left) of the nose. Seven patients had unilateral adhesions and one patient had bilateral adhesions. More specifically, unilateral adhesions developed in 2 MMC treated sides and 5 in the control side. Comparison of these results showed that this difference was not significant ($p = 0.264$). The majority of adhesions were rated as mild (5 adhesions, 55.5%). Four patients presented extensive adhesions, rated as moderate (2 patients) or severe (2 patients). All of these adhesions occurred in the control side of the nose, a fact with statistical significance ($p = 0.043$).

Table 1 presents in detail the characteristics of adhesions in the study group. There was no correlation between adhesion formation and recurrent sinusitis in the study group ($p = 0.432$).

The presence of antrostomy stenosis did not correlate with patient's gender, age and side of the nose. Stenosis was observed in 2 sides treated with MMC and 9 control sides (Table 2). This difference between the two groups was statistically significant ($p = 0.032$). Recurrent symptoms of sinusitis occurred in three patients on the saline side, showing a trend towards significance ($p = 0.083$). Moreover a positive correlation was found between the incidence of antrostomy stenosis and recurrent sinusitis in the control side ($r = 0.509$, $p = 0.004$).

Table 2. Comparison between mitomycin-c side and control side regarding antrostomy stenosis and recurrent sinusitis symptoms.

	Patients (n [%])	MMC side (n [%])	Control side (n [%])	p value
Stenosis	11 [36.6]	2 [6.6]	9 [29.7]	0.032
Recurrent sinusitis	3 [9.9]	0	3 [9.9]	0.083

Postoperative bleeding occurred in two patients and was treated with conservative management. One of them developed mild adhesions in the middle meatus of the MMC side.

Further sinus surgery was required in one patient because of nearly blocked antrostomy and recurrent sinusitis symptoms. The other two patients with postoperative recurrent sinusitis were successfully managed with medical treatment and serial follow-up assessments.

No systemic or local side effects from the application of topical intranasal Mitomycin C were observed by the medical staff or reported by the patients.

Neither the occurrence of adhesions nor the incidence of antrostomy stenosis or recurrent sinus infections was found to correlate with the extent of disease as determined by the preoperative CT staging score.

DISCUSSION

There are several reasons for endoscopic surgery failure such as abnormality of mucociliary transport, persistent disease and osteomeatal complex obstruction [1,15]. The last one is of major importance and can be a result of adhesion formation and antrostomy stenosis. This is suggested by Musy and Kountakis [16] who reported that the commonest anatomic finding in revision endoscopic surgery was an obstructed osteomeatal complex and specifically a stenosed middle meatal antrostomy in 39% of cases. Moreover, other authors suggested that the degree of antrostomy patency is directly related with the patient symptoms [13].

Table 1. Characteristics of postoperative adhesions in the study group.

		Side of adhesion		
Location of adhesions (n= 30 patients)	Patients (n [%])	MMC side (n [%])	Control side (n [%])	p value
Unilateral	7 [23.3]	2 [6.6]	5 [15.6]	0.264
Bilateral	1 [3.3]			

Location of adhesions (n= 30 nasal cavities)	MMC side (n [%])	Control side (n [%])	p value
Right	2 [7.1]	3 [10.5]	
LefT	1 [3.5]	3 [10.5]	
Mild	2 [10.5]	3 [10.5]	
Moderate-Severe	0	4 [7.1]	0.043

MMC use in endoscopic sinus surgery aims to decrease postoperative scar formation. Although basic scientific evidence and ophthalmological experience provided theoretical support for the MMC use, clinical studies failed to demonstrate a clear modification of the postoperative healing process [7,8,11]. One of the raisons might be the single peri-operative application of MMC. Bleeding during the operation decreases absorption of MMC and this fact may cause inadequate fibroblasts inhibition. Other authors have also suggested that the increased vascularity of nasal mucosa may reduce the efficacy of MMC application during dacryocystorhinostomy compared with trabeculectomy [3]. However, a study about MMC application in frontal sinus surgery presented initial promising results with a two or three stage application in some cases [9].

Given the dose dependent activity of MMC on fibroblasts demonstrated in basic scientific studies [3], the establishement of MMC clinical efficacy probably requires not only different times of application but different doses as well. However, the use of increased MMC doses should be done carefully as the safety of MMC is not yet established. There are reported cases of local toxicity in ophthalmology [18] and airway complications [19] from debris caused by MMC application after surgery for upper airway stenosis. Although there are no reported cases of complications in sinus surgery, all studies used low concentrations of MMC.

This study assessed the efficacy of MMC using a two-stage application procedure allowing a more prolonged effect on the mucosa of the middle meatus. Wound healing in the postoperative period after endoscopic sinus surgery is a prolonged and complex process mediated by several cell types [20]. Although this period can be long and stenosis has been reported years after surgery, the first 6-8 weeks up to 3 months are the most important [10,20,21]. Based on this fact, the second application of MMC in our study was performed during this early postoperative stage.

When injured mucosal surfaces are in close proximity at the completion of sinonasal surgery, fibrous tissue may grow between these surfaces to create an adhesion. It is believed that adhesions of a sufficient size and proper location can obstruct an adjacent sinus ostium and lead to recurrent sinus infection. In our study the sides treated with MMC developed slightly less adhesions and definitely not as severe as in control sides. However, these results did not correlate with recurrent sinusitis symptoms. This is in agreement with other, similar studies and may reflect a limited role of adhesions in postoperative recurrent maxillary sinusitis [7].

Our study showed that MMC application in two stages can decrease the incidence of antrostomy stenosis 6 months after surgery. Considering the significance of the antrostomy patency on the degree of patient symptoms, the use of MMC could be a very useful tool in the postoperative period in order to reduce revision surgery. The use of a simple ear currette to assess the antrostomy size is considerably promising as it is easily applicable in the operating room and the clinical setting. This method simplifies the measurement of antrostomy dimensions and can be added in the every day practice, as it is not time consuming.

There are clinical studies showing only a short-term effect of MMC in antrostomy stenosis [8, 11]. However, a study on rabbits suggested that the higher the concentration of MMC, the lower the rate of antrostomy closure [22]. Specifically the MMC 0.4 mg/ml group had an antrostomy closure at 4 weeks and the MMC 1.0 mg/ml group at 12 weeks [22]. We should also have to consider that short-term application of MMC inhibits the growth of fibroblasts, but they are still capable to contribute to other aspects of wound healing [23]. In addition, other authors suggested that 70% of fibroblasts survive after a 5-minute MMC application (0.4 mg/ml) with evidence of regrowth within 2 to 3 days [8]. These results suggest that we need to study higher doses and multiple applications in order to assess the efficacy of MMC in sinus surgery. However, this should be done carefully in order to balance the beneficial effect of MMC with its harmful effect. The small number of patients in MMC studies is another significant limitation. Larger randomized studies, probably multicentric are needed, before definitive conclusions regarding the efficacy and safety of MMC in endoscopic sinus surgery can be drawn.

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