

Prevention of Adhesion after Endoscopic Sinus Surgery: Role of Mitomycin C

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Abstract- Adhesions after endoscopic sinus surgery (ESS) are a potential cause of surgical failure. Mitomycin-C (MMC) is recently proposed as a solution for these adhesions. This study was performed to investigate the effect of Mitomycin C in reducing scar formation and adhesion in the nasal mucosa after endoscopic nasal surgery. This double blind randomized clinical trial study was performed on 37 patients with bilateral chronic rhinosinusitis. At the end of ESS, randomly impregnated mesh with MMC was placed in one side and another mesh impregnated with saline in the opposite side for 5 minutes. Patients were followed at least for three months, and the results of diagnostic endoscopy were recorded. Post operative adhesion occurred in 12 (32.4%) patients (2 bilateral/10 unilateral). Among total of 14 adhesions, 4 (10.8%) were in the MMC side and 10 (27%) in the control side. This differences was close to statistically significant ($P=0.058$). MMC may reduce adhesions after ESS, but further studies with different doses, sample size and frequent use of topical MMC is recommended.

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Introduction

Endoscopic sinus surgery (ESS) has been accepted as the choice treatment modality of chronic sinus disease. This is mainly because this approach: 1) maintains the sinus mucosa; 2) establishes the sinus ventilation and sinus drainage pathway from the natural openings 3) eliminates the pathology effectively (1). Efficacy of ESS is clearly described within the past two decades, however, narrowing and adhesion formation after ESS is a potential cause of surgical failure (2).

Previous studies have shown the overall incidence of adhesions after ESS about 11-36% and the incidence of adhesions requiring surgical intervention is about 1-2% (3-6). So far to prevent or reduce adhesions after ESS, the spacers, nasal packing containing absorbent material, such as anti adhesion pack containing hyaluronate sodium or sodium carboxymethylcellulose and anatomical barriers are used. However, these methods had a relatively limited success in preventing the

adhesions. Mitomycin C (MMC) is a natural antibiotic derived from *Streptomyces caespitosus*. In 1956 antibacterial effect of MMC was reported for the first time (7). Gradually the drug ability to create cross-link between DNA chains and the alkylating effects were discovered and it was used as a chemotherapeutic agent in treatment of various solid tumors such as bladder, gastric and colorectal cancers. According to anti proliferative effects of MMC through its ability to inhibit fibroblast activity, this drug has been used as an anti-scar on various ophthalmological procedures such as glaucoma, pterygium, and dacryocystorhinostomy since 1980 (8).

Several studies have been performed on effects of MMC on scar formation after surgery, such as airway restoration, choanal atresia repair, esophageal stricture and endoscopic sinus surgery. The results are incongruent till now (2, 9-13). Therefore, the usage of MMC remains at the level of research in otorhinolaryngology.

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Prevention of adhesion after endoscopic sinus surgery

This study was performed to investigate the effect of MMC in reducing scar formation and adhesion in the nasal mucosa after endoscopic nasal surgery.

Patients and Methods

Informed consent was obtained from patients and the study protocol was reviewed and approved by Yazd University of Medical Sciences Research Ethics Review Board. During this prospective, double blind randomized clinical trial, patients with bilateral chronic rhinosinusitis with or without polyposis referred to Shahid Sadoughi General Hospital (Yazd, Iran) were enrolled. Those patients whom had underlying disease such as cystic fibrosis, immune deficiency, and movement disorders of cilia such as kartagener syndrome, uncontrolled diabetics, tuberculosis or bleeding disorders at the same time were excluded from the study. Forty patients suffering from chronic rhinosinusitis resistant to 8 week course of medical treatment, with or without polyposis, were randomly divided in two groups. Three patients were excluded due to the lack of adequate follow up. In one group, MMC impregnated mesh placed in right middle meatus and in the other half placed in the left side. All surgeries were done by one surgeon (senior author) and under general anesthesia. After injecting appropriate topical decongestive, the procedure were performed by Messerklinger technique. The maxillary sinus os opening was in the range of 1.5 cm. At the end of ESS, according to random grouping samples, a cotton mesh as 6 cm stained by 1.5 ml of 0.45 mg/ml MMC solution was placed in one side middle meatus, ethmoid cavity and around the maxillary sinus os and another cotton mesh with the same size impregnated with 1.5 ml of saline solution was placed in another side and after 5 minutes, the mesh were removed and middle meatus of both sides were packed with Merocel. All of the patients were discharged from hospital the day after surgery (Post operative day) and the medication were as follows: cefixime capsules 400 mg once/daily for 10 days, washing nasal cavity three times a day with normal saline and topical corticosteroid spray 2 puff, 2 times a day in each nasal cavity for three weeks. After 72 hours the Merocel was removed and patients were followed at least for three months. The first follow up of patients were 7-10 days after surgery and the second follow up endoscopy was 1.5 month after surgery for debridement.

The third follow up endoscopy was performed at least three months after surgery and adhesion, granulation tissue formation, polypoid mucosal hypertrophy, narrowing of maxillary sinus os in bilateral

nasal cavities based on selected criteria in the study by Nayak *et al.*, was defined as follows (14):

Type A: Adhesion at the junction of the anterior middle turbinate and lateral nasal wall.

Type B: Partial adhesion between the middle turbinate and lateral nasal wall.

Type C: Complete adhesion between the middle turbinate and lateral nasal wall with the obliteration of middle meatus.

Type D: Adhesion between the middle turbinate or inferior with septum.

Extension and rate of granulation tissue was graded to three grades based on the criteria described in the study by Hu *et al.*, (15) to mild (less than 10%), Moderate (10-50%) and severe (more than 50%). Extension and rate of mucosal hypertrophy in the middle meatus were divided to three grades of mild (less than 10%) moderate (10-50%) and severe (more than 50%). The rate of stenosis and narrowing of the maxillary sinus os was defined by measuring with graded suction tip during diagnostic endoscopy:

Mild narrowing: antrostomy size 6-9mm

Moderate narrowing: antrostomy size 3-5 mm

Severe narrowing: antrostomy size less than 2 mm.

Post-operative endoscopist was unaware of the patient's categorization. Statistical Package for Social Sciences (SPSS; version 16.0) was used for data analysis.

Results

A total of 37 patients were studied, 22 male (60.5%) and 15 (40.5%) female. Age range was 14-66 years (mean 38) with follow up period 3-5 months (mean 3.5 month). In 19 patients (51.4%) MMC was placed on the right side and in 18 patients (48.6%) was placed on the left. Among 37 patients, 29 (78.4%) had a chronic rhinosinusitis with polyposis and 8 cases (21.6%) had a chronic rhinosinusitis without polyposis. Three patients had past history of failed surgery and the others were the first time being operated.

Adhesions after ESS occurred in 12 patients (32.4%) which in two of them were bilateral and in 10 it was unilateral.

Of total 14 adhesions occurred during follow up period, the type of adhesion were as follows: 2 type A, 7 type B, 1 type C and 4 type D. Severe synencha (type C) only occurred in one case which was unilateral and had MMC. Other adhesions were mild and without interfering in the direction of sinus drainage. Granulation tissue occurred in 15 patients (40.5%), bilateral in 3 and unilateral in 12.

Table 1. Prevalence of adhesion, granulation tissue, polypoid mucosa, and maxillary ostium narrowing in MMC and control group

Parameter	Status	MMC	Control	McNemar's test
Adhesion	Positive	4 (10.8%)	10 (27%)	0.058
	Negative	33 (89.2%)	27 (73%)	
Granulation tissue	Positive	6 (16.2%)	12 (32.4%)	0.083
	Negative	31 (83.8%)	25 (67.6%)	
Polypoid mucosa	Positive	8 (21.6%)	5 (13.5%)	1
	Negative	29 (78.4%)	32 (86.5%)	
Maxillary os narrowing	Positive	5 (13.5%)	6 (16.2%)	0.453
	Negative	32 (86.5%)	31 (83.8%)	

Of total 18 granulation tissue formations, two of them were moderate and 16 were mild; hypertrophied polypoid mucosa occurred in 9 patients (4 bilateral and 5 unilateral). Of total 13 cases with polypoid hypertrophied mucosa, two of them were moderate and 11 cases were mild. The Location of polypoid hypertrophied mucosa was in the frontal recess (five cases), antrum and maxillary sinus opening (five cases) ethmoid (one case) and sphenoid (two cases). Stricture of maxillary sinus opening occurred in 10 (24%) patients (bilateral in one and unilateral in 9). Regarding maxillary sinus os narrowing, two were severe and others were mild. Except adhesion that has a significant statistical difference, other variables, there were no significant statistical differences, between MMC group and controls (Table 1 and 2).

No complication, sign of systemic toxicity, or local toxic effect of MMC were seen.

Discussion

Results shown above indicate that although MMC reduced postoperative adhesions but the difference was not statistically significant and had no effect in reducing formation of granulation tissue, polypoid hypertrophied mucosa or prevention of narrowing of the maxillary sinus os. No difference was also found in the side of topical MMC application.

In a study by Anand *et al.*, on 29 patients with chronic rhinosinusitis resistant to medical treatment, MMC impregnated mesh and saline impregnated mesh randomly were used for each side of nasal cavity at the end of the surgery. They showed that the incidence of adhesion (9 cases of 29) between the two sides has no significant statistical difference. However this might have been due to small sample size used in the study. In their study the main outcome measure was the adhesions, while in our study, in addition to adhesion, granulation tissue formation, polypoid mucosal hypertrophy and narrowing of maxillary sinus os were also investigated. In both studies the incidence of adhesion was very close to each other (32.4% versus 31%).

In another study by Kim *et al.*, on 20 patients with bilateral chronic rhinosinusitis resistant to treatment, the effects of mitomycin C was evaluated on anterostomy size and were found to be effective only in the first month after surgery. But after six months (long term) follow up, MMC has no effect in reducing incidence of narrowing or obstruction of anterostomy. This finding is congruent with our results (16).

Chung *et al.*, studied 55 patients with resistant bilateral chronic rhinosinusitis. At the end of ESS, they randomly used impregnated mesh in one side and normal saline impregnated mesh on the other side.

Table 2. Prevalence of adhesion and granulation tissue regarding revision surgery or presence of polyposis

Parameter	Status	Adhesion	P	Granulation tissue	P
Polyposis	Positive (n=29)	7	0.08	14	0.1
	Negative (n=8)	5		0	
Revision surgery	Positive (n=3)	2	0.24	0	0.25
	Negative (n=34)	10		15	

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In the study by Chung *et al.*, patients were followed for 4.1 months. Although the incidence of adhesion was higher than control, but the difference was not statistically different. This study also reviews the mucosal polypoid hypertrophy changes and showed that the effect of MMC in reducing mucosal polypoid hypertrophy is obvious only 1-2 weeks after the use of MMC, but these changes did not last in the subsequent examinations (17). In comparison to our study, although our sample size and duration of follow up was not as long as their study, the over result on prevention of adhesions after ESS was statistically similar. In addition their result didn't specify any adverse effects of using topical MMC in their patients. In the study carried out by Konstantinidis *et al.*, on 30 patients undergoing revision ESS, at the end of surgery and also four weeks after surgery, the topical MMC was used in the middle meatus. After six month follow up the authors concluded that topical MMC in the two turns, is a safe medication that prevent adhesion and stricture of anterostomy os (18).

Kim *et al.*, performed a double blind RCT on 38 patients with maxillary sinus mucocel, at the end of endoscopic anterostomy, they used topical MMC and concluded that topical MMC is useful in prevention of stricture of maxillary sinus (19).

In a systematic review Karkous *et al.*, reviewed studies between 1991-2007 regarding the use of topical MMC in the nose and sinuses. They concluded that such use of topical MMC is safe (20). In conclusion, MMC may be effective in reducing adhesions after ESS, but our study failed to show any statistical difference. Inability to find statistically significant results may be due to small sample size. Overall, more studies are needed to assess the effects of topical MMC in prevention of post surgery adhesions. In addition, longer follow up period may show possible side effects of prolonged topical application of MMC in ESS.

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