Role of Mitomycin-C in Prevention of Post Operative Adhesions After Endoscopic Sinus Surgery—A Prospective Study

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Abstract To evaluate the role of Mitomycin-C in preventing synechia formation and ostial stenosis following endoscopic sinus surgery. This prospective study was conducted in VMMC and Safdarjung hospital from November 2007 to August 2008. 30 subjects aged between 16 and 60 of either sex in two groups were included in the study. All these patients with bilateral nasal polyposis underwent endoscopic sinus surgery with topical application of Mitomycin-C and were subjectively and objectively assessed for improvement of symptoms and post operative synechia formation. Patients showed improvement in subjective symptoms mainly nasal obstruction and hyposmia as well as decreased incidence of synechia formation and ostial stenosis post surgery following Mitomycin-C application. After doing this study we could conclude that Mitomycin-C applied topically following endoscopic sinus surgery was helpful in improvement of symptoms like nasal obstruction and hyposmia as well as decreased adhesion rate and middle meatal antrostomy closure rate. Topical application of Mitomycin-C was safe in a dose of 0.4–0.8 mg/ml applied over 5 min and offered significant improvement both subjectively and objectively.

Keywords Endoscopic sinus surgery · Mitomycin-C · Adhesion rate · Middle meatal antrostomy closure rate

Introduction

Rhinosinusitis is widely believed to comprise a spectrum of inflammatory and infectious diseases concurrently affecting the nose and paranasal sinuses. Synechia and stenosis formation following endoscopic sinus surgery represents a potential cause of surgical failure. Mitomycin-C (MMC) has been used successfully in other fields to decrease post-operative scar formation due to its ability to suppress fibrosis and vascularity in both vivo and vitro. 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 by Hu D have demonstrated its antiproliferative effect [1]. Study of effect of MMC on cultured human nasal mucosa by Hu et al. [1] revealed that brief exposure of MMC inhibits fibroblast proliferation and increases fibroblast apoptosis. We hypothesize that the topical application of mitomycin-C reduces the incidence of stenosis and synechia formation following endoscopic sinus surgery.

Functional endoscopic sinus surgery (FESS) was originally designed to address obstruction in the ostiomeatal complex as described by Messerklinger has been fully accepted for treating chronic sinus disease. It aims to restore paranasal sinus ventilation and re-establish mucociliary clearance, which in turn lead to the resolution of sinus disease and maintenance of healthy sinus mucosa endoscopic approaches are much more acceptable to patients with less pain, shorter recoveries, and no or minimal external scarring.

We undertook this prospective, randomized study to determine the role of MMC in preventing synechia formation and ostial stenosis following endoscopic sinus surgery.

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Materials and Methods

This study was conducted in Department of ENT, VMMC and Safdarjang Hospital, New Delhi from November 2007 to August 2008.

Study Population

A total of 30 patients undergoing endoscopic sinus surgery for bilateral chronic rhinosinusitis with sinonasal polyposis were included in the study. One group of 15 patients were studied with 0.4 mg/ml (group A) and other 15 with 0.8 mg/ml (group B) of topical Mitomycin-C application. Patients aged between 16 and 60 years with bilateral chronic rhinosinusitis with sinonasal polyposis were included in the study. Patients with revision surgery and with known systemic disorders like uncontrolled like diabetes and hypertension were excluded from the study.

Method

Informed consent was taken from all the patients for the planned procedure in performa approved by our institutional ethical committee. They were also informed about the topical use of Mitomycin-C.

Our institutional ethical committee has recommended 0.4 and 0.8 mg/ml of topical MMC concentration. One vial contains 2 mg of MMC which is diluted with 5 and 2.5 ml sterile water to obtain the above concentration, respectively.

All patient's were subjected to routine haematological tests, diagnostic nasal endoscopy and non-contrast Computed Tomogram Scan of nose and paranasal sinuses with 2–5 mm coronal and axial cuts.

Procedure

All procedures were carried out under local anaesthesia after proper premedication. The amount and location of sinus disease present determined the extent of sinus surgery performed for each patient. Polyps were removed and specimen sent for histopathological examination in all and culture and sensitivity for fungus in some cases.

At the completion of the procedure, a cotton pledget saturated with 0.4l and 0.8 mg/ml of MMC was applied randomly in either the right or left middle meatus of group A and B respectively.

After a period of 5 min, the cotton pledget was removed and the nasal cavity was irrigated. Each patient served his or her own control with a similar saline-soaked cotton placed on the corresponding opposite side.

Rigid nasal endoscopy was done first at the interval of weekly for first month and then monthly up to three months

after surgery and as long as possible depending on the need to clean debris and the extent of the patients disease. The findings were noted in the post operative examination proforma as approved. The patient were assessed for:

Subjective improvement Headache, nasal obstruction, rhinorrhoea, postnasal drip, hyposmia, etc.

Objective assessment Bilateral nasal endoscopic examination was carried out with 0 degree rigid endoscope to note any synechiae, if present their site and patency of maxillary sinus ostium or ostiomeatal complex (OMC).

Data Collection and Statistical Analysis:

A standardized set of data was abstracted for each patient. The following statistical parameters were evaluated from the data collected:

Adhesion rate The number of procedures in which one or more adhesions are formed divided by the total number of procedures performed.

Antrostomy closure rate The number of cases developing antrostomy closure divided by the total number of cases (nasal cavities).

Observation and Result

A total number of 30 patients of bilateral chronic rhinosinusitis with sinonasal polyposis were taken for the study. These patients were divided into two groups.

Group A Consisted of 15 patients in whom 0.4 mg/ml of Mitomycin-C (MMC) was applied topically.

Group B Consisted of 15 patients in whom 0.8 mg/ml of Mitomycin-C (MMC) was applied topically.

All cases were followed up for a minimum period of three months post operatively and assessed subjectively and objectively.

Age and Sex Distribution of Cases

Group A 11 males, 4 females with average age of 32 years.

Group B 10 males, 5 females with average age of 34 years.

Present in symptoms of cases in Table 1.

Duration of Symptoms

Group A: 28 months and B: 20 months (Average duration).

The maximum number of cases in group A and group B had nasal obstructions for last 1–5 yrs.

Table 1 Symptomatology

Presenting symptoms	Group A (n) (%)	Group B (n) (%)
Nasal obstruction	14 (93.33%)	14 (93.33%)
Sneezing	11 (73.33)	12 (80%)
Nasal discharge	11 (73.33%)	10 (66.67%)
Headache	9 (60%)	8 (53.33%)
Hyposmia	6 (40%)	7 (46.67)

Preoperative Direct Rigid Nasal Endoscopic (DNE) findings

In our study all patients had bilateral chronic rhinosinusitis with sinonasal polyposis with nasal discharge. The distribution of the patients according to the DNE findings is shown in the Table 2.

In our study, middle turbinate pathology was present in all cases like paradoxical middle turbinate, enlarged and polypoid middle turbinate.

We found Ostiomeatal complex pathology in all cases including infundibular edema, discharge and polyps. The uncinate process was polypoidal and medialised in most of the cases.

Sinonasal polyposis was present in all cases bilaterally ranging from grade II to III which was in accordance with the endoscopic staging proposed by Lund VJ. (1995).

Operative findings The nasal intraoperative findings were more or less same as seen on preoperative DNE and CT scan. The major findings were documented as shown in Table 3.

In our case study of group A, 12 cases (80%) were having sinonasal polyposis with no evidence of fungal infection whereas in three cases (20%) there was fungal disease.

Table 2 Preoperative diagnostic nasal endoscopic finding in both groups

Group	Middle turbinate pathology	Nasal polyposis	Ostiomeatal complex pathology
A			
Right	Present	Present	Present
Left	Present	Present	Present
B			
Right	Present	Present	Present
Left	Present	Present	Present

Table 3 Type of pathology in each group

Group	Sinonasal polyposis (n %)	Fungal disease (n %)
A	12 (80%)	3 (20%)
B	10 (66.67%)	5 (33.33%)

In group B, ten cases (66.67%) were having sinonasal polyposis whereas in five cases (33.33%) there was fungal disease.

Surgery Score

The total number of surgical procedures done in both groups A and B are shown in Table 4

Post operative findings All patients underwent direct rigid nasal endoscopic examination with 0 and 30 degree endoscope under local anaesthesia weekly for one month and then monthly up to three months. All patients were also assessed for subjective improvement. The findings were documented as shown in Tables 5, 6.

In our study adhesions were assessed with 0 degree endoscope and antrostomy status was assessed with 30 degree endoscope with the help of angled maxillary sinus cannula (double ended maxillary sinus ostium seeker).

Symptomatic improvement mainly observed in nasal obstruction and hyposmia. The findings of both groups were documented as shown in Table 7.

Objective improvement (Assessment) All patients were subjected to bilateral postoperative DNE to assess the adhesion presence and MMA/OMC closure. In each group we have observed 30 nasal cavities were assessed. A total of 18 adhesions in 60 nasal cavities were seen. Out of 18, 12 were seen in group A and 6 in group B. Out of 12 in group A, 8 were seen on control side and 4 on MMC treated side. Out of 6 in group B, 5 were seen on control side and 1 on MMC treated side. The findings were documented as shown in Table 8.

Similarly in each group we have observed MMA/OMC status using the angled maxillary sinus canula. The findings were documented as shown in Table 9

Statistical analysis was done in both groups using χ^2 test/Fisher's exact test and normal test for testing the significant difference of two proportion. The adhesion rate and antrostomy closure rate were calculated as shown in Tables 10 and 11.

$$\text{Adhesion rate} = \frac{\text{Number of Adhesions}}{\text{Total number of procedures}} \times 100$$

$$\text{MMA closure rate} = \frac{\text{Number of closed Antrostomy}}{\text{Total number of nasal cavities} \times 100}$$

Table 4 Summary of surgical procedure in each group

Group	Middle meatus antrostomy (n)	Ethmoidectomy (n)	Sphenoidectomy (n)	Frontal Sinostomy (n)	Total
A	60	60	30	10	160
B	60	60	20	10	150

Table 5 Postoperative subjective assessment

Follow-up period (week)	Improvement in nasal obstruction (n)		Improvement in hyposmia (n)	
	Control side (n)	Mitomycin-C side (n)	Control side (n)	Mitomycin-C side (n)
Group A				
1	2	6	0	0
2	3	7	0	1
3	3	7	1	2
4	4	8	1	2
8	5	10	2	3
12	6	13	2	5
Group B				
1	2	6	0	0
2	3	7	0	1
3	3	8	1	3
4	4	10	2	5
8	6	12	3	7
12	8	14	3	7

Table 6 Postoperative objective assessment

Follow-up period (week)	Adhesion/synechiaie presence (n)		Middle meatus antrostomy/OMC closed (n)	
	Control side (n)	Mitomycin-C side (n)	Control side (n)	Mitomycin-C side (n)
Group A				
1	0	0	0	0
2	4	1	0	0
3	5	2	2	0
4	8	4	6	2
8	2	1	10	4
12	1	0	12	5
Group B				
1	0	0	0	0
2	3	0	2	0
3	4	1	5	0
4	5	1	7	0
8	2	0	8	1
12	1	0	10	1

Table 7 Postoperative improvement in symptoms

Symptom relieved	Group A (n) (%) MMC/control	Group B (n) (%) MMC/control
Nasal Obstructions	13 (86.67%)/6 (40%)	14 (93.33%)/8 (53.3%)
Hyposmia	5 (33.33%)/2 (13.3%)	7 (46.67%)/3 (20%)

In our study we calculated adhesion rate at the end of one month as we observe adhesions maximally at the end of one month. In our study mitomycin-c application was

Table 8 Objective assessment of postoperative adhesions in both groups

Side	Presence of Adhesions (n) %	Total (n) %	P-value
Group A			
Control	8 (53.33%)	12 (40%)	0.264
MMC treated	4 (26.66%)		
Group B			
Control	5 (33.33%)	6 (20%)	0.169
MMC treated	1 (6.67%)		

Table 9 Objective assessment of postoperative middle meatal antrostomy patency

Side	Patent (n) %	Closed (n) %	P Value
Group A			
Control	3 (10%)	12 (40%)	0.025
MMC	10 (33.33%)	5 (16.66%)	
Group B			
Control	5 (16.66%)	10 (33.33%)	0.002
MMC	14 (46.66%)	1 (3.33%)	

Table 10 Postoperative adhesion rate in each group

Side	Adhesion rate %	Total %
Group A		
Control	5	7.5
MMC	2.5	
Group B		
Control	3.33	4
MMC	0.66	

Table 11 Postoperative middle meatal antrostomy closure rate in each group

Side	MMA closure rate%	Total%
Group A		
Control	40	56.66
MMC	16.66	
Group B		
Control	33.33	36.66
MMC	3.33	

done only once at the time of surgery as adhesion rate beyond one month would not have any correlation to MMC application. The adhesions shown in our tables are in different nasal cavities of different patients.

Similarly we have calculated MMA closure rate at the end of three month as we observed closure maximally at this period. It can be explained on the basis that wound contracture may occur for a longer period.

Discussion

Sinusitis is one of the most common health care problems world wide, and there is evidence that it is increasing in prevalence and incidence [2–5].

Estimates suggest that sinusitis is more widespread than arthritis or hypertension. True incidence and prevalence in India is not known since an unknown proportion does not seek medical attention [6]. With factors such as pollution, smoke, viruses, fungi, bacteria, genetic factors, and anatomic anomalies contributing singly or in combination to initiation and development of the disease, identifying a cause of illness, even in an individual patient is difficult. Endoscopic sinus surgery has enjoyed impressive success curing chronic disease in sinuses and has virtually replaced the Caldwell-Luc procedure for correction of problems with the maxillary sinus.

Unfortunately, a significant number of patients have persistent maxillary symptoms after one or more endoscopic sinus operations. Recurrent mucosal disease and anatomic obstruction are two commonly cited causes of failed endoscopic sinus surgery [7]. Among the anatomic causes, ostial stenosis and adhesion formation appear to be most frequent. Ramadan 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 [7]. This fact emphasise that surgeon skill is not the most important factor deciding the adhesion formation as other local and postoperative measures play significant role.

They had pointed out the amount of raw area during the surgery and person's innate fibroblastic activities both play

an important role in scar formation after the surgery. The application of Mitomycin-C intraoperative addresses the fibroblastic proliferation issue.

Various measures have been tried to reduce adhesion formation. Malki D showed morbidity associated with nasal splints does not justify their use in routine nasal surgery [8]. Splints added significantly to post-operative discomfort in both groups, with no demonstrable benefit to the patient.

Alternative techniques of middle turbinate medialization include metallic clips (Moukarzel N) or trans-septal sutures (Thornton RS) to stabilize the middle turbinates [9, 10]. Both techniques are successful in preventing unfavorable synechiae and middle turbinate lateralization without middle meatus packing.

A second but related intraoperative measure is middle meatal spacers or packing to prevent bleeding, synechiae, and lateralization of the middle turbinate.

Friedman et al. [11] have used a Telfa pack for 24–48 h after FESS.

FloSeal placed at the end of the procedure to minimize postoperative bleeding and synechiae formation.

Middle meatal antrostomy stents have been described with improved outcomes and decreased synechiae formation [12].

Frontal sinus stents have definite improvement when used in modified Lothrop procedure.

Even after using all the above mentioned techniques the rate of adhesion formation has been reported to range from 11 to 35% [13]. More over some of these measures add considerable morbidity to postoperative care requiring prolonged care and increasing the cost of the treatment also.

Studies of MMC on cultured fibroblasts have demonstrated an antiproliferative effect at concentrations of 0.04 mg/ml and cytotoxic effects at higher concentrations [14]. A single 5 min topical application has a measurable effect on cell proliferation and cellular morphology for up to 36 h [14].

This study is intended to show that if MMC can be used safely in human sinonasal mucosa to prevent adhesion formation and to delay healing of intranasal antrostomy. We believe that this delay in fibrosis will allow reepithelization to take place before scar can form, thus increasing the success rate of FESS.

Whether more applications of Mitomycin C will offer more benefit is controversial issue. Only more work on topical Mitomycin may answer that question. Gray et al. had shown no additional benefit MMC injections over topical applications. Also there were more ulcerations on the side where MMC was injected. Darzi et al. [15] had shown that other topical or injected drugs such as Triamcinolone and 5- fluorouracil have also been used presenting

moderate symptomatic relief, but final results referring to scar reduction are not always satisfactory.

In our study we found no adverse effects from a one time topical application of Mitomycin-C.

In our study single intraoperative use of topical Mitomycin C in concentration 0.4 and 0.8 mg/ml applied over 5 min have been shown to decrease adhesion formation in patients undergoing functional endoscopic sinus surgery.

Our study aims to show the effect of Mitomycin-C in prevention of synechiae formation and closer of ostiomeatal complex. We found more the concentration of MMC, better the result. However, our study had small case series hence any reference to this study needs critical analysis.

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