

# Efficacy of Mitomycin-C for Prevention of Adhesion Formation after Functional Endoscopic Sinus Surgery in Cases of Chronic Rhinosinusitis: A Prospective Cross-sectional Study

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## ABSTRACT

**Objective:** To determine whether topical application of mitomycin-C at the conclusion of FESS decreases the incidence of postoperative adhesion formation.

**Study design:** Prospective cross-sectional study.

**Materials and methods:** Between June 2011 and June 2013, 42 patients (65 sides) aged between 16 and 66 years diagnosed to have chronic rhinosinusitis (CRS) underwent FESS. At the conclusion of the ESS, cotton ribbon wick soaked with 1 ml mitomycin-C (0.4 mg/ml) was placed in right/left/ both middle meati, near the widened sinus ostia for a period of 4 minutes. Following application, nasal cavity was irrigated with sterile normal saline. Patients were examined weekly for 1 month after surgery. Additional examinations were done at the end of 2nd and 3rd months postoperatively. At the end of 3 months follow-up, the outcome was assessed subjectively by symptoms and objectively by endoscopic findings.

**Results:** At the end of 3 months follow-up, a significant decrease (80%) in symptom scores was observed ( $6.64 \pm 1.80$ ,  $p < 0.001$ ). Similarly in sinonasal outcome test (SNOT) score we observed a significant reduction (71%) in scores ( $17.76 \pm 8.17$ ,  $p < 0.001$ ) and 3.1% cases showed adhesions.

**Conclusion:** CRS patients have remarkable improvement in their symptoms after FESS. Topical application of mitomycin-C at the conclusion of FESS/ESS has a role in prevention of adhesion formation.

**Keywords:** Chronic rhinosinusitis, Synechia, Adhesions, FESS/ESS, Topical mitomycin-C, SNOT score.

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**Conflict of interest:** None

## INTRODUCTION

Chronic rhinosinusitis (CRS) is a very frequently encountered disease in day to day general and otolaryngologic practice, affecting over 30 million individuals globally each year and more than 2,00,000 people annually requiring surgical intervention. It is more prevalent than arthritis and hypertension affecting 5 to 15% of studied population as per the western literature.<sup>1,2</sup> Functional endoscopic sinus surgery (FESS)/endoscopic sinus surgery (ESS) as described by Messerklinger has been accepted as the choice of treatment modality for chronic sinus disease.<sup>3</sup> Though there are advances in instrumentation and surgical technique, postoperative adhesions, synechia formation continue to occur between 1 and 27%.<sup>4</sup> The incidence of adhesions requiring surgical intervention is 1 to 2%.<sup>5</sup>

*Mitomycin-C (MMC):* MMC is an alkylating antineoplastic antibiotic that prevents replication of fibroblasts and epithelial cells, in otolaryngology MMC is currently under inquiry for the prevention of laryngotracheal stenosis, as an adjunct to FESS to prevent closure of the maxillary sinus antrostomy.<sup>4</sup> MMC operates by disrupting base pairing of DNA molecules in the G-1 phase of cell cycle, and inhibits formation of RNA and protein synthesis—this way inhibits proliferation of fibroblasts. Additional function is inhibition of apoptosis in fibroblasts and blockage of angiogenesis. Topical applications of MMC over last decade extended to fields of plastic surgery and rhinology especially endoscopic sinus surgery (ESS) and dacryocystorhinostomy (DCR).<sup>6,7</sup> The concentration of MMC ranged from to 1.5 ml 0.3 mg/ml to 0.6 mg/ml, whereas dose applied ranged from 0.5 ml and duration of topical MMC application was 5 minutes in majority (7 out of 9) of studies, 4 minutes in 2 studies. Application method was in the way of soaked cotton pledgets 5 in 9 studies, ribbon gauze in 2 studies and Merocel pack in 1 study. No studies report any adverse

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effects or systemic toxicity of topical MMC applied for 5 minutes and in maximum concentrations 0.6 mg/ml and maximum dose of 1.5 ml. Years of experiences from ophthalmologists shown that MMC in concentration of 0.4 mg/ml for 5 minutes appears to be very safe.<sup>7</sup>

The aim of the study was to determine whether topical application of mitomycin-C at the conclusion of FESS decreases the incidence of postoperative adhesion formation.

## MATERIALS AND METHODS

*Study design and duration:* Prospective cross-sectional study, June 2011 to June 2013.

*Source of data:* Patients attending the OPD/IPD of KLES Dr Prabhakar Kore Hospital and MRC, Belgaum, a tertiary referral hospital were included. The patients with symptoms suggestive of chronic sinusitis as per rhinosinusitis task force (RSTF) criteria were evaluated by their symptoms, subjected to SNOT score, CT scan of paranasal sinuses (PNS) and endoscopic findings. Forty-two patients between the ages 17 and 66 years with clinical and radiological profile of chronic rhinosinusitis undergoing ESS by single surgeon were taken up for the study. The study was approved by the institutional ethical committee. Written and informed consent was taken from all patients regarding the procedure as per the proforma approved by institutional ethical committee.

*Inclusion and exclusion criteria:* Patients with features suggestive of chronic CRS with or without nasal polyposis, willing to undergo CT scan PNS and ESS were included in the study.

Patients with acute exacerbation of symptoms, established asthma, suspected cystic fibrosis, patients refusing to undergo CT scan, patients with established or impending complications, patients refusing endoscopic surgery and patients with prior sinus surgeries were excluded from the study.

*Methodology:* During the 2-year study period between June 2011 and June 2013, 42 patients underwent ESS at the hands of single surgeon, in 23 cases, ESS was done bilaterally and, in 19 cases, ESS was done unilaterally thus making a total of 65 operated sides. All patients were subjected to detailed history taking about their symptoms and a thorough and meticulous clinical examination. Subjective evaluation included documentation of severity of the 4 symptoms—facial pain/pressure, nasal obstruction, nasal discharge and disturbances of smell, and SNOT<sup>8</sup> score. Objectively endoscopic findings (Lund Kennedy scoring) and CT scan of paranasal sinuses (Lund Mackay scoring) was done to document the findings.

After thorough counseling about the procedure the patients were subjected to ESS. Out of 42 cases 38 were

operated under local anesthesia and four cases that were not cooperative were operated under general anesthesia. Broadly the ESS included uncinectomy, middle meatal antrostomy, anterior or total ethmoidal clearance, sphenoidal and frontal recess clearance. Additional procedures like septoplasty, turbinoplasty and middle turbinate resection were performed in indicated cases. After the completion of procedure, a cotton ribbon wick soaked in 1 ml of mitomycin-C (MMC) in a concentration of 0.4 mg/ml was placed in middle meatus and near maxillary sinus ostia, sphenoid sinus ostia and frontal recess area for a period of 4 minutes. One vial contains 2 mg of MMC which was diluted with 5 ml sterile water to obtain the above concentration. Following application, nasal cavity was irrigated with about 60 ml sterile normal saline. At the end of surgery, light anterior nasal packing was done using ribbon gauze soaked with steroid and antibiotic ointment. All patients were discharged the day after surgery after pack removal on oral antibiotic for 2 weeks, nasal saline washing three times a day, topical steroid spray twice a day for 3 weeks in each nasal cavity.

Follow-up visits were done at weekly for first 2 weeks and then at 1st, 2nd and 3rd months. At follow-up visit, the following factors were evaluated:

- *Subjective parameters:* Facial pain/pressure, nasal block, discharge and hyposmia and SNOT score.
- *Objective parameters:* Presence of adhesions/synechiae, crusting, discharge, polypoidal changes and measurement of maxillary sinus ostial size.

Adhesions were noted as per the types A-D: type A—adhesion at the junction of anterior end of middle turbinate and lateral wall, type B—partial adhesion between middle turbinate and lateral wall, type C—complete adhesion between middle turbinate and lateral nasal wall with obliteration of middle meatus and type D—adhesion between middle turbinate or inferior turbinate with septum.<sup>5</sup>

For the measurement of ostial size a graded suction tip was used. For maxillary sinus ostium following grades were used. Grade 1—0 to 5 mm, grade 2—6 to 10 mm and grade 3—10 mm.

## STATISTICAL ANALYSIS

Statistical analysis was done using SPSS-16 version and apart from demographic data of cases, paired t-test, Wilcoxon signed rank test, McNemer's test were used and  $p < 0.05$  was considered as significant.

## RESULTS

In this study, 42 patients (22 males, 20 females) between the ages 17 and 66 were evaluated. The mean age was  $32.3 \pm 11.95$  years.

**Table 1:** Comparison of pre- and postoperative symptom scores

Symptoms	Severity grading— preoperative							Severity grading— 3 months postoperative							Statistical test applied
	0	1	2	3	4	5	Total	0	1	2	3	4	5	Total	Wilcoxon's signed rank test
Facial pain	13	0	5	15	9	0	42	41	1	0	0	0	0	42	p < 0.001
Nasal obstruction	0	1	1	12	26	2	42	15	27	0	0	0	0	42	p < 0.001
Nasal discharge	10	4	7	18	3	0	42	17	25	0	0	0	0	42	p < 0.001
Hyposmia	34	2	4	0	2	0	42	34	6	0	0	2	0	42	p = 0.046
Mean of preoperative score								8.24 ± 2.34							
Mean of postoperative score								1.59 ± 1.08							
Mean difference								6.64 ± 1.80							
Paired t-test								p < 0.001							

**Table 2:** Pre- and postoperative total SNOT score comparison

Mean of preoperative score	25.02 ± 11.55
Mean of postoperative score	07.26 ± 5.01
Mean difference	17.76 ± 8.17
Paired t-test	p < 0.001

All 42 (100%) patients presented with nasal obstruction and in 40 patients it was of more severe nature ( $\geq$  grade 3). The other symptoms in order of frequency of presentation were facial pain in 29 (69%), nasal discharge in 32 (76.1%) and smell disturbance in 8 (19.4%) patients. The mean preoperative symptom score was  $8.24 \pm 2.34$ .

When assessed 3 months postoperatively, facial pain was relieved in 28 (96.6%) of 29 patients, nasal obstruction was improved in 41 (97.6%) of 42 cases and nasal discharge was improved in 28 (87.5%) of 32 patients. Out of 8 cases of hyposmia, 4 cases had improvement in severity and 4 cases had no improvement. For facial pain, nasal discharge, nasal obstruction the postoperative score improvement was statistically significant ( $p < 0.001$ ) and for hyposmia also it was significant ( $p = 0.046$ ). The mean postoperative score was  $1.59 \pm 1.08$  (decreased by 80%) and mean difference was  $6.64 \pm 1.80$  which was statistically significant ( $p < 0.001$ , Table 1).

Total SNOT score was obtained by taking sum of all 20 questions pre and postoperatively. The overall mean preoperative SNOT total score was  $25.02 \pm 1.35$  and postoperative total score was  $7.26 \pm 5.01$  (decreased by 71%) with mean difference of  $17.76 \pm 8.17$ . The improvement in SNOT score was statistically significant ( $p < 0.001$ , Table 2).

Preoperative endoscopy (Lund Kennedy score)—42 patients constituted 84 sides endoscopically. Discharge was present in 65 sides, odema was present in 64 sides and polyp was present in 24 sides. Mean Lund Kennedy score (out of 6) on right side was  $2.3 \pm 1.74$  and on left side was  $2.9 \pm 1.62$ .

CT scan PNS (Lund Mackey score) details were noted to know the involvement of sinuses and extent of disease. Maxillary sinus and osteomeatal complex were showing positive findings in 61 (93.85%) sides each, ethmoids were involved in 48 (73.83%) sides [anterior ethmoids in 15 (23.07%) and total ethmoids in 33 (50.76%) sides] and

**Table 3:** Operative procedures performed

Procedure done	Right side	Left side	Total (%)
Uncinectomy	30	34	64 (98.50)
Ant. ethmoidectomy	5	10	15 (23.07)
Total ethmoidectomy	14	19	33 (50.76)

frontal and sphenoid sinuses were less involved. The mean score on right was  $4.59 \pm 3.71$  and on left side was  $5.19 \pm 3.24$  (Fig. 1).

*Procedures done:* In 42 patients, 23 patients underwent ESS bilaterally and 19 patients unilaterally thus making total of 65 sides of surgery. Out of these 65 procedures uncinectomy was done in 64 (98.5%), middle meatus antrostomy with osteomeatal clearance was done in 62 (95.4%), total ethmoidectomy was done in 33 (50.7%), anterior ethmoidectomy was done in 15 (23.1%), frontal recess clearance in 18 (27.7%), sphenoid sinus clearance in 21 (32.3%) (Table 3).

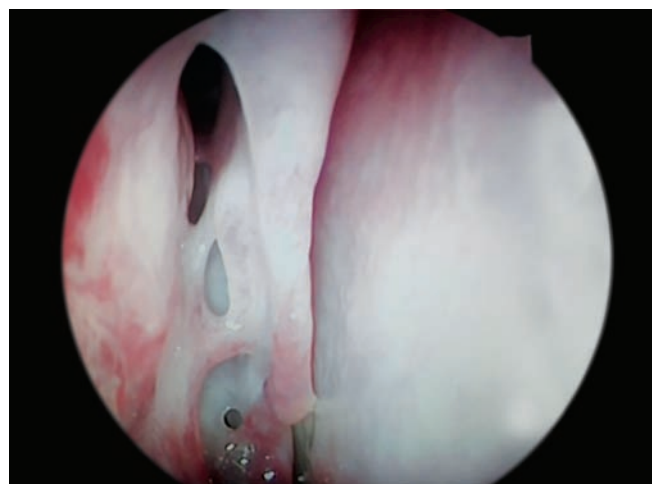
Additional procedures done were septoplasty in 19 patients and turbinoplasty/partial resection of middle turbinate in 16 cases on each side.

At 1 month follow-up, synechia was found in 19 (29.2%) cases while crusting, polypoidal mucosa and discharge were found in 52 (80%), 44 (67.7%) and 64 (98.5%) cases respectively. The synechia were mild (Type A) to moderate (Type B) grade which were released, cottonoid soaked with decongestant was placed. Suction-clearance and debridement of crusts was done. During second follow-up, we had synechia in 8 (12.3%), crusting in 4 (6.2%), polypoidal mucosa in 9 (13.8%) and discharge in 39 (60%) cases. At third follow-up, we had 2 (3.1%) cases with synechia (Type A), no crusting, polypoidal mucosa in 1 (1.5%) and discharge in 3 (4.6%) cases (Table 4, Fig. 2).

At first follow-up, there were 60 maxillary sinus ostia of grade 3 and 2 of grade 2 and at second follow-up 33 were grade 3 and 29 were grade 2. At third follow-up, we had 59 grade 2 and 3 grade 3 cases which shows progressive narrowing of maxillary sinus ostium from first to second and from first to third follow-up, which was statistically significant ( $p < 0.001$ , McNemer's test). No local or systemic side-effects of MMC application were noted in any of our patients.



**Fig. 1:** Computed tomography scan showing involvement of frontal, maxillary and ethmoidal sinuses bilaterally



**Fig. 2:** Partial adhesion between right middle turbinate and lateral nasal wall, clear frontal recess area

**DISCUSSION**

At the completion of sinonasal surgery when injured surfaces are in close proximity, the regenerating epithelium and fibrous tissue may grow between these surfaces creating an adhesion. Attempts to limit such adhesion formation with anatomical barriers have met with limited success.<sup>4</sup> Animal studies in rabbits suggest that MMC slows the postoperative healing process of nasal mucosa, reduces stenosis without affecting re-epithelialization. Experimental studies observed the effects of brief exposure of MMC on cultured human nasal mucosa fibroblasts.<sup>7</sup>

Chung et al,<sup>9</sup> in their case-control study, reported 29% adhesions occurring within 2 months of these 3.6% were in MMC treated side and rate of adhesions were less as compared on control side. A case-control trial by Gupta M and Motwani<sup>10</sup> showed 3% synechiae formation at end of 3 months.

In this study, the rate of adhesion formation was 3.1% adhesions at 3rd month follow-up and was comparable to above two studies.

In a case-control study by Baradaranfar MH et al<sup>5</sup> 32.4% had adhesions., among these 10.8% were on MMC side and 27% were on control side which shows the beneficial effect of MMC in prevention of adhesions. Studies by Venkatraman V<sup>11</sup> and Tilakraj Singh<sup>3</sup> showed decreased incidence of adhesions, improvement in symptoms and decreased adverse tissue reactions (like

discharge, polypoidal mucosa, crusting) after topical MMC application and more the concentration of MMC, better the results.

Kim ST et al<sup>12</sup> in their study showed beneficial effect of MMC at 3 months follow-up, but no effect in decreasing the incidence of stenosis and closure of antrostomy at 6 months and in long-term follow-up. According to this study, MMC has only a short-term effect and no effect on long-term. None of these studies reported any local or systemic side effect of MMC application.

The results from available studies<sup>6,7</sup> reveal the usage of MMC in varied duration, frequency and concentrations in ESS.

**CONCLUSION**

Local application of MMC at end of ESS has beneficial role in prevention of adhesion formation without any side effects/complications. Limitations of our study were limited sample size as cases operated by single surgeon were included and there is a need for case control trial for strengthening the results. Further studies are required in this field to establish the concentration and frequency of MMC usage.

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**Table 4:** Postoperative endoscopic findings

	First follow-up (%)	Second follow-up (%)	Third follow-up (%)
Synechiae	19 (29.2)	8 (12.3)	2 (3.1)
Crusting	52 (80)	4 (6.2)	0 (0)
Polypoidal mucosa	44 (67.7)	9 (13.8)	1 (1.5)
Discharge	64 (98.5)	39 (60)	3 (4.6)

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