

EFFECTIVENESS OF MITOMYCIN-C FOR PREVENTION OF ADHESION FORMATION AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS/ESS) IN CASES OF CHRONIC RHINOSINUSITIS: A PROSPECTIVE HOSPITAL BASED INTERVENTIONAL 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 hospital based interventional study. **MATERIALS AND METHODS:** Between June 2011-June 2013, 42 patients (65 sides) aged between 16-66 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 4mins. 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 month post-operatively. 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 ± 1.80 , $p < 0.001$). Similarly in Sino-nasal outcome test (SNOT) score we observed a significant reduction (71%) in scores (17.76 ± 8.17 , $p < 0.001$) and 3.1% cases showed adhesions. **CONCLUSIONS:** 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 rhino- sinusitis, Synechiae, Adhesions, FESS/ESS, Topical Mitomycin-C, SNOT score.

INTRODUCTION: Chronic rhino sinusitis (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.^{1,2} 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.³ Though there are advances in instrumentation and surgical technique, postoperative adhesions, synechiae formation continue to occur between 1-27%.⁴ The incidence of adhesions requiring surgical intervention is 1-2%.⁵

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

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sinus antrostomy.⁴ 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).^{6,7} The concentration of MMC ranged from 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 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.⁷

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 hospital based interventional study between 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. 42 patients between the ages 17 to 66 years with clinical and radiological profile of chronic rhino-sinusitis undergoing ESS by single surgeon was 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 two-year study period between June 2011 to 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 SNOT⁸ score. Objectively endoscopic findings (Lund Kennedy Scoring) and CT scan of para-nasal sinuses (Lund Mackay scoring) was done to document the findings.

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After thorough counseling about the procedure the patients were subjected to ESS. Out of 42 cases 38 were operated under local anaesthesia and 4 cases who were not cooperative were operated under general anaesthesia. 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 1ml of Mitomycin-C (MMC) in a concentration of 0.4mg/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 5ml 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 two weeks, nasal saline washing three times a day, topical steroid spray twice a day for three weeks in each nasal cavity.

Follow up visits were done at weekly for first two weeks and then at 1st, 2nd and 3rd month. 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.⁵

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 10mm and Grade 3 - > 10mm

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 male, 20 female) between the ages 17 to 66 were evaluated. The mean age was 32.3 ± 11.95 years. 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 pre op symptom score was 8.24 ± 2.34 .

When assessed 3 month post-operatively, 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 post-operative score improvement was statistically significant ($p < 0.001$) and for hyposmia also it was significant ($p = 0.046$). The mean post-operative score was 1.59 ± 1.08 (decreased by 80%) and mean difference was 6.64 ± 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 post operatively. The overall mean pre-operative SNOT total score was 25.02 ± 1.35 and post-operative total score was 7.26 ± 5.01 (decreased by 71%) with mean difference of 17.76 ± 8.17 . The improvement in SNOT score was statistically significant ($p < 0.001$, Table 2).

Pre-operative 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 ± 1.74 and on left side was 2.9 ± 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 frontal and sphenoid sinuses were less involved. The mean score on right was 4.59 ± 3.71 and on left side was 5.19 ± 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%). 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 synechiae 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 synechiae were mild(Type A) to moderate(Type B) grade which were released. Suction-clearance and debridement of crusts was done. During second follow up we had synechiae 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 synechiae (Type A), no crusting, polypoidal mucosa in 1(1.5%) and discharge in 3(4.6%) cases. (Table 3, 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.

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.⁴ Animal studies in rabbits suggest that MMC slows the postoperative healing process of nasal mucosa, reduces stenosis without affecting re-epithelialization.

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Experimental studies observed the effects of brief exposure of MMC on cultured human nasal mucosa fibroblasts.⁷

Chung et al⁹ 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 Motwani¹⁰ 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 al⁵ 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 V¹¹ and Tilakraj Singh³ 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 S T et al¹² 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^{6,7} reveal the usage of MMC in varied duration, frequency and concentrations in ESS.

In 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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Fig. 1: CT scan showing involvement of Bilateral Frontal, Maxillary and ethmoid sinuses

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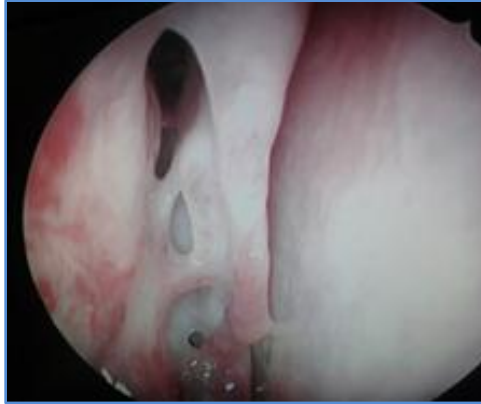


Fig. 2: Type a adhesion-Partial adhesion between right middle turbinate and lateral nasal wall, clear frontal recess area

Symptoms	Severity grading- Pre-op							Severity grading – 3 Months Post-op							Statistical Test Applied
	0	1	2	3	4	5	To tal	0	1	2	3	4	5	To tal	
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 pre-op score	8.24± 2.34														
Mean of post- op score	1.59± 1.08														
Mean difference	6.64± 1.80														
Paired t-test	p<0.001														

Table 1: Comparison of pre and post-operative symptom scores

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Mean of pre-op score	25.02± 11.55
Mean of post-op score	07.26± 5.01
Mean difference	17.76± 8.17
Paired t-test	p<0.001

Table 2: Pre and Post-operative total snout score comparison

	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%)

Table 3: Post-operative endoscopic findings

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