



**MITOMYCIN-C AS PANACEA FOR PREVENTION OF ADHESION FORMATION
AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS/ESS) IN CASES OF
CHRONIC RHINOSINUSITIS (CRS)**

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ABSTRACT

Objective: To determine the beneficial effect of topical application of Mitomycin-C at the conclusion of FESS in reduction of the incidence and grade of postoperative adhesion formation. **Study Design:** Prospective hospital based interventional study. **Materials and Methods:** Between May2011-July2014, a total of 150 patients underwent FESS. Among these, 75 were included in Group A (Interventional-MMC) and 75 in group B (Control-Saline). The group-A underwent topical MMC application and Group-B normal saline application at the end of FESS. In both Group A and Group B, the age group varied from 17-66 years and there were 30 unilateral and 45 bilateral sides -thus making a total of 120 operative sides in each group. Patients were followed up weekly for first two weeks and at end of 1st, 2nd and 3rd month. Rate of adhesions were recorded and graded as per types A-D. **Results:** Rate of adhesions at first follow up was 28.33% and 60.83%, at second follow up 15.83% and 36.67% and at third follow up 5% and 25% in Group A and group B respectively. The expected difference in the rate of adhesions between the groups was 11% as per the research hypothesis. The observed difference of 20% was higher than the expected one strengthening the research hypothesis. On comparison, the grades of adhesions in group A were significantly less than group B (p<0.05). **Conclusions:** Topical application of Mitomycin-C at the conclusion of FESS/ESS has a role in prevention of adhesion formation and reduces both the incidence as well as the grade of adhesion.

KEYWORDS: Chronic rhino- sinusitis, Synechiae, grade of adhesions, FESS/ESS, Topical Mitomycin-C.

INTRODUCTION

Chronic rhino sinusitis (CRS) is the most common encountered disease affecting over 30 million individuals each year. Annually around more than 2,00,000 people require surgical intervention. As per the western literature, it is more prevalent than hypertension and arthritis and affects around 5% to 15% of the population.^[1,2] Functional endoscopic sinus surgery (FESS) / Endoscopic sinus surgery (ESS), described by Messerklinger is the choice of treatment modality for chronic sinus disease.^[3] In spite of advances in instrumentation and surgical technique, there is 1-27% rate of postoperative adhesions/ synechiae formation.^[4] The incidence of adhesions requiring surgical intervention is around 1-2%.^[5]

Mitomycin- C (MMC) is an alkylating antineoplastic antibiotic which prevents replication of fibroblasts and epithelial cells. Currently, in otolaryngology MMC is under inquisition for the prevention of laryngotracheal stenosis and as an adjunct to FESS to prevent closure of the maxillary sinus antrostomy.^[4] MMC acts in the G-1 phase of cell cycle by disrupting base pairing of DNA molecules. It prevents proliferation of fibroblasts by inhibiting formation of RNA and protein synthesis. Inhibition of apoptosis in fibroblasts and blockage of angiogenesis are its additional functions. Over last decade, topical applications of MMC has extended to fields of plastic surgery and rhinology, especially in surgeries like endoscopic sinus surgery (ESS) and dacryocystorhinostomy (DCR).^[6,7] The concentration of

topical MMC ranged from 0.3 mg/mL to 0.6 mg/mL, whereas dose applied ranged from 0.5 mL to 1.5 mL. Duration of topical MMC application was 5 minutes in majority (7 out of 9) of studies and 4 minutes in 2 studies. Application method was in the way of soaked cotton pledgets in 5 studies, ribbon gauze in 2 studies and Merocel pack in 1 study. No studies reported any adverse effects or systemic toxicity of topical MMC applied for 5 minutes and maximum concentration was of 0.6 mg/ml and maximum dose of 1.5 ml. Ophthalmologists have shown that MMC in concentration of 0.4 mg/ml for 5 minutes to be very safe⁷ There are few studies which take into account grades of post operative adhesion formation after topical MMC application. The aim of our study was to determine whether topical application of Mitomycin-C at the conclusion of FESS decreases the incidence of rate and grades of postoperative adhesion formation.

MATERIALS AND METHODS

Study design and Sampling Method

The study was a prospective hospital based interventional study. It comprised of 150 patients - 75 patients in Group A (Interventional-MMC) and 75 patients in group B (Control-Saline). The groups were comparable in terms of Age, Sex, Symptoms, Pre-operative CT scoring and Pre-operative endoscopic scoring as per the guidelines of the study design (Table.1). The patients with clinical, pre-operative CT scan and endoscopic profile of Chronic Rhino-Sinusitis (CRS) undergoing FESS were included in the study.

Study duration

The study was conducted "between" May 2011 to July 2014 at tertiary referral hospital and all the patients underwent uniform recording of their clinical recordings, surgical procedure as needed and follow up protocol as per the standard operating protocol (SOP). The follow-up period varied from 3 months to 12 months. The minimum follow up being 3 months as per the protocol.

Ethical approval

The study was approved by the institutional ethical committee. After confirmation that topical application of MMC may be beneficial to subjects, it is cost effective and there are no side effects noted as per the available literature, the research was approved as per the letter no KLEU/D/6564-67 dated 29th June 2010. Written and informed consent was taken in Kannada/ Marathi/ English languages from all patients regarding the procedure as per the proforma and standard operating protocol (SOP) 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.

Sample size: Sample size was calculated based on the reported rate of adhesions.^[8] Considering 10% dropouts during the study period, the final sample size of 120 sides was taken in each group.

Research hypothesis

A study by Chung *et al.*^[8] showed 14.5% adhesions in controls (Normal saline) and 3.6% in cases (MMC). The expected decrease in the rate of adhesions would be 11% as compared to normal saline. With this research hypothesis, the study was carried out to know the effect of topical MMC on post-operative adhesions formation with respect to the rate of adhesions, grades and difference in the rate of adhesions.

Source of Data and study setting

Patients attending the OPD/IPD of KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi, a tertiary referral hospital were included for the study. The subjects underwent FESS and were followed up as per the protocol.

Methodology

During the three years and 2 months study period "between" May 2011-July 2014, total 150 patients underwent FESS. All patients were subjected to detailed history taking about their symptoms and a thorough and meticulous clinical examination. Endoscopic findings (Lund Kennedy Scoring) and pre-op CT scan of PNS (Lund Mackay scoring) was done to document the findings. After thorough counseling about the procedure, the patients were subjected to FESS.

Among 150 patients, 75 patients were included in Group A (Interventional-MMC) and 75 patients in group B (Control-Saline). The group-A (MMC group) underwent topical MMC application at the end of FESS and the Group-B (Saline group) underwent normal saline application at the end of FESS.

In Group A (75 patients with topical MMC application group), the age group varied from 17-66 years and there were 30 unilateral and 45 bilateral sides -thus making a total of 120 operative sides. Similarly in Group B (75 patients with normal saline [NS] application group), the age group varied from 17-66 years and there were 30 unilateral and 45 bilateral sides -thus making a total of 120 operative sides. Thus the sample size of 120 sides was reached in each group.

Out of 150 patients, 133 were operated under local anaesthesia and 17 patients (8 in group-A and 9 in group-B) who were not cooperative were operated under general anaesthesia. Broadly the FESS included uncinectomy, middle meatal antrostomy with maxillary

sinus clearance, anterior or total ethmoidal, sphenoidal and frontal recess clearance.

After the completion of procedure in group-A, a cotton ribbon wick soaked in 1ml of Mitomycin-C (MMC) in a concentration of 0.4mg/ml was placed 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 to remove remaining MMC at the local site.

Likewise in Group-B, a cotton ribbon wick soaked in 1ml of 0.9% normal saline was placed for a period of 4 minutes.

At the end of surgery, light anterior nasal packing was done using ribbon gauze soaked with steroid and antibiotic ointment. All patients were discharge on 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. 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. Type A was with mild grade of adhesion and Type D was severe grade of adhesion.^[5]

Statistical Analysis

A statistical analysis was carried out by using independent t test for continuous demographic

characteristics, chi-square test for categorical data, Wilcoxon matched pairs test for prospective categorical data using SPSS 20.0 version. The statistical significance was set at 5% level of significance ($P < 0.05$).

RESULTS

In this study total 150 subjects, who were fulfilling the inclusion criteria, were divided into 2 groups, each group comprising of 75 subjects. In both group A and group B number of patients with unilateral involvement were 30 and bilateral involvement were 45 and thus total operative sides in each group were 120. The age range in group A and group B was 17-66 and the mean age in group A (cases) was 34.5 and in group B (controls) was 36.6. On comparison, both groups were comparable and statistically there was a fair distribution of cases between two groups ($p=0.343$, Table-1). The number of males (61.3% in Group A and 69.3% in Group B) were more than females (38.7% in Group A and 30.67% in Group B) and Chi square test revealed $p = 0.3033$ signifying a fair distribution of the cases amongst both sexes.

The total Lund McKay CT scoring was done for group A and B. On comparing the two groups, they were found to have similar mean scores of both left and right side (Table-1). The difference between the two groups was statistically insignificant (unpaired t test, $p > 0.05$) which implies that both the groups were comparable with respect to CT scoring.

Total Lund Kennedy endoscopic scoring of the two groups was done bilaterally (Table-1). On statistical analysis of the two groups by unpaired t test, the cases and controls were found to be comparable in terms of endoscopic findings on both right and left side ($p=0.78$ and 0.929 respectively).

Table 1: Demographic data, radiological (CT) and Endoscopic comparison between group A and group B.

Sr. No		Group A	Group B	t	P
1.	Age Range	17-66	17-66	T=0.951	0.343
	Mean	34.5	34.6	Df=148	
	SD	12.75	13.17		
2.	CT Right	5.1 ± 3.46	4.9 ± 3.3	0.264	0.792
3.	CT Left	6.4 ± 6.34	5.4 ± 3.23	1.265	0.208
4.	Endoscopic Right	3.2 ± 4.14	3.1 ± 1.85	0.280	0.780
5.	Endoscopic Left	3.1 ± 1.63	3.1 ± 1.99	0.090	0.929

Middle Meatal Antrostomy (MMA) with clearance of maxillary sinus was the commonest procedure done in 98.33% patients (96.66% in Group-A and 100% in Group-B). Ethmoidal disease clearance was the second common procedure to be performed-Total ethmoidal clearance was done in 44.17 of patients (48.33% in Group-A and 40% in Group-B). Clearance of anterior ethmoids was performed in 22.49% of patients and it was done in almost equal number of patients (23.33% in

Group-A and 21.66% in Group-B). Sphenoid sinus clearance was done in 22.92% of patients (Group-A 25.83% and Group-B 20%). Frontal clearance was done in 14.58% of patients and was least affected in both the groups. (Group-A 19.16% and Group-B 10%).

Rate of adhesion (Table 2)

The rate of adhesions found at first, second and third follow up were studied in group A (cases) and group B

(controls). The rate of adhesions found were significantly less in group A as compared to group B.

At first follow up the rate of adhesions in group A was 28.33% and in group B was 60.83%. On comparing there was a significant difference found between the groups (Chi-square=25.6511, p=0.00001).

At second follow up the rate of adhesions in group A was 15.83% and in group B was 36.67%. On comparing there was a significant difference found between the groups (Chi-square=13.4521, p=0.0002).

At third follow up the rate of adhesions in group A was 5% and in group B was 25%. On comparing there was a significant difference found between the groups (Chi-square=18.8241, p=0.00001).

The rate of adhesions were compared in both the groups, at first and second follow up, first and third follow up and second and third follow up. In all the observations there was a significant difference found at each of the above mentioned follow up periods (p<0.05).

Table 2: Comparison of Group A and Group B with Adhesion at FU1, FU2 and FU3.

Adhesion	Status	Group A	%	Group B	%	Total
FU1	Absent	86	71.67	47	39.17	133
	Present	34	28.33	73	60.83	107
	Chi-square=25.6511, p=0.00001*					
FU2	Absent	101	84.17	76	63.33	177
	Present	19	15.83	44	36.67	63
	Chi-square=13.4521, p=0.0002*					
FU3	Absent	114	95.00	90	75.00	204
	Present	6	5.00	30	25.00	36
	Chi-square=18.8241, p=0.00001*					
Wilcoxon matched pairs test	Total	120	100.00	120	100.00	240
	FU1 vs FU2	Z=3.4078	p=0.0007*	Z=4.7030	p=0.00001*	
	FU1 vs FU3	Z=4.6226	p=0.00001*	Z=5.7115	p=0.00001*	
	FU2 vs FU3	Z=3.1798	p=0.0015*	Z=3.2958	p=0.0010*	

*p<0.05

Grade of adhesions (Table 3)

At first follow up (FU-1), in group A 71.67% of patients had no adhesions and in group-B 39.17% did not have adhesions. The severe type C and D adhesions were more in group B (29.17%) whereas a lesser in group A (5%), signifying less severity of adhesions in group A. The difference was found to be statistically significant (Chi-square=36.0614, p=0.00001).

At second follow up (FU-2), in group-A 84.17% patients had no adhesions and in group-B 63.33% had no adhesions. The type-C adhesions found in group B were 1.67%. The type-B adhesions observed in group B (27.5%) were more than in group A (5%). The difference was found to be statistically significant (Chi-square=24.9513, p=0.00002).

At third follow up (FU-3), in group A 95% of patients had no adhesions (Fig.1) and 5% had no adhesions in group B. Type-A adhesions (Fig.2) were more in group B (25%) than in group A (5%). The difference between the two groups was found to be statistically significant. (Chi square=18.8241, p=0.00001).



Fig. 1: Post-operative healthy mucosa, No adhesions.

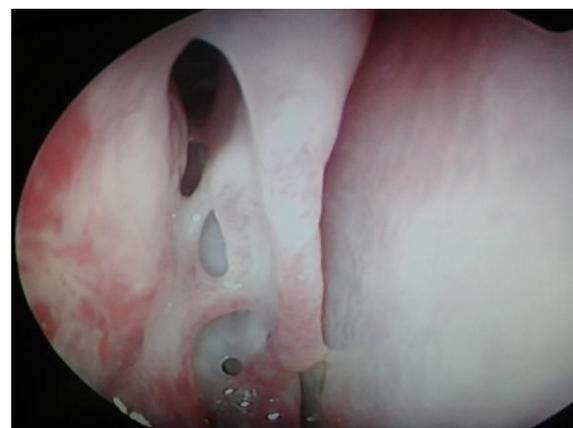


Fig. 2: Post-operative Type A adhesion.

Table 3: Comparison of Group A and Group B with Adhesion Grades at FU1, FU2 and FU3.

Adhesion	Grades	Group A	%	Group B	%	Total
FU-1	A	86	71.67	47	39.17	133
	B	15	12.50	13	10.83	28
	C	13	10.83	25	20.83	38
	D	6	5.00	35	29.17	41
	Chi-square=36.0614, p=0.00001*					
FU-2	A	101	84.17	76	63.33	177
	B	13	10.83	9	7.50	22
	C	6	5.00	33	27.50	39
	D	0	0.00	2	1.67	2
	Chi-square=24.9513, p=0.00002*					
FU-3	A	114	95.00	90	75.00	204
	B	6	5.00	30	25.00	36
	Chi-square=18.8241, p=0.00001*					
	Total	120	100.00	120	100.00	240
Wilcoxon matched pairs test	FU1 vs FU2	Z=5.0862	p=0.00001*	Z=7.3227	p=0.00001*	
	FU1 vs FU3	Z=5.0862	p=0.00001*	Z=7.4244	p=0.00001*	
	FU2 vs FU3	Z=3.8230	p=0.0001*	Z=5.7767	p=0.00001*	

*p<0.05

The grades of adhesions were compared in both the groups, at first and second follow up, first and third follow up and second and third follow up. In all the observations there was a statistically significant difference found with respect to grades of adhesions. Thus, the grades of adhesions observed in group A were significantly less than in group B (p<0.05).

DISCUSSION

At the completion of sinonasal surgery due to close proximity of the injured surfaces, the regenerating epithelium and fibrous tissue grows between these surfaces creating an adhesion. Attempts to prevent such adhesion formation with anatomical barriers have shown little success.^[4] Animal studies in rabbits have shown that MMC reduces stenosis and slows the postoperative healing process of nasal mucosa, without affecting re-epithelialization. There are experimental studies observing the effects of exposure of MMC on cultured human nasal mucosa fibroblasts.^[7]

In this study the rate of adhesion formation at last follow up, was 5% in group A and 25% in group B. The

difference in the rate of adhesions was 20%. On statistical analysis there was a significant difference between the groups (Chi-square=18.8241, p=0.00001). The expected difference in the rate of adhesions between the groups was 11% as per the research hypothesis. The observed difference of 20% was higher than the expected one strengthening the research hypothesis.

In a case-control study by Baradaranfar MH et al (2011)⁵ total 32.4% had adhesions. Among these 27% were on control side and 10.8% were on MMC side and the difference was around 16%. Various authors like Chung et al (2002)^[8] had shown 14.5% adhesions in controls and 3.6% in cases and the difference was around 11%. Gupta M and Motwani (2007)^[9] in their study, had 37% adhesions in controls and 3% in cases, the difference being 34%.

Thus, there is a wide range in the difference of rate of adhesions in various studies which varies from 11-34% (Table-4) and our value lies in this range, being on the higher side of the range. This signifies the effectiveness of topical MMC.

Table 4: The rate of adhesions and the difference in rate of adhesions in various studies.

Sr. No	Author	Adhesions in cases (MMC)	Adhesions in controls (NS)	Difference in rate of adhesions
1.	Chung et al (2002) ^[8]	3.6%	14.5%	11%
2.	Gupta M et al (2006) ^[9]	3%	37%	34%
3.	Baradaranfar MH et al (2011) ^[5]	10.8%	27%	16%
4.	Present Study	5%	25%	20%

Studies by Venkatraman V^[10] and Tilakraj Singh^[3] showed decreased incidence of adhesions, improvement in symptoms and decreased adverse tissue reactions (like discharge, polypoidal mucosa, crusting) after topical

MMC application. They further suggested that more the concentration of MMC, better the results.

Kim S T et al.^[11] 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. None of these studies reported any local or systemic side effect of MMC application.

The grades of adhesions at each follow-up in the present study showed that type C and D were more in group B than group A. The 3rd follow-up showed none of the patients having type B, C or D adhesions but there were type A adhesions in both group A (5%) and group B (25%). There was a gradual shift from higher to lower grade of adhesions at each follow-up. The comparative statistical analysis between the groups showed significant difference ($p < 0.05$) at each follow ups.

A study by Baradaranfar MH *et al* (2011)^[5] showed 14 adhesions out of which- 2 were type A, 7 type B, 1 type C and 4 type D. Out of these 14, 1 was severe while rest 13 were mild and without interfering in the direction of sinus drainage. On comparison of our study with the above study, our study had less number of type B and C adhesions and more of type A adhesions. This could be attributed to the fact that Baradaranfar MH *et al* (2011)^[5] included revision cases also in their study, which were excluded from our study.

A study by Chung JH *et al* (2002)^[8] had more number of mild (59%) and less number of moderate (18%) and severe (23%) adhesions within 2 months of surgery.

Similarly Gupta M and Motwani (2007)^[9] in their study found all grades of adhesions predominantly occurring on control side.

Therefore, MMC has a role in decreasing the severity of adhesion formation but meticulous follow-up and proper management of these adhesions is of paramount importance.

CONCLUSION

The topical application of MMC at the end of FESS was helpful with a definite role in reducing the rate of postoperative adhesion formation, without any side effects/complications. Also, the topical MMC application was useful in reducing the grade of postoperative adhesions. Further studies are required in this field to establish the concentration and frequency of MMC usage.

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