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Systematic Review

The impact of mitomycin C in endoscopic sinus surgeries: a comprehensive review

Shivangi Manglik[1]*, Vijay Kalra[2]

Department of Otorhinolaryngology, Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

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***Correspondence:**
Dr. Shivangi Manglik,
E-mail: shivangimanglik@ymail.com

ABSTRACT

Chronic rhinosinusitis (CRS) is an inflammation of the nasal and paranasal sinus linings, often resulting in various debilitating symptoms. Functional endoscopic sinus surgery (FESS) is a common treatment for CRS, aiming to alleviate symptoms by restoring sinus drainage and mucosal repair. However, postoperative complications, including adhesion formation, remain a concern. This systematic review aims to evaluate the effectiveness of mitomycin-C (MMC) in reducing postoperative complications, particularly adhesion formation, in patients undergoing ESS. A systematic review of available evidence on the role of MMC in FESS was conducted. Studies were selected based on predefined inclusion criteria, and relevant data were extracted and synthesized. Nineteen studies met the inclusion criteria, encompassing a total of 763 subjects. The majority of studies reported a reduction in postoperative adhesion formation with MMC use, although statistical significance varied. MMC dosages and application methods varied across studies, contributing to heterogeneity in outcomes. Overall, MMC showed promise in reducing adhesion formation and improving surgical outcomes in FESS. However, further high-quality, prospective, randomized controlled trials are warranted to establish optimal dosage, application methods, and long-term efficacy of MMC in FESS for CRS.

Keywords: CRS, FESS, MMC, Adhesions

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common condition marked by inflammation of the nasal and paranasal sinus linings, which causes nasal obstruction, nasal discharge, facial pain or pressure, and olfactory loss. Nasal polyps may or may not accompany the condition. With clinical improvements reported by about 90% of patients, FESS is currently the most successful treatment for CRS that is resistant to conventional therapy. The concept behind sinus surgery stems from Messerklinger's studies on mucociliary clearance and its role in the pathogenesis of sinusitis. The goals of FESS in the treatment of sinusitis are to enlarge sinus ostia, restore adequate aeration of sinuses, improve mucociliary transport, and provide a better route for topical therapies.[1] FESS aims to gain maximal result (restoring normal function) with minimal trauma and morbidity.[2] The notion behind FESS may seem straightforward, but the anatomical variability and the broad range and severity of diseases addressed in every FESS remain challenges for the surgeon in every case. Pre-operative planning and meticulous management of the postsurgical patient, in addition to rigorous and thorough surgical technique for sinus surgery is the crucial step to obtain optimal results and to avoid all possible complications.

The reported side effects of FESS can be roughly divided into three categories: immediate postoperative complications, like bleeding and crusting; short-term complications, like infection; long-term complications, like adhesion formation, ostial stenosis; refractory disease; and disease recurrence.

Primarily an antineoplastic drug MMC has been found to reduce incidence of scar tissue.

It has been shown to inhibit fibroblast proliferation and activity, which can reduce scar formation.[3] The chemical structure of MMC is depicted in Figure 1.[4]

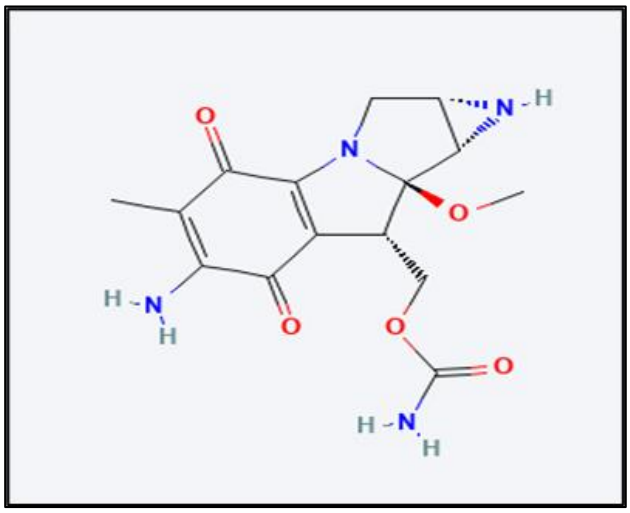

Figure 1: Chemical structure of MMC.

Our objective of the present review was to consolidate multiple studies that depicted use of MMC in endoscopic sinus surgeries and analyse if it reduced the risk of postoperative complications predominantly formation of adhesions or synechiae.

METHODS

We conducted a systematic online search on Google Scholar and PubMed using the terms “FESS”, “MMC” and “adhesions”. Inclusion criteria were, papers published in the last 22 years (i.e., 2002 to 2024); a cohort size of equal to or greater than 20. Excluded from our analysis were case reports and non-English papers. No age limit was set in inclusion and exclusion criteria. To analyse the literature, we collected data on cohort size, the age range of cohort, dose of topical MMC used, time of application (intraoperative or early post-operative), frequency of application, procedure of application, post-operative follows up protocol, efficacy of application and data was collected on any side effects or complications.

RESULTS

Using the search terms "FESS," "MMC," and "adhesions," with a filter set from 2002 to 2024, Google Scholar and PubMed yielded 19 relevant results meeting our inclusion criteria, which were then selected. The results of these studies have been summarised in Table 1-3 and Figure 2.

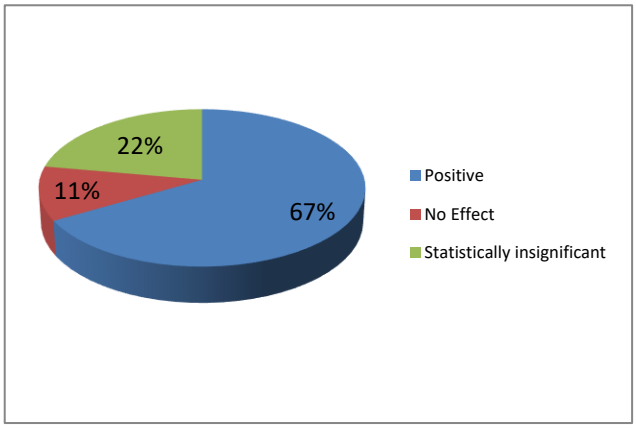

Figure 2: The efficacy of procedure.

Table 1: Summary of study demographics of included clinical studies.

Publication	Study design	Cohort size (N)	Population/ age group (in years)
Chung et al[5]	Prospective study	55	Not specified
Anand et al[6]	Prospective study	29	Not specified
Kim et al[7]	Prospective study	20	Not specified
Gupta et al[8]	Prospective study	30	Not specified
Chan et al[9]	Prospective study	-	Not specified
Konstantinidis et al[10]	Prospective study	30	Not specified
Baradaranfar et al[11]	Prospective study	37	Not specified
Singh et al[12]	Prospective study	30	16-60
Venkatraman et al[13]	Prospective study	50	Not specified
Harugop et al[14]	Prospective study	42	16-66
Khoshsirat et al[15]	Prospective study	30	Not specified
Sadek et al[16]	Prospective study	30	21-52
El Dabaa et al[17]	Prospective study	60	18-50
Ibrahim et al[18]	Prospective study	60	Not specified
Elhussieny et al[19]	Prospective study	50	Not specified
Anwar et al[20]	Prospective study	40	15-29
Ramadan et al[21]	Prospective study	30	18-60
Humayun et al[22]	Prospective study	51	20-42

Table 2: Summary of clinical studies based on peri-procedural protocol.

Authors	Operative/ procedure steps	Conc. of MMC	Quantity of MMC used	MMC application procedure	Duration of application	Control group
Chung et al[5]	FESS	0.4 mg/mL	1 mL	Cotton pledget soaked in MMC placed in middle meatus	4 minutes	Contralateral side treated with saline
Anand et al[6]	FESS	0.5 %	-	Pledget soaked in MMC placed in middle meatus	5 minutes	Contralateral side treated with saline
Kim et al[7]	Middle meatal antrostomy	0.4 mg/mL	1.5 mL	Piece of merocele soaked with MMC applied at site of middle meatal antrostomy.	5 minutes	Contralateral side treated with saline
Gupta et al[8]	FESS using Messerklinger technique	-	-	Cotton wick soaked in MMC placed in middle meatus	-	Contralateral side treated with saline
Chan et al[9]						
Konstantinidi set al[10]	FESS	0.5 mg/mL	1 mL	Pledget soaked in MMC placed in middle meatus	5 minutes	Contralateral side treated with saline
Baradaranfa r et al[11]	Bilateral ESS			Mesh impregnated with MMC placed on 1 side	5 minutes	Contralateral side treated with saline
Singh et al[12]	Bilateral ESS	0.4-0.8 mg/mL	-	Cotton pledget saturated with MMC placed in middle meatus	5 minutes	Contralateral side treated with saline
Venkatrama n et al[13]	Bilateral ESS			Cotton pledget soaked in MMC placed in middle meatus		Contralateral side treated with saline
Harugop et al[14]	Uncinectomy, middle meatus antrostomy, anterior/total ethmoid clearance, sphenoidal, frontal recess clearance± septoplasty, turbine -plasty, middle turbinate resection	0.4 mg/ml	1 mL	Cotton ribbon wick soaked in MMC placed in middle meatus, maxillary sinus ostia, sphenoid sinus ostia, frontal recess area, followed by irrigation with 60ml normal saline.	4 minutes	-
Khoshsirat et al[15]	FESS	1 mg/mL	-	Not specified	-	Contralateral side treated with saline
Sadek et al[16]	FESS using Messerklinger technique ± septoplasty	0.5 mg/mL	-	2×2 cm cotton pledge soaked in MMC placed at middle meatal antrostomy site	5 minutes	Contralateral side treated with saline
El Dabaa et al[17]	FESS	-	-	Topical application of MMC at end of FESS	-	Contralateral side treated with saline
Ibrahim et al[18]	FESS	-	-	Topical application of MMC at middle meatal antrostomy site in test group of 30 subjects	-	Control group of 30 subjects without application of MMC
Elhussieny et al[19]	FESS	-	-	Nasal packs medicated with MMC applied in test group of 25 subjects	-	Control group of 25 subjects without application of MMC
Anwar et al[20]	Endoscopic removal of antrochoanal polyp with middle meatal antrostomy	0.2 mg/mL	1 mL	Piece of cotton soaked with MMC applied through middle meatal antrostomy inside maxillary sinus on site of origin of antro-choanal polyp in test group of 20 subjects	5 minutes	Control group of 20 subjects without application of MMC
Ramadan et al[21]	FESS	-	-	Post-op nasal packing soaked in MMC on 1 side	-	Post-op nasal packing soaked in PVA on other side.
Humayun et al[22]	Bilateral FESS	0.8 mg/mL	-	Neuro pattie saturated with MMC applied on 1 side followed by irrigation with normal saline	5 minutes	Contralateral side treated with 0.9% normal saline.

Table 3: Summary of systematic reviews and meta analyses included in this review.

Authors	Study design	No. of studies included	Parameters studied	Summary
Numthavaj et al[23]	Systematic review and meta-analyses	11	Formation of nasal synechiae, maxillary sinus ostium stenosis	Applying MMC topically after FESS could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short term by 66% and 74%, respectively.
Lu et al[24]	Systematic review	77	Rate of restenosis, number of procedures, and post-surgical patency	Topical MMC improved surgical outcomes in many Otolaryngological procedures compared to controls.

DISCUSSION

The aim of endoscopic sinus surgery is to maintain both physiological function and anatomical integrity. The surgical approach is customized to suit each patient's specific needs. FESS focuses on restoring proper sinus drainage and promoting mucosal healing.

Endoscopic surgery may fail due to issues like abnormal mucociliary transport, persistent disease, and obstruction in the osteomeatal complex.[25] Notably, obstruction, often stemming from adhesion formation and antrostomy stenosis, is a significant concern.[26] Mucy and Kountakis found that in revision endoscopic surgery, the most frequent anatomical issue was a blocked osteomeatal complex, particularly a narrowed middle meatal antrostomy in 39% of cases.[27] Recent advances in endoscopic technology, as well as detailed preoperative and intraoperative analysis of complex anatomy made possible by improved radiographic technology such as computed tomography scans, magnetic resonance imaging scans, and image guidance navigation systems, abet in reducing the risk of complications.

Various methods have been explored to mitigate adhesion formation following FESS. Berluchhi et al found that hyaluronan nasal packing (MeroGel) effectively reduced adhesions.[28] Kastl et al reported no significant impact with carboxymethyl cellulose packing.[29] Chandra et al observed no discernible differences between FloSeal and thrombin-soaked gelatin foam.[30] Baguley et al investigated the use of silastic splints in the middle meatus, noting reduced adhesions but increased early nasal obstruction and discomfort.[31]

Determining the optimal nasal packing following ESS remains a topic of ongoing debate. While practices vary among sinus surgeons, the common goals include achieving effective haemostasis, promoting rapid healing, ensuring patient comfort, and minimizing post-operative adhesion formation.

Japanese researchers first found mitomycin in samples of the bacterium *Streptomyces caespitosus* in 1955.[32]

In vitro studies show how a brief exposure to MMC induces corneal epithelial cells to release proteins and other factors that function in a paracrine way to enhance debris removal and enlist resident epithelial and immune cells as well as stromal fibroblasts to support regenerative and not fibrotic wound healing.[33] This anti-fibrotic activity of MMC has been investigated by various researchers.

Over the span of 22 years, from 2002 to 2024, a total of 18 studies aimed at assessing the effect of MMC in ESS, encompassing a diverse cohort of 674 participants meeting the study's inclusion criteria. Among these investigations, 14 studies adopted a contralateral side as the control group, while 3 studies established separate experimental groups, administering MMC treatment to one group and withholding it from the other for comparative analysis.

The age range of subjects enrolled in these studies varied widely, spanning from 15 to 66 years, with a predominant focus on the adult population, typically defined as individuals aged 18 years and older. Across the reviewed studies, MMC consistently demonstrated safety and efficacy in reducing post-operative adhesion formation among adult participants. However, a conspicuous gap in research exists concerning the impact of MMC in the paediatric population, underscoring the imperative for further extensive investigations to elucidate its effects relative to those observed in adults.

Regarding the site of MMC application, a predominant majority of studies (11 out of 18) focused on the middle meatal antrostomy, a common surgical procedure in ESS. Conversely, only one study specifically examined the efficacy of MMC application at the frontal recess area. Intriguingly, six studies did not distinctly specify the area of MMC application within the sinus cavity. Among the studies concentrating on the middle meatal antrostomy, an overwhelming majority (9 out of 11) reported positive effects of MMC in reducing synechiae formation and preventing stenosis, with only two studies indicating no significant difference in outcomes. However, the topical application of MMC at the frontal recess area demonstrated ineffectiveness in reducing postoperative

frontal recess stenosis. These findings underscore the potential differential efficacy of MMC application at distinct anatomical sites within the sinus cavity, emphasizing the need for further validation through additional research.

The majority of studies employed local MMC application techniques utilizing cotton carriers such as pledgets or wicks, with only two studies utilizing specialized neuro patties, which yielded a 50% effectiveness rate. Mesh and merocele were utilized in two studies, yielding non-significant results. These findings suggest that cotton wicks or pledgets may offer superior outcomes when used as carriers for MMC application, warranting further investigation into optimal delivery methods.

Intraoperatively, MMC was topically applied at varying concentrations, ranging from 0.2 mg/ml to 1.0 mg/ml, with quantities administered typically falling within the range of 1-2 ml.

In most studies, the duration of local MMC application at the site of action was consistently set to 4-5 minutes. However, due to variations in study protocols and methodologies, definitive conclusions regarding the relationship between application time and effectiveness cannot be conclusively drawn at this time.

The development of post-operative adhesions was the primary focus of the analysis across the reviewed literature. The majority of selected studies (approximately 66.67%) reported improvements in the primary outcome of adhesion prevention. While four studies demonstrated positive results with MMC usage, they were unable to discern statistically significant data. Only two studies indicated no improvement at all, as depicted in Figure 2.

In a previously done multivariate meta-analysis and systematic review of 11 separate studies by Numthavaj et al in 2013 it was found that applying MMC topically after ESS could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short term by 66% and 74%, respectively.[23]

Luu et al published a similar meta-analysis and systematic review in 2021 that included all published uses of MMC across various otorhinolaryngology procedures, with the results being heterogeneous but indicating that topical MMC improves outcomes in otorhinolaryngology procedures.[24]

In conclusion, the findings from these 18 studies offer valuable insights into the utilization of MMC in endoscopic sinus surgery in mitigating post-operative adhesion formation. While the majority of studies demonstrated positive effects of MMC, variations in methodology and outcomes underscore the need for further research to establish optimal protocols and comprehensively understand its efficacy across different patient populations.

Limitations

Overall, the risks of bias were high in studies having case series without blinding, and were susceptible to selection bias. Only randomized controlled trials can limit this bias. In addition, patient groups were not homogenous as site and duration of application of MMC varied.

CONCLUSION

The formation of adhesions after FESS may again lead to rhinosinusitis and need for a revision surgery. Various interventions including spacers and nasal packings have been used to prevent adhesions after FESS. The most common outcome noted in the present review is reduction in the incidence of adhesion formation after the application of MMC.

Due to heterogeneity in the procedure of use of MMC and research quality, complete data interpretation was restricted. High-quality prospective and randomized controlled trials are needed to confirm the favourable benefit of MMC in endoscopic sinus operations.

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