REVIEW ARTICLE

Efficacy of Mitomycin C for postoperative endoscopic sinus surgery: a systematic review and meta-analysis

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Background: Mitomycin C has recently been used to prevent nasal synechiae and sinus ostium stenosis after endoscopic sinus surgery.
Objective of review: To compare nasal synechiae rate between topical Mitomycin C and saline or no treatment.
Type of review: Systematic review and meta-analysis.
Data sources: MEDLINE, SCOPUS, and Cochrane Register of Controlled Trials databases were used to identify studies up to January 2013.
Evaluation method: Data were independently extracted by two reviewers (PN and KT). Studies which compared topical Mitomycin C with control where the outcomes of interest were nasal synechiae or sinus ostium stenosis were included. Baseline study characteristics, quality of study, numbers of patients between treatment and control groups, outcomes, and adverse events were extracted. A multivariate meta-analysis was separately applied for each outcome (nasal synechiae and maxillary sinus ostium stenosis).
Results: Among 11 included studies, most studies used Mitomycin C dose of 0.4–0.5 mg/mL 1–5 mL in the middle meatus for 5 min duration. Eight studies reported synechiae with 281 and 281 nasal cavities received Mitomycin C and saline, respectively. For outcome of nasal synechiae, a multivariate meta-analysis suggested that Mitomycin C was associated with a 66% (RR = 0.34, 95% CI: 0.18–0.65) lower risk of nasal synechiae with moderate heterogeneity (I^2 = 43%, 95% CI: 0–77%). Subgroup analyses by age and history of revision could reduce the degree of heterogeneity. Mitomycin C benefits were found in subgroups of age $\leq$ 40 years (RR = 0.27, 95% CI: 0.05–1.50) and patients without any history of revision (RR = 0.19, 95% CI: 0.06–0.58). Five studies with 134 and 140 nasal cavities for Mitomycin C and saline were included in pooling of maxillary sinus ostium stenosis. Mitomycin C was associated with 74% (RR = 0.26, 95% CI: 0.12–0.54) lower risk of maxillary sinus ostium stenosis when compared with saline with low heterogeneity (I^2 = 5%, 95% CI: 0–85%). There was no evidence of publication bias for both poolings.
Conclusion: Applying Mitomycin C topically after endoscopic sinus surgery could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short term by 66% and 74%, respectively. The treatment effects may be more beneficial in patients aged 40 years or younger or in patients without history of revision. However, our results were based on pooling trials with questionable methodological quality. Further trials with good research methodology and long-term follow-up should be conducted to confirm our results.

Background and rationale

Endoscopic sinus surgery (ESS) is the standard surgical procedure for refractory chronic rhinosinusitis which does not respond to proper medical treatment. Formation of mucosal adhesions after sinus surgery is the most common cause for the failure of endoscopic sinus surgery, which occurs from 1% to 36%.[1] Both adhesion within the nasal cavity (nasal synechiae) and stenotic scars at the sinus ostium can lead to obstruction of sinus drainage, leading to recurrence of sinusitis.

Mitomycin C (MMC) is an antibiotic derived from the bacteria *Streptomyces caespitosus*[2] which has potential chemotherapeutic effects and thus has been used to treat various types of cancers.[3,4] Mitomycin C also has an antiproliferative effect by suppressing and modulating fibroblast activity and has been used to prevent scar formation in many surgical procedures, notably in ophthalmic surgery.[5]

Recently, Mitomycin C has been used in endoscopic sinus surgery, and some studies have found a benefit in prevention of scar formation[6–12] whereas other studies did not.[13–16] The

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treatment effects across these studies were relatively imprecise because of small sample size. To our knowledge, there has been no previous meta-analysis in this area, so we conducted a systematic review of randomised controlled trials (RCT) to assess the efficacy of Mitomycin C compared with standard treatment for the prevention of synechiae or stenosis in endoscopic sinus surgery.

Methods

Search strategy

Studies published in English were identified from MEDLINE, SCOPUS, and the Cochrane Register of Controlled Trials up to January 2013 with the search terms such as 'Mitomycin C', 'Sinusitis', and 'Endoscopic Sinus Surgery'. Details of the search strategies used are listed in Table S1. Reference lists of identified studies were also checked to ensure that no relevant studies were missed.

Selection of studies

Titles and abstracts of identified studies were evaluated by one author (PN) and randomly checked by AT. Full texts of studies that were potentially relevant were obtained if a decision for selection could not be made from the abstract. RCTs which met the following inclusion criteria were eligible for review: studied on adult patients with chronic rhinosinusitis or mucocele, compared Mitomycin C *versus* control (e.g. saline, placebo or no treatment), and had the outcome of nasal synechiae or sinus ostium stenosis. Studies were not eligible if they had cystic fibrosis or immotile cilia syndrome, if reports were duplicated or if there were insufficient data.

Outcomes of interest

The primary outcomes of interest were synechiae and maxillary sinus ostium stenosis observed at 3 months after endoscopic sinus surgery, which were defined according to the original studies. Briefly, synechiae was defined as the formation of mucosal adhesion and maxillary ostium stenosis was narrowing of maxillary sinus ostium of <5 mm.[10] Both were visualised under nasal endoscopy.

Data extraction and risk of bias assessment

Two reviewers (PN and KT) independently performed data extraction. The quality of studies were assessed by PN and BR using the risk of bias assessment tool.[17] Disagreements were discussed and resolved by AT. The tool consists of sequence generation, allocation concealment, blinding of participants/personnel, incompleteness of outcome data, and selective outcome reporting.

Data were abstracted using a standardised data extraction form included baseline characteristics of studies (study design, year, and settings), participants' characteristics (i.e. mean age, percentage of male sex, bilaterality of disease and operation), percentage of revision patients, inclusion of specific diseases (e.g. allergy), extent of surgery, technique of surgery, duration of follow-up, and outcome (synechiae/stenosis) measurement. We also extracted information on the intervention, that is, concentration and amount of Mitomycin C, nasal packing method, site of application, and irrigation after application.

Statistical analysis

A risk ratio (RR) for both synechiae and maxillary sinus ostium stenosis was estimated for each study. Data were classified into two types according to the study designs of included studies. First, nine trials[6,7,9–14,16] performed cross-over designs in patients with bilateral sinusitis, in which Mitomycin C was randomly assigned to one side and control (saline) on the other side; so data from these trials were extracted as paired data. We could get complete information on matched pairs in five trials[6,10,13,14,16] whereas the other four trials[7,9,11,12] did not report data in sufficient detail to ascertain this. Second, one trial[8] recruited patients with unilateral sinusitis; each patient thus randomly received only one treatment and the data from this trial were treated as uncorrelated. One bilateral side study[11] used two concentrations of Mitomycin C *versus* placebo and this study was counted twice in pooling. Summary data were expanded to individual-level data using the expand command in STATA (StataCorp. 2011, College Station, TX, USA).

Pooling of treatment effects was performed in two steps. A binary regression analysis, accounting for correlated data where appropriate, was applied to estimate the treatment effect [i.e. log (RR)] along with its standard error. Because most trials (10/11) had correlated data, a multivariate random-effect meta-analysis was applied to pool the RRs across trials.[18] This method accounts for within subject-study correlation using Riley's method.[19] The heterogeneity of treatment effects across trials was assessed using Q tests and the I^2 statistic. If heterogeneity was present (Q test < 0.10 or $I^2 > 25\%$), the source of heterogeneity was explored by subgroup analyses and meta-regression. Exploration of potential publication bias was performed using an Egger test and a contour-enhanced funnel plot if required.

All statistical analyses were performed using STATA version 12 (StataCorp. 2011). Statistical significance was defined as a P value of <0.05.

Results

Description of studies

As described in Fig. 1, 385 studies were identified. After removal of duplicates and non-Mitomycin C studies, 24 studies were left for review. Full papers of these articles were obtained, and 13 studies were excluded with reasons described in Fig. 1, leaving 11 trials for inclusion in this review.

Characteristics of the included studies are described in Table 1. Among 11 trials, 10[6,7,9–16] were paired designs, in which each patient received two treatments (bilateral sinusitis) and only one trial[8] was a parallel RCT (unilateral sinusitis). Most trials had a percentage of male patients ranged from 47% to 70%. The mean age ranged from 31 to 49 years. Six trials[6,8,13–16] included re-operation or revision patients. Most trials operated on the maxillary and ethmoid sinuses.

The most commonly used technique was the Messerklinger (5/11) for endoscopic sinus surgery. Mitomycin C or saline solution was applied after endoscopic sinus surgery. The concentrations of Mitomycin C used were 0.4,[6,7,9,11] 0.45,[14] 0.5,[8,10,12,13,15] 0.8,[11] and 1.0[16] mg/mL with a volume of 1,[6–8,10,12,13,16] 1.5,[9,14] and 5 mL.[11] The application time ranged from 4 to 5 min. Most trials used cotton pledget

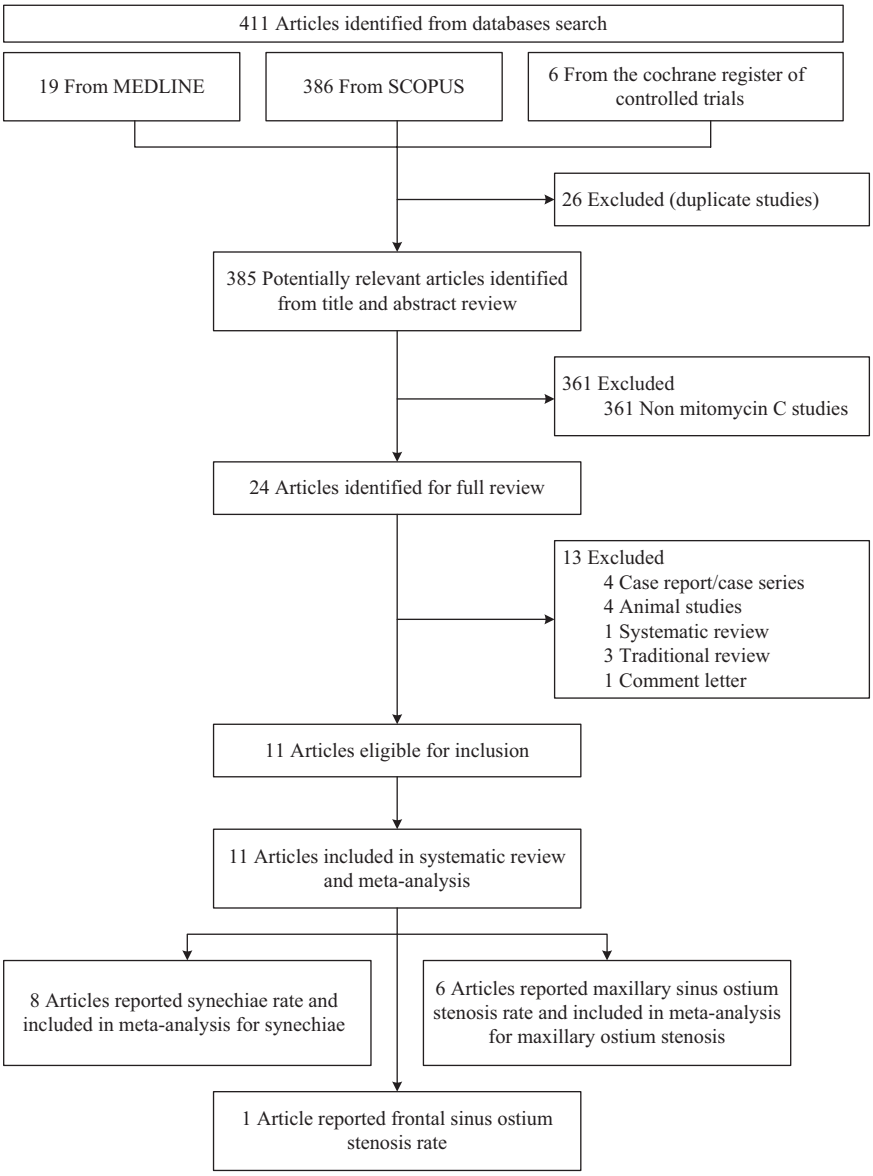

Fig. 1. Diagram of selection of studies.

Table 1. Characteristics of included studies

Author	Country	*n*	% Male	Mean age (years)	Follow-up (months)	Nasal side	Included revision patients	Extent of surgical procedures			
								Frontal Sinus	Ethmoid Sinus	Maxillary Sinus	Other Procedure
Nasal synechiae as outcome											
Chung *et al.*[6]	US	55	51	44.5	1	Bilateral	Yes	Yes	Yes	Yes	Septoplasty as required
Anand *et al.*[13]	US	29	55	49.0	3	Bilateral	Yes	No	Yes	Yes	No
Gupta *et al.*[7]	India	30	67	-	1	Bilateral	No	No	Yes	Yes	No
Venkatraman *et al.*[12]	India	50	54	32.0	0.25	Bilateral	No	No	Yes	Yes	No
Yamaoka *et al.*[16]	Brazil	15	53	42.8	12	Bilateral	Yes	Yes	Yes	Yes	Septoplasty and sphenoidotomy as required
Frontal sinus ostium stenosis as outcome											
Chan *et al.*[15]	Canada	38	60	49.0	6	Bilateral	Yes	Yes	Yes	Yes	No
Maxillary sinus ostium stenosis as outcome											
Kim *et al.*[9]	South Korea	20	70	31.0	6	Bilateral	Unknown	No	No	Yes	No
Kim *et al.*[8]	Korea	38	47	46.5	1	Unilateral	Yes	No	No	No	Endoscopic inferior medial antrostomy, Endonasal or Caldwel-Luc
Nasal synechiae and maxillary sinus ostium stenosis as outcome											
Konstantinidis *et al.*[10]	Greece	30	53	39.5	6	Bilateral	No	No	Yes	Yes	Septoplasty as required
Baradaranfar *et al.*[14]	Iran	27	61	38.0	3	Bilateral	Yes	No	No	Yes	No
Singh *et al.*[11]	India	30	70	–	3	Bilateral	No	Yes	Yes	Yes	No

Author	Technique	Mitomycin C Concentration (mg/mL)	Amount (mL)	Application time (minutes)	Packing method	Packing position	Irrigation after packing
Nasal synechiae as outcome							
Chung *et al.*[6]	–	0.4	1	4	Neurological cottonoids	Middle meatus	Yes, 60 mL of sterile normal saline
Anand *et al.*[13]	–	0.5	1	5	Pledgets	Middle meatus	No
Gupta *et al.*[7]	Messerklinger	0.4	1	4	Cotton Plug	Middle meatus	Yes (Not specified)
Venkatraman *et al.*[12]	Messerklinger	0.5	1	5	Cotton pledget	Middle meatus	Yes, Saline
Yamaoka *et al.*[16]	Messerklinger	1.0	1	5	Cotton swab	Middle meatus	No
Frontal sinus ostium stenosis as outcome							
Chan *et al.*[15]	Messerklinger, Frontal recess using Kuhn & Javier's	0.5	Did not describe	4	Neuropatties	Frontal recess	Unknown
Maxillary sinus ostium stenosis as outcome							

Table 1. Continued

Author	Technique	Mitomycin C Concentration (mg/mL)	Amount (mL)	Application time (minutes)	Packing method	Packing position	Irrigation after packing
Kim *et al.*[9]	Through cutting forceps & curette, Microdebrider trim mucosa	0.4	1.5	5	Merocel	Opening of antrostomy site	Unknown
Kim *et al.*[8]	–	0.5	1	5	Pledget Soaked	Antrostomy Site	Unknown
Nasal synechiae and maxillary sinus ostium stenosis as outcome							
Konstantinidis *et al.*[10]	Conventional instrument (cut forceps, back-biting)	0.5	1	5	Neurosurgical cottonoid	Middle meatus (Repeated application 4 weeks after)	Yes, 30 mL of sterile NSS
Baradaranfar *et al.*[14]	Messerklinger Technique	0.45	1.5	5	Cotton Mesh 6 cm stained with Mitomycin C	Middle meatus, Ethmoid, Around maxillary sinus os	No
Singh *et al.*[11]	–	0.4 and 0.8	5	5	Cotton pledget	Middle meatus	Unknown

soaked with Mitomycin C applied in the middle meatus with/without irrigation by normal saline. All studies used normal saline as a comparator.

All studies performed rigid nasal endoscopy for outcome assessments. Five studies[6,7,12,13,16] reported nasal synechiae rate as their outcome, two[8,9] reported maxillary sinus ostium stenosis rate, and three[10,11,14] reported both nasal synechiae rate and maxillary sinus ostium stenosis rate. One study[15] reported frontal sinus ostium size, and thus, this study was not included in pooling.

Definitions of synechiae and maxillary sinus ostium stenosis varied from more to less objective measures: Baradaranfar *et al.*[13] classified maxillary sinus ostium stenosis as mild, moderate, and severe if the maxillary sinus ostium width was 6–9, 3–5, and <2 mm, respectively. Similarly, Konstantinidis *et al.*[6] defined maxillary sinus ostium stenosis as a size of antrostomy below 5 mm. Kim *et al.*[7] defined ostium patency as 75–100%, narrow as 25–75%, and stenosis as 0–25% compared to the initial ostium measurement. Although the definitions used varied, all studies compared the numbers of synechiae or stenoses between treatment groups. The duration of follow-up ranged from 1 week to 1 year. Most trials reported the percentage of adhesion/stenosis at 3 months' time.

Additional endoscopic findings (e.g. polypoid mucosa,[6,7,12,14] granulation tissue[7,12,14], crusting and discharge,[7,12] and mucosal hypertrophy[6]) were also reported. Clinical symptoms were also reported in some studies; these included recurrent symptoms of rhinosinusitis,[6,10] nasal obstruction,[11,12] nasal discharge[12] and hyposmia.[11] A saccharin test was reported by only one study.[9]

All trials reported no major side effects of topical application of Mitomycin C, but minor side effects such as postoperative bleeding were reported by one study.[10]

Risk of bias assessment

Two reviewers performed risk of bias assessments with an agreement of 81.8% (kappa statistic = 0.726, $P < 0.001$), and the validated results are described in Table 2. Overall, most studies (7 of 11) did not explicitly describe how their randomisation sequences were generated. No studies mentioned whether concealment was used. Many studies (8/11) mentioned that physicians who performed nasal endoscopy for outcome assessments were blinded from treatments, but all trials were free from bias of selective reporting of outcomes. Eight studies were potentially biased from not properly applying statistical analysis for correlated data or unbalanced baseline characteristics.

Table 2. Quality assessment of included studies

Author	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Comments
Chung *et al.*[6]	?	–	+	+	+	+	Analysis had accounted for correlated data using McNemar
Anand *et al.*[13]	+	–	+	–	+	–	High rate of lost to follow-up and did not mention statistical method used
Chan *et al.*[15]	+	?	+	–	+	+	Analysis had accounted for correlated data using matched pair Wilcoxon test
Gupta *et al.*[7]	?	–	+	+	+	–	Analysis did not account for correlated data
Kim *et al.*[9]	?	–	+	+	+	–	Analysis did not account for correlated data for stenosis, but did for other secondary outcomes
Konstantinidis *et al.*[10]	?	–	+	+	+	–	Analysis did not account for correlated data
Kim *et al.*[8]	?	–	?	–	+	–	15/50 lost to follow-up and may result in confounding bias
Baradaranfar *et al.*[14]	?	–	+	+	+	+	Analysis had accounted for correlated data using McNemar
Singh *et al.*[11]	+	?	–	+	+	–	Analysis did not account for correlated data
Venkatraman *et al.*[12]	?	?	?	+	+	–	Analysis did not account for correlated data
Yamaoka *et al.*[16]	+	?	+	+	+	–	Analysis did not account for correlated data

?, Unclear; +, Yes; –, No.

Meta-analysis

Nasal synechiae. Eight studies[6,7,10–14,16] had nasal synechiae as the outcome with 281 and 281 nasal cavities which received Mitomycin C and saline, respectively. RRs along with 95% confidence intervals (CI) were estimated using binary regression, see Table 3.

A multivariate meta-analysis was then applied to pool RRs across studies, which suggested that the treatment effects had moderate heterogeneity with an I^2 of 43% (95% CI: 0–77%). The pooled RR was 0.34 (95% CI: 0.18–0.65), that is, the risk of nasal synechiae was 66% significantly lower in nasal cavities treated with Mitomycin C than saline, see Fig. 2.

For exploring the source of heterogeneity, each of eight factors (i.e. age, history of revision, percentage of male, concentration use, irrigation, duration of application, follow-up time and quality of study on blinding) were considered in the meta-regression model. Only age and history of revision reduced the degree of heterogeneity and a subgroup analysis was performed accordingly (Table 4). Pooling treatment effects in the age group ≤ 40 years yielded a homogenous pooled RR of 0.27 (95% CI: 0.05–1.50), whereas it was highly heterogeneous in the age group >40 years (RR = 0.35, 95% CI: 0.10–1.16). Among patients without any history of revision, the Mitomycin C group had 81% significantly lower risk of synechiae (RR = 0.19, 95% CI: 0.06–0.58) compared with standard treatment, whereas there was no significant effect in patients with history of revision.

In addition, a subgroup analysis according to Mitomycin C concentration was also performed. This suggested similar Mitomycin C effects in the concentration of 0.45 mg/mL or lower (RR = 0.33, 95% CI: 0.10–1.10) and Mitomycin C concentration of 0.5 mg/mL or higher (RR = 0.33, 95% CI: 0.07–1.64). In addition, sensitivity analyses were performed by exclusion of studies that had performed frontal sinus surgeries,[6,11,16] or studies that had multiple application of Mitomycin C,[10] or studies that did not blind outcome assessors[11,12] did not change the results much with the pooled RR of 0.32 (95% CI: 0.07–1.50), 0.31 (95% CI: 0.13–

Table 3. Risk ratios and pooled risk ratios of synechiae and maxillary sinus ostium stenosis

Author	Total sides	No. of events/ Total No. of control sides	No. of events/ Total No. of Mitomycin C sides	RR (95% CI)
Outcome: Synechiae				
Chung *et al.*[6]	122	14/61	8/61	0.51 (0.25–1.02)
Anand *et al.*[13]	58	5/29	7/29	1.53 (0.55–4.28)
Gupta *et al.*[7]	60	11/30	1/30	0.06 (0.01–0.43)
Konstantinidis *et al.*[10]	60	6/30	3/30	0.44 (0.11–1.86)
Baradaranfar *et al.*[14]	74	10/37	4/37	0.33 (0.10–1.05)
Singh *et al.*[11] (0.4 mg/mL)	30	8/15	4/15	0.32 (0.05–1.99)
Singh *et al.*[11] (0.8 mg/mL)	30	5/15	1/15	0.14 (0.01–1.84)
Venkatraman *et al.*[12]	100	13/50	2/50	0.12 (0.03–0.53)
Yamaoka *et al.*[16]	28	9/14	3/14	0.15 (0.03–0.85)
Pooled	562	81/281	33/281	0.34 (0.18–0.65)
Outcome: Maxillary sinus ostium stenosis				
Kim *et al.*[9]	40	4/20	1/20	0.21 (0.02–2.46)
Konstantinidis *et al.*[10]	62	10/31	3/31	0.22 (0.05–0.94)
Kim *et al.*[8]	38	9/16	5/22	0.23 (0.06–0.95)
Baradaranfar *et al.*[14]	74	6/37	5/37	0.81 (0.23–2.89)
Singh *et al.*[11] (0.4 mg/mL)	30	12/15	5/15	0.13 (0.02–0.70)
Singh *et al.*[11] (0.8 mg/mL)	30	10/15	1/15	0.04 (0.00–0.54)
Pooled	274	51/134	20/140	0.26 (0.12–0.54)

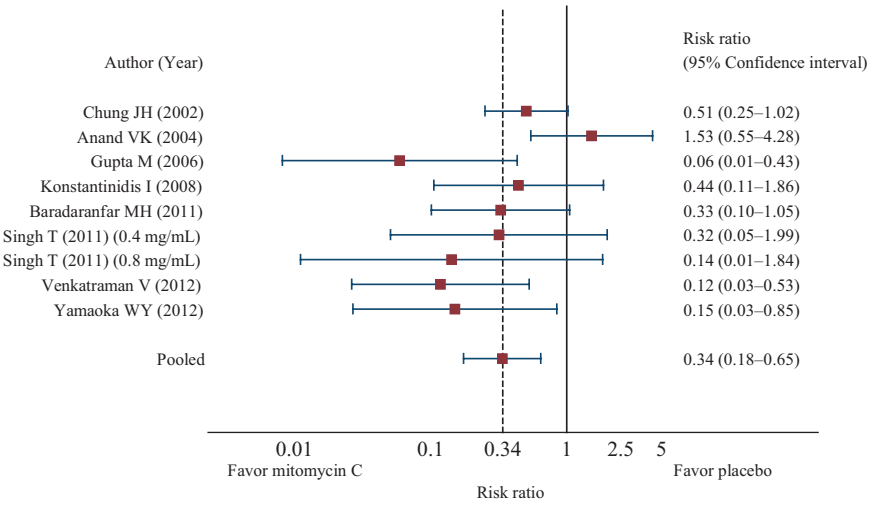

Fig. 2. Forest plot of Mitomycin C ***versus*** normal saline effects on synechiae: Multivariate meta-analysis.

0.74), and 0.40 (95% CI: 0.14–1.16), respectively. Furthermore, omit one study[12] that assessed the synechiae at 1 week yielded similar results to the overall pooling (RR = 0.38, 95% CI: 0.17–0.84).

A funnel plot for overall pooling suggested that one study was outside the range of the symmetrical funnel (see Figure S1); however, an Egger test suggested that there was no significant evidence of asymmetry (coefficient = −2.21, SE = 1.01, $P = 0.065$). The contour-enhanced funnel plot did suggest asymmetry, but the missing studies were in both the significant region (shaded region to the right in Fig. 3b) and non-significant region (white region). As a result, asymmetry of the funnel might have been caused by heterogeneity.

Maxillary sinus ostium stenosis. Five studies[8–11,14] reported maxillary sinus ostium stenosis as their outcome with 134 and 140 nasal cavities for Mitomycin C and saline groups,

Table 4. Exploration of the source of heterogeneity in meta-analysis of synechiae outcome

Factor	Number of studies	RR (95% CI)	I^2 (%)
Age			0
≤40	3	0.27 (0.05–1.50)	0
>40	6	0.35 (0.10–1.16)	58
Revision			14
No	5	0.19 (0.06–0.58)	0
Yes	4	0.51 (0.12–2.09)	55

respectively. RRs along with 95% confidence intervals were estimated using binary regression, see Table 3.

A multivariate meta-analysis was then applied to pool RRs across studies, which suggested that the treatment effects were low heterogeneity across studies with an I^2 of 5% (95% CI: 0–85%). The polled RR was 0.26 (95% CI: 0.12–0.54), that is, the risk of maxillary sinus ostium stenosis was 74% significantly lower in nasal cavities treated with Mitomycin C than saline, see Fig. 3.

A funnel plot for maxillary sinus ostium stenosis outcome did not suggest asymmetry (see Figure S2). Egger test also showed no significant evidence of asymmetry (coefficient = −2.81, SE = 1.33, P = 0.102).

Discussion

Summary of main result

Mitomycin C treatment effects showed moderate heterogeneity with ≈66% lower risk of synechiae compared with normal saline. The treatment effects were more beneficial and homogeneous in patients aged 40 or younger and patients without history of revision with 73–81% lower risk of synechiae, respectively. In addition, the effects of Mitomycin C on maxillary sinus ostium stenosis were homogenous across studies with the effect of 74% lower risk than normal saline.

Prevention of synechiae of the nasal cavity and maxillary ostium stenosis are keys to successful endoscopic sinus surgery. The postoperative period is important and good early postoperative care could reduce the chance of having synechiae. Application of a pharmacological agent such as Mitomycin C is another choice for prevention of scaring in addition to systemic and topical steroid treatment.[20]

Mitomycin C, an antiproliferative agent, works by disrupting the base paring of DNA molecules in the G-1 phase, which in turn inhibits the formation of RNA and protein synthesis and therefore inhibits the proliferation of fibroblasts. Additionally, it was found to induce apoptosis in fibroblasts and block angiogenesis.[20] Its use in the sinonasal tract was initially studied by Ingrams *et al.*,[21] in 1998, in which various concentrations (i.e. 0.04, 0.4 and 1 mg/mL) were applied for 5 min in surgically created rabbit antrostomies. They found that at a concentration of 0.4 mg/mL, the same concentration used in glaucoma surgery, the antrostomies remained open for up to 4 weeks compared to 1 week in the control group; there was also a trend towards a longer period of antrostomy patency with greater concentration. This was confirmed by two other studies in a rabbit model.[22,23]

Chung *et al.*,[6] first studied the use of Mitomycin C in endoscopic sinusitis surgery in 2002 and found positive

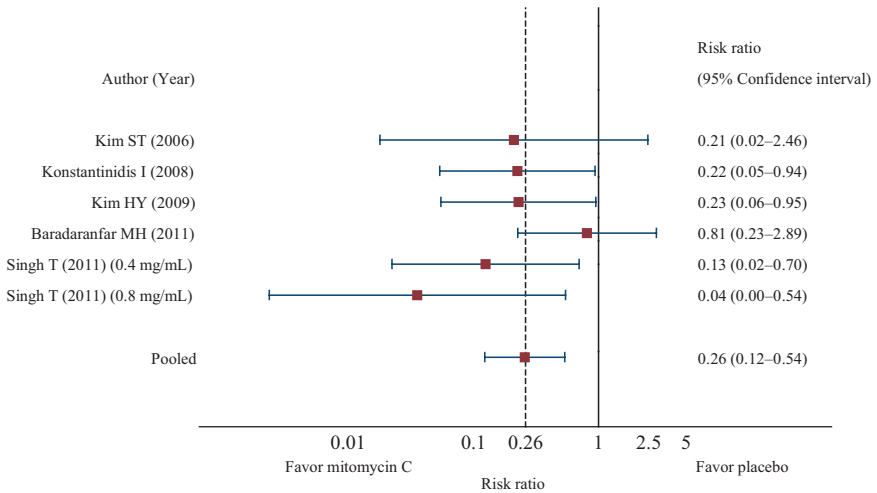

Fig. 3. Forest plot of Mitomycin C *versus* normal saline effects on maxillary sinus ostium stenosis: Multivariate meta-analysis.

result. Despite a trend of benefit of Mitomycin C in both animal and clinical studies, several studies have been conducted since, but found conflicting results. This is likely due to limited power in these small studies.

Our current review found no major side effect of Mitomycin C application in the nasal cavity, similar to the recently published review by Veen *et al.*,[20] which found no systemic side effect from topical use of Mitomycin C in the aerodigestive tract. However, as most included studies had followed patients only 3 months or shorter, long-term safety data are thus unknown and need further study.

Quality of evidence and comparison with other review

We focused only on RCTs in order to minimise confounders. All except one trial studied patients with bilateral chronic sinusitis, in which one nasal side was randomly assigned to Mitomycin C whereas the other nasal side was assigned to normal saline. Previous studies have not clearly accounted for this correlated data, which would have falsely amplified treatment effects. We therefore applied a binary regression to estimated treatment effects of each trial, and a multivariate meta-analysis to pool treatment effects across trials. Correlation within patients was accounted for in the analysis, and thus, the estimated treatment effects should be less biased. Subgroup analysis was performed to identify more homogeneous patient groups who should have maximal benefit from Mitomycin C. Lower concentration (<0.5 mg/mL) seems to be enough for the effect.

Potential biases in review

Although we focused only on randomized controlled trials, 8/11 studies were unclear in their method for generating randomisation sequences, and none of the studies concealed the randomisation lists. Baseline characteristics of patients between intervention groups might be different, and thus, selection bias might be present. Many studies did not blind outcome assessors who performed nasal endoscopy, so ascertainment bias might not be avoided. We could not assess long-term efficacy and safety of Mitomycin C because most included studies had short-term follow-up (i.e. <3 months).

Implication for clinical practice

Mitomycin C applied topically could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short-term period by 66% and 74%, respectively, without major adverse effects. However, long-term outcome and long-term safety data are unknown.

Implication for research

As discussed, some included trials have questionable methodology and also with short-term follow-up. A large trial with long-term follow-up is required.

Conclusion

Applying Mitomycin C topically after endoscopic sinus surgery could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short-term period by 66% and 74%, respectively, without major adverse effects. The treatment effects may be more beneficial in patients aged 40 or younger or in patients without history of revision. However, our results were based on pooling trials with questionable methodological quality, long-term outcome and safety data were limited. Further trials with good research methodology and long-term follow-up should be conducted to confirm our results.

Keypoints

- Mitomycin C, an antifibroblast chemotherapeutic agent, has recently been used in the prevention of mucosal adhesion after endoscopic sinus surgery.
- A meta-analysis of randomized controlled trials suggests 66% reduction rate of synechiae, and 74% reduction rate of sinus ostium stenosis in Mitomycin C compared with placebo.
- This effect seems to be more beneficial in patients aged 40 or younger or in patients without history of revision surgery.
- However, the previous trials methodology are questionable, and long-term outcomes are lacking.

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Conflict of interest

None to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Funnel and contour enhanced-funnel plots (Synechiae outcome).

Fig. S2. Funnel and contour enhanced-funnel plots (Maxillary sinus ostium stenosis outcome).

Table S1. Search Strategies.