Mitomicin C for the Prevention of Postoperative Synerchia after Endoscopic Sinus Surgery: Systematic Review & Meta-analysis

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การใช้ไมโตไมซิน ซี สำหรับป้องกันการตีบของโพรงจมูกหลังผ่าตัดไซนัสโดยการส่องกล้อง: การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์แบบอภิมาน

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งานวิจัยนี้เป็นส่วนหนึ่งของการศึกษาและฝึกอบรมตามหลักสูตรเพื่อวุฒิบัตรแสดงความรู้ความชำนาญในการประกอบวิชาชีพเวชกรรมสาขาโสต ศอ นาสิกวิทยาของแพทยสภา พ.ศ. 2554

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ข้าพเจ้าขอรับรองว่ารายงานฉบับนี้เป็นผลงานของ นพ. ปวิน นำธวัช ที่ได้ทำวิจัยขณะรับการฝึกอบรม ตามหลักสูตรการฝึกอบรมแพทย์ประจำบ้านและแพทย์ใช้ทุนสาขาโสต ศอ นาสิกวิทยา คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี ระหว่างปี 2552-2554 จริง

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คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

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ABSTRACT

CONTEXT: Mitomicin C (MMC) is recently used to prevent nasal synerchia after endoscopic sinus surgery.

OBJECTIVE: To conduct a systematic review and meta-analysis of randomized controlled trials (RCT) with aims at comparing topical Mitomicin C (MMC) with saline or no treatment in adult patients with chronic rhinosinusitis after underwent endoscopic sinus surgery.

DATA SOURCE: MEDLINE, SCOPUS, and Cochrane Register of Controlled Trials database were used to identify studies since inception to December 2011.

STUDY SELECTION: A RCT comparing topical MMC with no topical MMC was selected if the outcome of interest was synerchia or stenosis.

DATA EXTRACTION: Data were independently extracted by two reviewers (PN and KT). Baseline study characteristics, quality of study, numbers of patients between treatments and outcome, and adverse events were extracted.

RESULTS: Nine studies were included in the systematic review. Most studies applied MMC dosage of 0.4 to 0.5 mg/mL in middle meatus with 5 minutes duration. Nine studies were included in pooling with 309 nasal cavities receiving MMC and 303 cavities received saline. A multivariate meta-analysis was applied and suggested applying MMC was 63% (RR = 0.37, 95% CI: 0.19-0.65) lower risk of synerchia after ESS. The treatment effects were moderately heterogeneous (I^2=32%, 95% CI: 0-73%) but performing subgroup analyses in patients aged 40 years or younger and patients without history of revision found homogeneous effects. There was no evidence of publication bias.

CONCLUSION: Applying MMC topically could reduce a risk of synerchia after postoperative ESS without major adverse effect. The treatment effects may be more benefits in patients aged 40 years or younger or patients without history of revisions. However,

information of long term outcomes are lack and thus required to update when more studies are published.

BACKGROUND & RATIONALE

Endoscopic sinus surgery is the standard surgical procedure for refractory chronic rhinosinusitis that does not respond to the standard medical treatments. However, information of mucosal adhesion after sinus surgery is one of the most common cause for the failure of ESS with an incidence ranged from 1 to 36%[1]. Both adhesion of the nasal cavity and sinus ostium stenotic scar could lead to the obstruction of sinus drainage tract leading to recurrence of the sinusitis.

Mitomicin C (MMC), an antibiotic derived from bacteria *Streptomyces caespitosus*[2], has been found to have chemotherapeutic potential effects and thus has been applied in various types of cancers[3,4]. In addition, MMC also has an antiproliferative effect by suppressing and modulating fibroblast activity. As a result, MMC has been used to prevent scar formation in many surgical procedures, notably in ophthalmic surgery[5], e.g., glaucoma surgery, optic nerve sheath fenestration, pterygium surgery, and dacryocystorhinostomy.

Recently MMC has been applied in treatment of chronic sinusitis, some studies[6-11] found a benefit in prevention of scar formation in a nasal cavity after sinonasal procedures whereas some studies did not find the benefit[12-15]. Although some studies had found benefits of MMC, the treatment effects were imprecise due to sample sizes were small. For those studies with negative results of MMC, there might be a benefit of MMC but the studies were limited in power and thus could not detect the benefit. As for our knowledge, there is no previous a systematic review and meta-analysis, we therefore conducted a systematic review and meta-analysis to assess the efficacy of MMC comparing with standard treatment in ESS.

METHOD

Search strategy

One author (PN) identified relevant studies from MEDLINE, SCOPUS, and the Cochrane Register of Controlled Trials since inception to December 2011. Search terms used for identifying studies were:“Mitomicin C” and “Endoscopic Sinus Surgery”. Detail of search strategies used is described in the appendix. Reference lists of identified studies were also checked.

Selection of study

Titles and abstracts of identified studies were evaluated by one author (PN). Full texts of studies that potentially relevant were obtained if decision for selection could not make. Randomized controlled trials met following inclusion were eligible for review: studied on adult patients with chronic rhinosinusitis or mucocele, compared MMC versus placebo or no treatment, had the outcome as stenosis of ostium or adhesion of nasal cavity. Studies were not eligible if their studied patients were children, or patient with cystic fibrosis or immotile cilia syndrome, duplicated reports, and insufficient data.

Outcomes of interest

The primary outcome of interest was synerchiaor sinus ostium stenosis observed within 3 months after operation. Synerchia or stenosis was defined according to original included studies. The secondary outcomes of interest were synerchia or stenosis observed at 6 months after operation or longer, improvement of sinonasal symptom, improvement of quality of life, and adverse reaction of topical application of MMC.

Data extraction &risk of bias assessment

Two reviewers (PN and KT) independently performed data extraction and assessed for quality of studies. Disagreements were discussed among authors and consensus conclusions were made. Quality of studies was assessed by using the Risk of Bias Assessment tool described in the Cochrane handbook.[16] The tool includes assessments on sequence generation, allocation concealment, blinding of participants/personnel, incompleteness of outcome data, and selective outcome reporting.

Data were abstracted using provided data extraction form and entered into an electronic database file using Epidata software. Extracted data includes baseline characteristic of studies (study design, year, and settings), participants' characteristic (i.e. mean age, percentage of male sex, bilaterality of disease and operation, percent revision patient, inclusion of specific diseases (e.g., cystic fibrosis and mucociliary diseases), extent of sinus surgery, technique of surgery, duration of follow up, and methods of outcome (synerchia/stenosis) measurement. We also extracted information of intervention, i.e., concentration and amount of MMC, nasal packing method, site of application, and irrigation after application. Numbers of outcome were extracted as two-by-two tables of intervention and stenosis/synerchia.

Statistical analysis

A risk ratio (RR) of interventions on adhesion, stenosis, or synerchia was estimated for each study. Data from included trials could be classified into 2types according to their study designs. First, 8trials[6,8-13,15]performed cross-over designs bilateral sinusitis patients who were randomly assigned to receive MMC on one side and saline solution on another side. Data of these trials were thus extracted as paired data. We could get completeness of matched pair of synerchia/stenosis by treatments in 4trials[6,12,13,15]whereas other 4 trials[8-11] did not report

numbers of patients with outcome (adhesion/stenosis) on both side. Second, one trial[7] had conducted studies in patients with only one side of sinusitis. Each patient was thus randomly received only one treatment and the data of these trials were uncorrelated data. One study[10] used two concentrations of MMC versus placebo and this study was accounted in pooling twice. Summary data were then expanded into individual patient data using expand command in STATA.

Two steps of pooling treatment effects were performed as follow. A binary regression analysis with account for correlated data where appropriated was applied to estimate treatment effect (i.e., log(RR)) along with its standard error of adhesion/synerchia/stenosis comparing MMC vs. saline solution for each trial. Since most trials (8/9) were correlated data, a multivariate random-effect meta-analysis was applied to pool RRs across trials[17]. The method had accounted for within subject-study correlation using Riley method[18]. The heterogeneity of treatment effects across trials were assessed using Q test and a degree was quantified usingI^2statistic. If heterogeneity was present (Q test < 0.10 or I^2> 25%), a source of heterogeneity was explored by performing a subgroup analysis and meta-regression. Exploration of potential publication bias was performed using Egger test, and a contour-enhanced funnel plot if required.

All statistical analyses were performed using STATA version 12 (StataCorp. 2011. College Station, TX). Statistical significance is defined as having p value of <0.05.

RESULT

Description of Studies

Searching from MEDLINE, SCOPUS, and Cochrane Register of Controlled Trials yielded 19, 388, and 6 results, respectively. After remove duplicated and ineligible studies, 23 studies were left for review. Full papers of these articles were obtained, 14studies were excluded with following reasons: a case report/case series (n=4), animal studies (n=4), systematic review (n=1), traditional review (n=3), insufficient data (n=1), and comment letter (n=1). Finally, nine trials were included in this study; see Figure 1 for diagram of study selection.

Among 9 trials, 8 trials[6,8-13,15]were paired designs, in which each patient received 2 treatments and only 1 trial[7] was a parallel RCT. Most trials have similar percentage of male patients, i.e., range from 47 to 70. Mean age ranged from 31 to 49 years. Five trials included patients withre-operation or revision patients. Most trials operated on maxillary and ethmoid sinuses. All characteristics of included studies were described in table 1. The most common use of technique was Messerklinger (6/9)for endoscopic sinus surgery (ESS). After performing ESS, the application of MMC or saline solution was done.

The concentration of MMC used was varied from 0.4[8-10,15], 0.45[13], and 0.5[6,7,11,12]mg/mL with volume of 1 mL[6-8,11,12,15], 1.5[9], and 5[10]mL. Application time was ranged from 4 to 5 minutes. Most trials used cotton pledged soaked with MMC applied in Middle meatus without or with irrigation using normal saline afterwards. All studies used normal saline as a comparator with the same procedures as MMC.

All studies performed rigid nasal endoscopy for outcome assessments. Most studies reported adhesion or stenosis of sinus ostium without description but three studies explicitly described.

These definitions were varied from more to less objective measures; Baradaranfar et al[13] classified synerchia as mild, moderate, and severe if maxillary sinus ostium width was 6-9, 3-5, and <2 mm, respectively. Similarly, Konstantinidis et al[6] defined synerchia as a size of antrostomy below 5 mm. Kim et al[7] defined ostium patency as75-100%, narrow as 25-75%, and stenosis as 0-25% compared to initial ostium measurement. Although definitions used varied, all studies compared numbers of stenosis except one study[14] had the ostium size as the outcome. Therefore, this study was not included into meta-analysis. Duration of follow-ups ranged from 1 week to 6 months. Most trials reported percentage of adhesion/stenosis at 3 months' time.

Additional endoscopic findings, (e.g., polypoid mucosa[8,11,13,15], granulation tissue[8,11,13], crusting and discharge[8,11], and mucosal hypertrophy[15]) were also reported. Clinical symptoms were also reported in some studies, these included recurrent symptoms of rhinosinusitis[6,15], nasal obstruction as a symptom[10,11], nasal discharge as reported symptom[11] and hyposmia[10]. Saccharin test was reported by only one study[9].

All trials reported no major side effects of topical application of MMC but a minor side effects such as postoperative bleeding was reported by one study[6].

Risk of bias assessment

Risk of bias assessments was examined and listed in Table 2. Overall, most studies (7 out of 10) did not explicitly describe how their randomization sequences were generated. No studies mentioned whether concealments were applied. Most studies had applied blinding (7/10), in which patients or outcome assessors were blinded. Two studies might have bias from selective outcome reports. None of the studies was potentially biased from other sources.

Meta-Analysis

Nine studies[6-13,15] were included in the meta-analysis with 309 and 303 nasal cavities received MMC and saline, respectively. RRs along with 95% confidence intervals were estimated using a binary regression, see Table 3.

A multivariate meta-analysis was then applied to pool RRs across studies, suggesting that the treatment effects were moderately heterogeneous with the I^2 of 32% (95% CI: 0-73%). The pooled RR was 0.37 (95%CI: 0.20-0.65), i.e., the risk of having synerchia was 63% significantly lower in nasal cavities treated with MMC than saline, see Figure 2.

Since the heterogeneity was moderate, we further explored the source of heterogeneity by applying meta-regression analysis. Eight factors were considered by fitting each factor one by one into the meta-regression model. Only two factors, i.e., age and revision could reduce a degree of heterogeneity and thus a subgroup analysis was performed accordingly (Table 4). Pooling treatment effects within age group$\leq$ 40 years was homogenous with the pooled RR of 0.27 (95%CI: 0.08-0.88) whereas it was moderately heterogeneous in age > 40 years without significant effects (RR = 0.41, 95% CI: 0.13-1.24). Among patients without history of revision, the MMC was 80% significantly lower risk of synerchia (RR = 0.20, 95%CI:0.07-

0.61) compared with standard treatment whereas there was no significant effects in patients with history of revision.

A funnel plot was performed and suggested that one study was out of a range of a symmetrical line, see Figure 3. Applying Egger test suggested that there was evidence of asymmetry of the funnel (coefficient = -2.08, SE = 0.88, p = 0.045). However, the contour enhanced-funnel plot suggested that about 50% of studies were in the non-significant area and another 50% of studies were in significant area. As a result, asymmetry of the funnel might cause by heterogeneity rather than publication bias, see Figure 3.

DISCUSSION

We have performed a systematic review of MMC effects for treating chronic rhinosinusitis. The MMC treatment effects were moderately heterogeneous with approximately 63% lower risk of synerchia compared with normal saline. The treatment effects were more benefits in homogeneous patients by lower risk of synerchia of 73% to 80% in patients aged 40 or younger and patients without history of revision.

Prevention of synerchia or adhesion is one of key to successful endoscopic sinus surgery. The postoperative period is important and good early postoperative care could reduce a chance of having synerchia. Application of pharmacological agents such as MMC is another choice for prevention of scar in addition to systemic and topical steroid[19].

MMC, an antiproliferative agent, works by disrupting base paring of DNA molecules in G-1 phase, which in turns 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 sinonasal tract was firstly studied by Ingrams in 1998, in which various concentrations (i.e., 0.04, 0.4, and 1 mg/mL) were applied for 5 minutes in surgically created rabbit antrostomies[21]. This paper found that in the concentration of 0.4 mg/mL, which was the same concentration used in glaucoma surgery, the antrostomies remained opening for up to 4 weeks compared to 1 week in control group. There was also trend toward the longer period of antrostomy patency in greater concentration. This was confirmed by other two studies in rabbit model. A study by Rahal compared topical application of 1 mg/mL MMC in one side of surgically created antrostomy to another side[22]. It was found that after 3 weeks, the antrostomies that received topical MMC were found to have larger areas compared to control side. Also 7 out of 10 of control side closed while only

1 out of 10 MMC side closed. Park et al from South Korea in 2006[23] further explore the application of MMC in experimentally inflamed maxillary sinusitis model. Maxillary antrostomies were performed after induction of sinusitis induced with platelet activating factor, and measurement of area value of ostium was calculated objectively. After topically applied MMC of 0.4 and 1 mg/mL versus no treatment in another side as control, it was found that MMC created antrostomies were significantly wider than control group in 6 weeks. However, there was no significant difference between ostium area of two different MMC concentrations.

Chung et al. first studied the use of MMC in endoscopic sinusitis surgery in 2002[15]using 0.4 mg/mL MMC cotton pledget saturated with 1 mL. Although the study found lower significant synerchia rate in MMC group (3.6%) than control (14.5%), the effect was non- statistical significance. Despite the successful of application of MMC in both animal and clinical studies, several studies had been later conducted but found conflict results. Some studies found lower rate of synerchia in MMC group[6-11,13], while others did not[12,14]. This could be mainly due to power issues to detect the benefits.

The use of MMC has also been applied to the synerchia itself. A recent case series by Hesham et al[24] combined MMC with diode laser in patients with synerchia at middle turbinate and lateral nasal wall. They applied 0.4 mg/ml of MMC for 5 minutes to the middle meatus and found only 15% of patients had a recurrent synerchia within 6 months follow up.

Our current review found no major side effect of MMC application in nasal cavity, similar to the recently published review by Veen et al[20], which found no systematic side effect on topical use of MMC in aerodigestive tract.

Our review has some strength. We focused on only randomized control trials in our review to avoid confounding bias of treatment effects. All except one trial studied on patients with bilateral chronic sinusitis, in which one nasal side was randomly assigned to the MMC whereas another nasal side was received normal saline. Data for the two treatments were correlated and we therefore applied a multivariate meta-analysis to pool treatment effects across trials. Correlation within patients was accounted in the analysis and thus the estimated treatment effects should be unbiased. Subgroup analysis was performed to identify more homogeneous patients who should gain more benefits from MMC treatments. We however had limitations. Although we focused on only randomize controlled trials, 7/10 studies were unclear in generating randomization sequences. None of studies had concealed the randomization lists. All except one studies focused on bilateral patients but data were analyzed as if a unit of intervention was independent. As a result, other source of bias from improper data analyses might be present.

Nevertheless, the current study found out that there could have been publication bias through the funnel plot. This could be the source of the heterogeneity in the current review. In addition, many of included studies are of questionable methodology, especially about the sequence generation and underreport of allocation concealment. Future studies should aim for higher method of studies.

CONCLUSION

Applying MMC topically after postoperative endoscopic sinus surgery could reduce a risk of synerchia of 63%without major adverse effects. The treatment effects may be more benefits in patients age 40 or younger or in patients without history of revision. However, information of long-term outcomes is lack and thus required to update when more studies are published.

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Table 1. Characteristics of included studies

Author, Year (Reference)	Country	n	Male (%)	Mean age (yr)	Nasal side	Included revision patients	Extent of surgical procedures			
							Frontal Sinus	Ethmoid Sinus	Maxillary Sinus	Other Procedure
Chung et al, 2002 ([15])	US	55	51	44.5	Bilateral	Yes	Yes	Yes	Yes	Yes, Septoplasty as required
Anand et al., 2004 ([12])	US	29	55	49.0	Bilateral	Yes	No	Yes	Yes	No
Chan et al., 2006 ([14])	Canada	38	60	49.0	Bilateral	Yes	Yes	Yes	Yes	No
Gupta et al., 2006 ([8])	India	30	67	-	Bilateral	No	No	Yes	Yes	No
Kim et al., 2006 ([9])	South Korea	20	70	31.0	Bilateral	Unknown	No	No	Yes	No
Konstantinidis et al., 2008 ([6])	Greece	30	53	39.5	Bilateral	No	No	Yes	Yes	Yes, Septoplasty as required
Kim et al., 2009 ([7])	Korea	38	47	46.5	Unilateral	Yes	No	No	No	Yes, Endoscopic Inferior medial antrostomy, Endonasal or Caldwel-Luc
Baradaranfar et al., 2011 ([13])	Iran	27	61	38.0	Bilateral	Yes	No	No	Yes	No
Singh et al., 2011 ([10])	India	30	70	-	Bilateral	No	Yes	Yes	Yes	No
Venkatraman et al., 2011 ([11])	India	50	54	32.0	Bilateral	No	No	Yes	Yes	No

Table 1. Continued

Author, Year (Reference)	Technique	MMC Concentration (mg/mL)	Amount (mL)	Application time (min)	Packing method	Packing position	Irrigation after packing	Duration of follow up (months)
Chung et al, 2002 ([15])	-	0.4	1	4	Neurological cottonoids	Middle Meatus	Yes, 60 mL of sterile normal saline	1
Anand et al., 2004 ([12])	-	0.5	1	5	Pledgets	Middle Meatus	No	3
Chan et al., 2006 ([14])	Messerklinger Technique, Frontal Recess - Kuhn &Javer	0.5	-	4	Neuropatties	Frontal recess	Unknown	
Gupta et al., 2006 ([8])	Messerklinger	0.4	1	4	Cotton Plug	Middle Meatus	Yes (Not specified)	1
Kim et al., 2006 ([9])	Through cutting forceps & curette, Microdebrider trim mucosa	0.4	1.5	5	Merocel	Opening of antrostomy site	Unknown	6
Konstantinidis et al., 2008 ([6])	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	6
Kim et al., 2009 ([7])	-	0.5	1	5	Pledged Soaked	Antrostomy Site	Unknown	1
Baradaranfar et al., 2011 ([13])	Messerklinger Technique	0.45	1.5	5	Cotton Mesh 6 cm stained with MMC	Middle Meatus, Ethmoid, Around maxillary sinus os	No	3
Singh et al., 2011 ([10])	-	0.4	5	5	Cotton pledget	Middle Meatus	Unknown	3
Venkatraman et al., 2011 ([11])	Messerklinger	0.5	1	5	Cotton pledget	Middle meatus	Yes, Saline	0.25

Table 2. Quality assessment of included studies

Author, Year (Reference no.)	Sequence	Concealment	Blinding	Incomplete outcome data	Selective Outcome Reporting	Free from other bias
Chung et al. 2002, [15]	Yes	Unclear	Yes	Yes	Yes	Unclear
Anand et al. 2004,[12]	Yes	Unclear	Yes	No	Yes	Unclear
Chan et al. 2006, [14]	Yes	Unclear	Yes	No	Yes	Unclear
Gupta et al. 2006, [8]	Unclear	Unclear	Yes	No	Yes	Unclear
Kim et al. 2006, [9]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Konstantinidis et al. 2008, [6]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kim et al. 2009, [7]	Unclear	Unclear	Unclear	No	Yes	Unclear
Baradaranfar et al. 2011, [13]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Singh et al. 2011, [10]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Venkatraman et al. 2011, [11]	Unclear	Unclear	Unclear	Yes	Yes	Unclear

Table 3. Risk ratios of included studies and pooled risk ratio

Author, Year (Reference no.)	Total sides	No. of normal saline	No. of MMC	RR (95% CI)
Chung et al. 2002, [15]	122	61	61	0.51 (0.25-1.02)
Anand et al. 2004,[12]	58	29	29	1.53 (0.55-4.28)
Gupta et al. 2006, [8]	60	30	30	0.06 (0.01-0.43)
Kim et al. 2006, [9]	40	20	20	0.21 (0.03-1.33)
Konstantinidis et al. 2008, [6]	60	30	30	0.44 (0.11-1.86)
Kim et al. 2009, [7]	38	16	22	0.35 (0.07-1.78)
Baradaranfar et al. 2011, [13]	74	37	37	0.32 (0.10-1.05)
Singh et al. 2011, [10] (0.40 mg/mL MMC)	30	15	15	0.14 (0.01-1.84)
Singh et al. 2011, [10] (0.80 mg/mL MMC)	30	15	15	0.32 (0.63-1.60)
Venkatraman et al. 2011, [11]	100	50	50	0.12 (0.02-0.61)
Pooled	612	303	309	0.37 (0.19-0.65)

Table 4. exploration of the source of heterogeneity

Factor	Number of studies	RR (95% CI)	I^2
Age			0%
<= 40	4	0.27 (0.08-0.88)	0%
> 40	6	0.41 (0.13-1.24)	51.69%
Revision			14.28%
No	5	0.20 (0.07-0.61)	0%
Yes	5	0.53 (0.22-1.29)	32.56%

Figure 1. Diagram of selection of studies

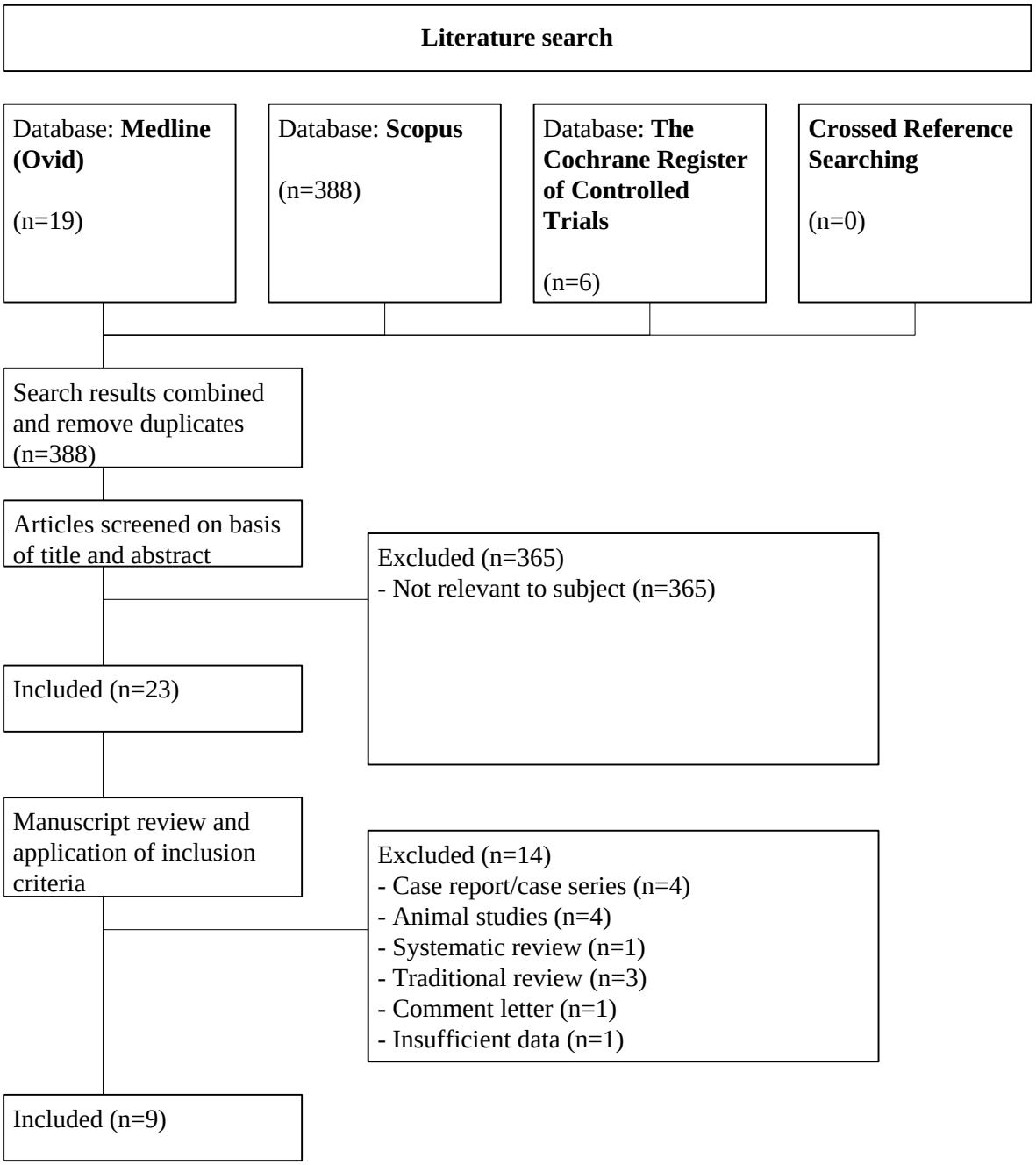


Figure 2. Forest plot of the treatment effects on having synerchia in MMC versus normal saline groups: Multivariate meta-analysis

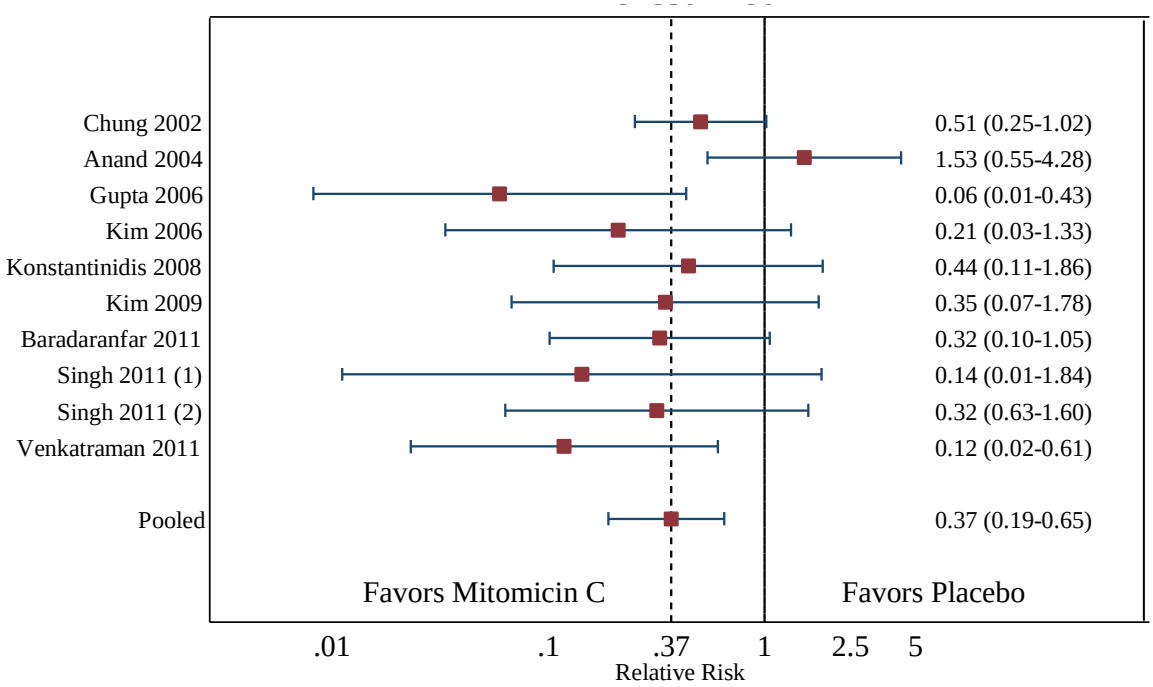
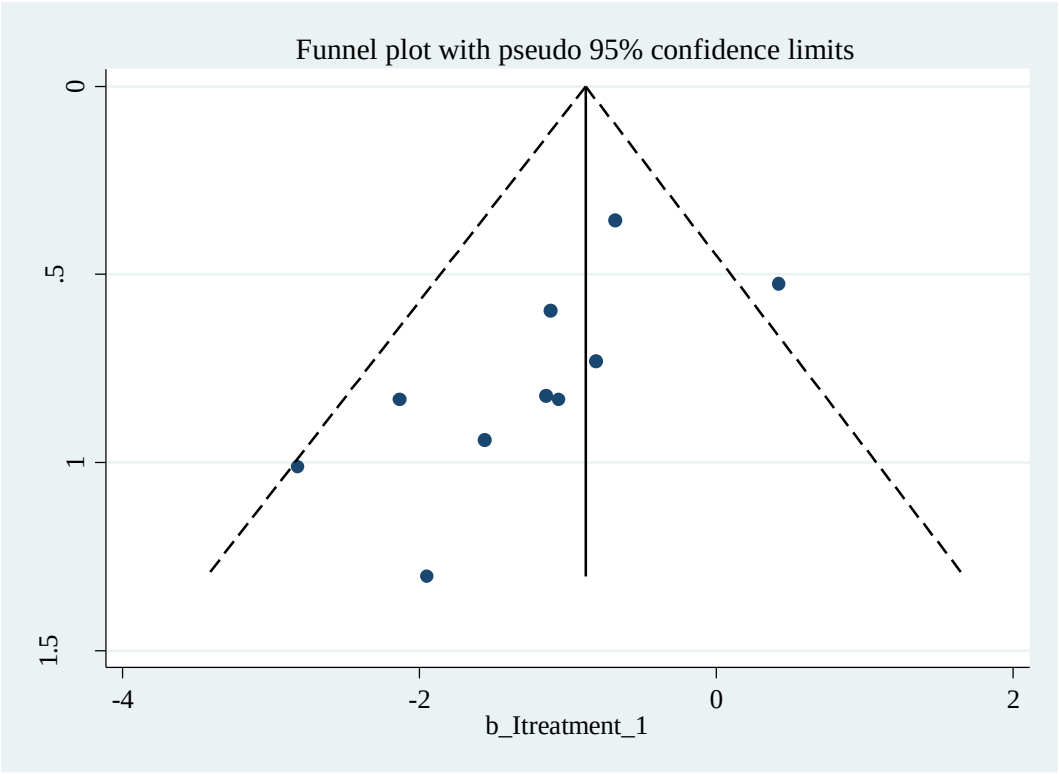
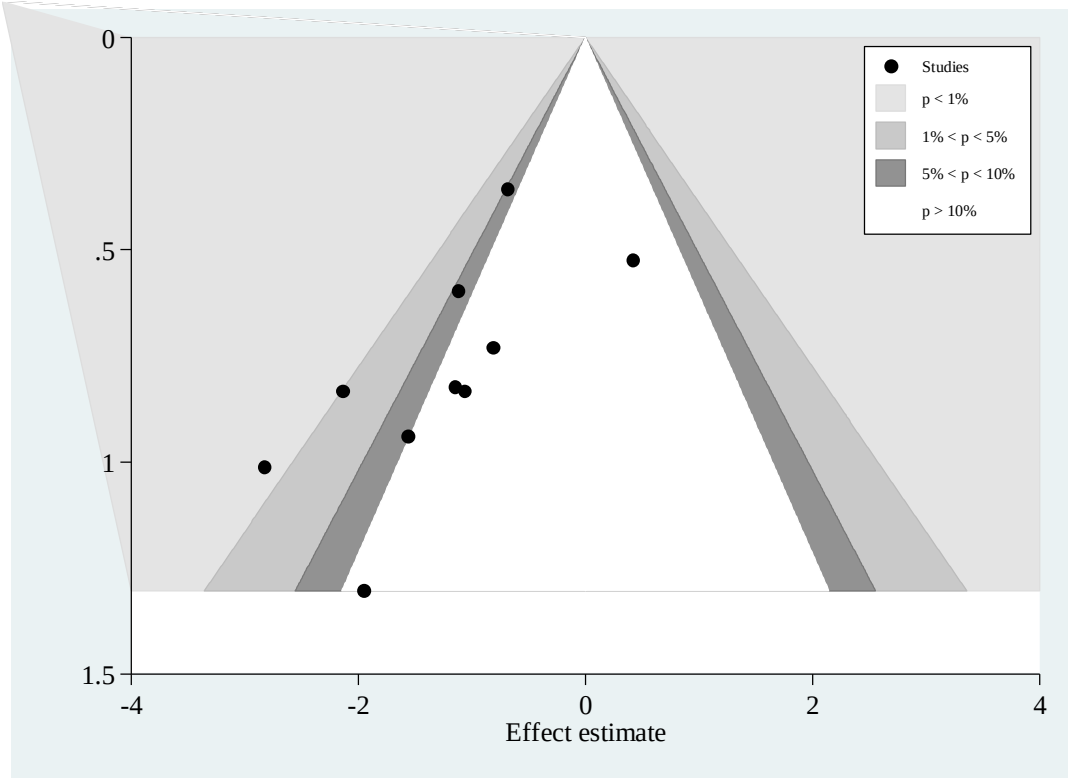


Figure 3. Funnel and contour enhanced-funnel plots

a)



b)



APPENDIX

Search Strategies

a) Medline

1	expMitomycin/ or Mitomycin C.mp. or Mitomycin.mp.
2	(Mitomicin C or Mitomicin).mp.
3	exp Sinusitis/
4	(rhinosinusitis or nasosinusitis or sinusitis or pansinusitis or ethmoiditis or sphenoiditis).mp.
5	(inflam* and sinus*).mp.
6	3 or 4 or 5
7	exp Endoscopy/
8	(endoscop* or uncinectomy or antrostomy or antrotomy or ethmoidectomy or sphenoidotomy).mp.
9	(sinus and surg*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
10	FESS.mp.
11	ESS.mp.
12	exp Surgery/
13	7 or 8 or 9 or 10 or 11 or 12
14	6 and 13
15	1 or 2
16	14 and 15

b) SCOPUS

(mitom?cin OR mitom?cin c) AND ((endoscop* sinus*surgery) OR (ess OR fe ss) OR (sinus* W/15 surgery) OR(uncinectomy OR maxillary antro*tomy OR middle meatalantro*tomy OR frontal sinus surgery OR ethmoid sinussurgery O R ethmoid?tomy OR sphenoid sinus surgeryOR sphenoid?tomy))
uncinectomy OR maxillary antro*tomy OR middle meatalantro*tomy OR front al sinus surgery OR ethmoid sinussurgery OR ethmoid?tomy OR sphenoid sinu s surgeryOR sphenoid?tomy
sinus* W/15 surgery
ess OR fess
endoscop* sinus* surgery

Mitomycin C in postop ESS - Data Extraction Form Version 1.1

Study ID _____

Reviewer _____

Date _____

Study Title _____

First Author _____ Journal _____ Year _____

Study Design ☐ RCT ☐ Quasi-Experimental ☐ Cross Over ☐ Other _____

Comment/Description of Study Design _____

Setting (Hospital, City, Country, Year) _____

Participants

Total n _____

Male sex (%) _____ Mean Age _____

Baseline disease assessment:

Severity: Method used _____ Description _____

Bilaterality: ☐ Unilateral disease ☐ Bilateral disease

Include revision patients? ☐ Unknown ☐ No ☐ Yes

Include specific patients with other diseases (such as cystic fibrosis, mucociliary disease, etc)

☐ Unknown ☐ No ☐ Yes

Operation of ESS

☐ Frontal Sinus Surgery ☐ Ethmoidectomy ☐ Maxillary antrostomy

☐ Other

Describe

_____

Technique of ESS

_____

Intervention (Mitomycin C)

Concentration & Amount _____

Duration of application _____

Packing method/agent _____

Apply at _____

Irrigation after application?

☐ Unknown ☐ No ☐ Yes describe method _____

Risk of bias assessment (Adapted from PRISMA guideline)

Item	Yes	No	Unclear	Note
Was the allocation sequence adequately generated? *(Adequate sequence generation?)*				
Was allocation adequately concealed? *(Allocation concealment?)*				
Was knowledge of allocation interventions adequately prevented during the study? *(Blinding?)*				
Were incomplete outcome data adequately addressed? *(Incomplete outcome data addressed?)*				
Are reports of the study free of suggestion of selective outcome reporting? *(Free of selection reporting?)*				
Was the study apparently free of other problems that could put it at a high risk of bias? *(Free of other bias?)* Premature trial termination Post randomization exclusion Unbalance baseline characteristics Adequately describe methods of data analysis Per-protocal analysis/modified ITT				Description of other bias:

Outcome

Outcome Measurement Method _____

Definition of Synerchia _____

Duration of Follow up _____

Time:	Synerchia or stenosis	No synerchia
Mitomycin C Group	a	b
Comparator Group	c	d
No of patients with synerchia bilaterally		

Time:	Synerchia or stenosis	No synerchia
Mitomycin C Group	a	b
Comparator Group	c	d
No of patients with synerchia bilaterally		

Time:	Synerchia or stenosis	No synerchia
Mitomycin C Group	a	b
Comparator Group	c	d
No of patients with synerchia bilaterally		

Description of other outcomes reported

Side effect of intervention

Major

_____

Minor

_____