SYSTEMATIC REVIEW

REVISED Efficacy of mitomycin-C on anterior urethral stricture after internal urethrotomy: A systematic review and meta-analysis [version 3; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background and Aim

Mitomycin-C is a potent agent that plays an important role in tissue healing and scar formation. This study aims to investigate the efficacy of Mitomycin-C in treating anterior urethral stricture after internal urethrotomy.

Methods

Studies evaluating efficacy of mitomycin-c for anterior urethral stricture post urethrotomy were searched using Pubmed, Scopus, Sciencedirect, MEDLINE, and Cochrane Reviews as directory databases. The search was done in March 15th 2020. Terms being used in the searching process were "mitomycin-c" or "mitomycin", "urethral stricture", "urethral stenosis", "internal urethrotomy", "optical urethrotomy" and its synonyms. Every study with the design of retrospective or prospective clinical study being done in human subject was included. Study appraisal conducted in accordance to Oxford University Center for Evidence-Based Medicine. The conclusion of each study was summarized and the calculation of random effects from every study was conducted in meta-analysis. Random effects model is chosen because small number of studies and quite different.

Results

Three studies involving 311 patients were included in this review, all of them reported less recurrence of in patients treated with mitomycin-c post urethrotomy ($p < 0.001$). Risk ratio of all studies was 0.41 with 95% confidence interval (0.25-0.68).

Conclusion

Mitomycin-C has the potential of efficacy in treating anterior urethral stricture post internal urethrotomy. Relatively few numbers of studies may impact in the strength of this review and further studies need to

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Approval Status

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version 3			
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Any reports and responses or comments on the article can be found at the end of the article.

be done.

Keywords

mitomycin-c, urethral stricture, internal urethrotomy

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Author roles: **Irdam GA:** Conceptualization, Methodology, Writing – Review & Editing; **Wahyudi I:** Conceptualization, Data Curation, Methodology, Supervision, Writing – Review & Editing; **Andy A:** Conceptualization, Formal Analysis, Investigation, Validation, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 2

Several changes have been made. In the methods section: inclusion and exclusion criteria has been restructured, study selection, data extraction, and risk of bias assessment have also been added. In results section: study flow diagram has been changed according to PRISMA guide, risk of bias, and result of side effects have been added. In Discussion: the first four paragraph has been deleted, risk of bias has been discussed, heterogeneity has been discussed, definition recurrence has been mentioned.

Any further responses from the reviewers can be found at the end of the article

Background

Urethral stricture often impairs quality of life and may result in a large economic burden¹. There are several procedures available for treating this condition, ranging from minimally invasive procedures like internal optical urethrotomy (IOU) to invasive procedure such as urethroplasty, with or without grafting, and tissue engineering². However, despite the methods available, urethral stricture often recurs. Several manipulations have been tried to prevent urethral stricture, such as indwelling catheter insertion, urethral calibration procedure, and home self-catheterization. Unfortunately, repeated instrumentation can cause scar formation. Moreover, it can also complicate subsequent reconstruction, which can lead to several complications^{3,4}. On the other hand, there have been several studies evaluating the effects of antifibrotic drugs such as glucocorticoid and mitomycin-C on urethral strictures. Mitomycin-C is an agent that has the potential to inhibit mitosis, fibroblast proliferation, formation of blood vessels, and synthesis of protein and collagen. This agent plays role in tissue healing process and scar formation by reducing the release of matrix proteins by inhibiting proliferative fibroblasts⁵.

To our knowledge, there have not been any systematic reviews or meta-analyses regarding the efficacy of mitomycin-C in treating anterior urethral stricture post internal urethrotomy. Thus, the present study aims to investigate the efficacy of mitomycin-C in treating anterior urethral stricture post internal urethrotomy. We hope that by conducting this review and analysis, a definite conclusion regarding the efficacy of such treatment could be achieved.

Methods

This systematic review was conducted based on guidelines from the Oxford University Center for Evidence-Based Medicine⁶. Our present study aims to determine whether mitomycin-C provide better efficacy compared to controls (without mitomycin-C) in adult patients with anterior urethral stricture after internal urethrotomy.

Inclusion and exclusion criteria

Inclusion criteria were (1) Study type: RCT (Randomized Control Trial) until March 15th 2020; (2) Intervention and

comparator: internal urethrotomy with addition Mitomycin-C vs internal urethrotomy without Mitomycin-C; (3) Patients: humans with anterior urethral stricture; (4) Primary outcome: efficacy of Mitomycin-C administration, determined by risk ratio; and (5) Secondary outcome: side effects from Mitomycin-C administration. Exclusion criteria were (1) Animal study; (2) case reports; (3) case series; (4) book chapters; and (5) editorials.

Search strategy

To find suitable studies to be included in this review, we used PubMed, Scopus, ScienceDirect, MEDLINE, and Cochrane Reviews as directory databases. We used combination of keywords “((((((mitomycin c[MeSH Terms]) OR mitomycin[MeSH Terms]) OR mitomycin c)) AND (((((((((((urethral stricture[MeSH Terms]) OR urethral strictures[MeSH Terms]) OR stricture, urethral[MeSH Terms]) OR strictures, urethral[MeSH Terms]) OR urethral stenosis[MeSH Terms]) OR urethral stenoses[MeSH Terms]) OR stenosis, urethral[MeSH Terms]) OR stenoses, urethral[MeSH Terms]) OR urethral stricture) OR urethral strictures) OR stricture, urethral) OR strictures, urethral) OR urethral stenosis) OR urethral stenoses) OR stenosis, urethral) OR stenoses, urethral)) AND “urethra/surgery”[MeSH Terms]) AND Humans[Mesh]”. We also used term “human” as limiting term to exclude every study that was not conducted on human subjects.

Study selection and data extraction

A single reviewer screened the articles based on the titles, abstracts, and full text. Then, the data on author, publication year, details of studies subjects, details of studies intervention, and results are extracted.

Risk of bias assessment

Another single reviewer assessed the risk of bias using the Cochrane Risk of Bias Tool, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Every domain was judged with 3 levels (low risk, unclear risk, and high risk).

Analysis and concluding the review

We evaluated the study using appraisal worksheet for randomized clinical trial from Oxford University Center for Evidence-Based Medicine to stratify the risk of bias⁶. Using Revman 5.3 software, recurrence number from all selected studies were analyzed. Data were analyzed using forest plots with calculation of random effects. It was also done using Revman 5.3 to show relative risk/risk ratio for recurrence rate variable dan p-value. We summarized the conclusion of each study at the table along with its appraisal. We decided to use random effects model since the small amount of study and the difference between them.

Results

Literature search

Searching process (searching strategy showed in [Figure 1](#)) by using five databases found 49 study articles. There were 13

Figure 1. Study flow diagram.

articles eliminated after screening for duplication. The remained 36 articles were reduced to seven articles after title and abstract screening, leaving seven full text articles to be reviewed. Based on study design, we eliminated three articles, leaving four articles to be summarized in systematic review and meta-analysis.

Study characteristics and quality assessment

Four selected studies were conducted in 2007, 2015, 2016, and 2019^{2,4,7,8}. All studies evaluated the effectivity of mitomycin-C given after internal urethrotomy for anterior urethral stricture. From these selected articles, three evaluated the usage of submucosal injection of mitomycin-C for anterior urethral stricture after urethrotomy. How mitomycin-C was injected differed in every study. Mazdak *et al.*⁴ study used 0,1 mg of Mitomycin-C in 2 ml of distilled water injected in four quadrants, Ali *et al.*² study used 0,1% Mitomycin-C injected in three

quadrants, and Islam *et al.*⁷ study used 0,1 mg in 2 ml of distilled water in two quadrants. Moradi *et al.*⁸ study evaluated intraluminal injection of Mitomycin-C in hydrogel base, consisting of 0.8 mg Mitomycin-C with 1cc water and propylene glycol to PF-127 poloxamer. The hydrogel base was injected through a small feeding tube to reach the site of stricture. All studies applied mitomycin-C after internal urethrotomy procedure and were conducted in populations with different age means. Each of studies' quality was assessed using guide from Oxford University Center for Evidence-Based Medicine; this is explained in [Table 1](#) and [Table 2](#).

Outcome measures

We included the studies in which recurrence was defined by a patient having obstructive symptoms, obvious stricture at retrograde urethrography, or uroflowmetry with maximum flow rate less than 12 mL/s, and stricture was measured using

Table 1. Characteristics of subjects in included studies.

Studies	Average age (year)		Pre-intervention stricture site		Procedure of internal urethrotomy	Clinical feature				Cause of injury	
	MMC group	Control group	MMC Group	Control group		Urinary retention	Bladder Outlet Obstruction	Azotemia	Urosepsis	Mitomycin-C Group	Control group
Moradi <i>et al.</i> , 2016 ³	54.55 ± 21.25	53.75 ± 24.75	Anterior urethral stricture		Trans-urethral incision at 12 o'clock via cold knife urethrotomy	N/A				N/A	
Ali <i>et al.</i> , 2015 ²	37.31 ± 10.1	40.1 ± 11.4	Bulbar urethra: 84.6% Penile urethra: 15.4%	Bulbar urethra: 78.1% Penile urethra: 21.9%	Internal Optic urethrotomy	Mitomycin-C group				Road traffic: 59% Iatrogenic: 30.8% Straddle: 9% Infective: 1.3%	Road traffic: 71.2% Iatrogenic: 21.9% Straddle: 6.8% Infective: -
						70.5%	16.6%	10.2%	2.5%		
						Control group					
						57.5%	31.5%	9.5%	1.3%		
Mazdak <i>et al.</i> , 2007 ⁴	29.8 (15–70)	29.2 (11–66)	Anterior urethral stricture		Trans- urethral incision at 12 o'clock via cold knife urethrotomy	N/A				Straddle injury or other blunt perineal trauma	
Islam <i>et al.</i> , 2019 ⁷	49.43 ± 8.10	48.98±7.20	Anterior urethral stricture		Internal Optic Urethrotomy	N/A				Idiopathic, lichen sclerosis, urethritis, or unknown	

[1] MMC, mitomycin C.

Table 2. Summary and appraisal of the selected articles.

Studies	LoE	Sample size	Methods of mitomycin-C application	Timing of mitomycin-C application	Follow up end-point	Validity				Importance	Applicability		
						Randomized allocation	Similarity of group	Equal Treatment	Minimal Loss to Follow-up	Blinding	Relevance	Feasibility	Benefit Overweight the Harm
Moradi <i>et al.</i> , 2016 ⁶	1b	40	Intraluminal injection of 0.8 mg mitomycin-C + propylene glycol through indwelling catheter	After Internal Urethrotomy	12 months	Not stated	Yes	Yes	Yes	Not stated	Unsure	Yes	Yes
Ali <i>et al.</i> , 2015 ²	1b	180	Submucosal injection of 0.1% mitomycin-C at three quadrants (1, 11, & 12 o'clock position) using TLA needle	After Internal Urethrotomy	18 months	Yes	No	Yes	Yes	Not stated	Unsure	Yes	Yes
Mazdak <i>et al.</i> , 2007 ⁴	1b	40	Submucosal injection of 0.1 mg mitomycin-C in four quadrants (1,5,7, & 11 o'clock position) using 22-Gauge cystoscopic needle	Before Internal Urethrotomy	6 months	Not stated	Yes	Yes	Yes	Not stated	Unsure	Yes	Yes
Islam <i>et al.</i> , 2019 ⁷	1b	80	Submucosal injection of 0.1 mg Mitomycin-C in two quadrants (11 & 1 o'clock) using 21-gauge cystoscopic needle	After internal Urethrotomy	6 months	Yes	Yes	Yes	Yes	Not stated	Unsure	Yes	Yes

[i] LoE, level of evidence; RR relative risk; ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat.

retrograde urethrogram or ultrasonography of the urethra. The outcome that measured was recurrence rate (percentage).

Risk of Bias

The summary of the risk bias assessment can be found in Figure 2. All of the studies stated that they have undergone randomization. But only Ali *et al.* and Islam *et al.* mentioned the randomization method. A common problem with all the studies included in this review is that there was no clear concealment and blinding statement. All of the studies are completed and have relatively small loss to follow-up rates. Mazdak *et al.* didn't mentioned recurrence criteria resulting high risk in selective reporting, but other studies mentioned^{2,4,7,8}.

Results and heterogeneity of the studies

All selected articles stated that Mitomycin-C had a significant effect on preventing or delaying urethral stricture recurrence post internal urethrotomy. All studies reported that the time-based recurrence rates in the two groups differed, where lower recurrence rates were found in the group given Mitomycin-C^{2,4,7,8}. From study characteristic that is quite different and small number of studies, we choose to use random-effects model in forest plot showed in Figure 3. This forest plot suggests that there were significant differences between cases and control group. It showed from risk ratio is 0.41 with 95% confidence interval of 0.25 until 0.68, with p value <0.05. As for side effects are reported minimal and insignificant^{2,8}.

Discussion

All the studies included in this review treated the two groups equally and had relatively small loss-to-follow-up rates. A common problem with all the studies included in this review is that there was no clear blinding statement. Mazdak *et al.*⁴ and Moradi *et al.*⁸ study stated that their studies are randomized. But, the randomization procedure was not stated in the study method. On the other hand, although Ali *et al.*² had randomized its subjects, age characteristics in the two groups were significantly different. Mazdak *et al.*⁴ also didn't mentioned recurrence criteria, which could result in high risk bias. There was also a relevant study by Azzawi *et al.*⁹ that matches our inclusion criteria. But we are unable to access the full text, so we decide to exclude it. As for heterogeneity, from the calculation might not be important difference ($I^2=27\%$, $p = 0.19$). But the small

number of studies, that calculation may not work well. From the studies we could notice the difference in age and methods in administering Mitomycin-C, those difference might add up the heterogeneity.

All studies support the use of mitomycin-C to prevent or delay anterior urethral stricture after internal urethrotomy, which in this review defined by a patient having obstructive symptoms, obvious stricture at retrograde urethrography, or uroflowmetry

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Ali 2015	+	?	?	?	+	+
Islam 2019	+	?	?	?	+	+
Mazdak 2007	?	?	?	?	+	-
Moradi 2016	?	?	?	?	+	+

Figure 2. Risk of Bias Summary.

Figure 3. Forest plot for recurrence rate. Test for heterogeneity Tau-square = 0.09; chi-square = 4.78; $df = 3$; p-value = 0.19; I-squared = 37%.

with maximum flow rate less than 12 mL/s, and every stricture in this review are all primary stricture.. This was confirmed by a less rate of recurrence rate in Mitomycin-C patients^{2,4,8}; we found that those who had Mitomycin-C administered had lower incidence of recurrence during one year and 18 months of follow up (RR = 0.32, P < 0.001). This was also confirmed by a series of cases by Farrell *et al.*¹⁰, Farrell *et al.*¹¹, and Sourial *et al.*¹² Mazdak *et al.*⁴ injected mitomycin-C into the urethral submucosa and reported that patients with mitomycin-C injection had lower rates of stricture recurrence. Opposing this study, some researchers proposed that submucosal injection could increase the complication rate and reduce the duration of the effective dose within the tissue, which yielded a scientific discussion¹³. Ayyildiz *et al.*¹⁴ assessed the efficacy of Mitomycin-C for preventing urethral scar by applying the agent topically to the traumatized region in rats. They concluded that mitomycin-C applied locally reduced fibrosis significantly in a dose-independent manner.

Although all studies support the use of Mitomycin-C to prevent or delay post urethrotomy urethral stricture and the side effects reported in the studies reviewed are minimal, in Ali *et al.*² and Moradi *et al.*⁸ are insignificant, but Mazdak *et al.*⁴ and Islam *et al.*⁷ didn't assess any side effects, the results of this review need to be followed up with caution. The limitation of this study can be seen from only a few studies that discuss this topic. Some of the existing studies are not enough to be generalized to a wider population, given that selected studies were carried out in Iran and Pakistan^{2,4,7,8}. Therefore their application needs to be carried out wisely and cautiously. Research

related to this in the future can still be done with different populations.

Due to short period of follow up time in all studies, some authors^{2,4} concluded that the study of Mitomycin-C needed firm results regarding long term success. Mazdak *et al.*⁴ added that stricture may recur within two years after internal urethrotomy.

Conclusion

Mitomycin-C could be used as a potential additional treatment for anterior urethral strictures after internal urethrotomy. However, further studies are required to investigate the safety and efficacy of this method for treating anterior urethral strictures, as only a limited number of studies presently exist.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Open Science Framework: PRISMA checklist for 'Efficacy of mitomycin-C on anterior urethral stricture after internal urethrotomy: A systematic review and meta-analysis'. <https://doi.org/10.17605/OSF.IO/APU9B>¹⁵.

The updated PRISMA checklist is available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Reviewer Report 16 January 2023

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Muhammet İrfan Dönmez

Istanbul University, Istanbul, Turkey

In this study, the authors aimed to investigate the efficacy of Mitomycin-C in adult patients with anterior urethral stricture after internal urethrotomy. Three studies involving 311 patients were included and a systematic review was conducted. However, I do have some questions and concerns outlined below about their study.

1. According to abstract, three studies involving 311 patients were included in this review. However, flowchart indicates that four articles were included. Please clarify.
2. The search was done in March 15th 2020. If there are other current studies from the last two years, I believe that they should be updated, as well.
3. The review mentioned different usage and dosage of submucosal injection of mitomycin-C in four studies. Is it possible to give an opinion to the reader about which application method is more ideal? The difference and heterogeneity in age and methods in administering Mitomycin-C may cause misinterpretation of the results.
4. *We included the studies in which recurrence was defined uroflowmetry with maximum flow rate less than 12 mL/s.* What are the references that the mentioned studies use to determine this threshold value?
5. There was no assessment of side effects in two of the studies. In addition, the lack of clear concealment and blinding statement in all four studies included in this systematic review increases the risk of bias. Further, the time to recurrence cannot be clearly evaluated due to short follow-up period. This raises doubts about the reliability of the study outcomes. As a result, the main limitation of this systematic review is that the results cannot be generalized to a wider population as it only included a few studies. Based on this, giving the message in the conclusion that Mitomycin-C has potential for efficacy in the treatment of anterior urethral stricture after internal urethrotomy may mislead the reader.
6. There several errors of grammar and syntax that need attention.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: urethral stricture

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 August 2020

<https://doi.org/10.5256/f1000research.28494.r69072>

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Laetitia M. O. de Kort

University Medical Centre Utrecht, Utrecht, The Netherlands

I am satisfied with the adjustments.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 29 June 2020

<https://doi.org/10.5256/f1000research.26186.r64256>

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Farhad Shokrane F

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I thank the authors for applying a few of my suggestions:

- Running an update search and adding one of my suggested studies;
- Changing the Fixed-Effect Model to Random-Effects Model (Effects not Effect);
- Balancing their conclusion.

The manuscript can benefit from a native language editor.

Unfortunately, the majority of the comments and concerns are still standing: revising search strategy involving a search expert, restructuring inclusion and exclusion criteria, reporting/listing/analysing side effects as outcomes, adding new text headings in Methods for screening, data extraction, assessment of risk of bias, and explaining the processes that require involving at least two reviewer, following PRISMA checklist items, discussing the results of heterogeneity test, removing first four paragraphs from discussion or moving them to introduction, and assessing, including or citing Azzawi's study or mentioning the reason for its exclusion.

The authors have removed EBSCOhost and Ovid rather than mentioning the names of the listed of searched databases via these search interfaces.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence Synthesis, Systematic Review, Information Retrieval, Automation of Systematic Reviews, Living Evidence, Scoping Review, Cochrane Review, Database, Clinical Practice Guideline, Overview, Rapid Review, Randomized Controlled Trial, Open Data, Medical Journalism, Outcome, Intervention, Cochrane.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Jul 2020

Andy Andy

Thank you for your feedback, I really appreciate it. As for the method section and other feedbacks we'll be revising it. As for the journal database, we have changed from OVID and EBSCOHost with MEDLINE.

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 June 2020

<https://doi.org/10.5256/f1000research.26186.r64255>

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Laetitia M. O. de Kort

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My comments:

- The length of the stricture is important indeed and should not be left out.
- Still the definition of stricture recurrence is not mentioned in the discussion.
- Side effects and adverse events are still not mentioned.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Jul 2020

Andy Andy

Thank you for the feedback again. We really appreciate it. For the length of stricture after critical reading over the references, only Mazdak et al compare the length of the stricture. Meanwhile, others did not compare it even with the newest reference. The definition of stricture recurrence has been mentioned in outcome measures inside the result section, but I will add it to the discussion. As for side effects and adverse events that have been mentioned in the seventh paragraph and the references didn't mention specific side effects nor adverse events, they only mention insignificant and minimal.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 17 February 2020

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The authors have conducted the first systematic review to answer this research question. It is a valuable effort.

Abstract

1. EBSCOhost and Ovid are not databases. They are search interfaces or search engines for other databases. Please add the name of the databases that you search using these two tools.
2. Please add the exact search date (dd/mm/yyyy).
3. Please state the reason for not using Cochrane Risk of Bias tool for assessing risk of bias of RCTs.
4. Please add rationale for using fixed effect model.
5. The conclusion is so strong. With limited evidence, it is not easy to say that MMC has safety, efficacy, or long-term efficacy.

Methods

1. The search date is older than a year (17 months old). Please update the search. I spent a few minutes and identified following recent studies:
 - Azzawi (2018)¹
 - Islam *et al.* (2019)²
2. EBSCOhost and Ovid are not databases. They are search interfaces or search engines for other databases. Please add the name of the databases that you search using these two tools.
3. The search strategy reported for PubMed needs serious attention by a search expert such as a librarian or information specialist and through using PRESS checklist for peer-reviewing search strategies. If authors have no access to such person they can post a task on taskexchange.cochrane.org and request a volunteer to help them in exchange to offering Acknowledgement or Authorship, depending on their contribution.
4. When the number of results is little, usually the authors should seek other sources such as references of included studies, citations to relevant studies, contacting the authors of relevant studies, etc. Depending on amount of time and resources available for the team, I request them to use other methods to make sure no studies are missing.
5. Please structure Inclusion and Exclusion Criteria to subheadings: Patients, Intervention, Control/Comparison, and Primary and Secondary Outcomes.
6. I wondered why side effects of interventions have not been listed as collected outcome data.

7. Please add separate headings for Screening, Data Extraction, Assessment of Risk of Bias, and explain their processes.
8. Please follow the PRISMA reporting guideline items one by one.
9. Please state the reason for not using Cochrane Risk of Bias tool for assessing risk of bias of RCTs while it is available within RevMan.
10. Please share your RevMan file as Appendix in Open Science Framework so that the readers could reproduce your analysis.
11. Please add rationale for using fixed effect model.

Results

1. Please follow the original PRISMA flow diagram in which duplication is before screening.
2. I2 is not the only way to notice heterogeneity. Actually, I2 may not work well with small sample size and low number of studies. The other ways is to look at the heterogeneity in study details such as characteristics of population (age – compare Age in Moradi with age in Mazdak –, sex, etc.), interventions (method of administration or dosage), and outcomes (methods of measurement). Also N/As in the table are missing details that you may get contacting the authors and they may contribute to heterogeneity. Based on what I see in your description, the method of administration is different among studies plus age of the patients varies across studies.

Discussion

1. The first four paragraph of the discussion are not discussing the results and they seem to be relevant to Background.
2. Impact of small sample size, heterogeneity of included studies, adverse effects, subjectivity of outcome measure, not using placebo for control group on interpreting these results are some of the items that could have been discussed here. I also refer the authors to a commentary written by Ng and Chan on Mazdak *et al.* as the first RCT³.

I thank the authors for listing some of the limitations this reviews. I think a new version of this review should be submitted, before being approved.

References

1. Azzawi I: [15] The role of mitomycin C intralesional injection during visual internal urethrotomy in urethral stricture recurrence. *Arab Journal of Urology*. 2018; **16** (sup1): S8-S9 [Publisher Full Text](#)
2. Islam SU, Baloch WA, Shahid MA, Ansari I, et al.: Role of Mitomycin C in Anterior Urethral Stricture Recurrence after Internal Urethrotomy. *Pakistan Journal of Medical and Health Sciences*. 2019; **13** (2): 497-499
3. Ng C, Chan S: Re: Hamid Mazdak, Iraj Meshki and Fatemeh Ghassami. Effect of Mitomycin C on Anterior Urethral Stricture Recurrence after Internal Urethrotomy. *Eur Urol* 2007;51:1089–92. *European Urology*. 2007; **52** (3). [Publisher Full Text](#)

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence Synthesis, Systematic Review, Information Retrieval, Automation of Systematic Reviews, Living Evidence, Scoping Review, Cochrane Review, Database, Clinical Practice Guideline, Overview, Rapid Review, Randomized Controlled Trial, Open Data, Medical Journalism, Outcome, Intervention, Cochrane.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 27 Apr 2020

Andy Andy

Thank you for the feedback, we have revised according to most of your comments. Update also has been implemented. As for contacting the authors for N/A in tables, we have tried contacting the authors but there is no answer until now.

Competing Interests: No competing interests were disclosed.

Reviewer Report 03 February 2020

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Laetitia M. O. de Kort

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The subject of this review is interesting and relevant to clinical practice. The review is well written. I have some comments:

- The literature search was until September 2018. Why is an update missing?

- Complications and side effects of the MMC injections were not mentioned.
- There was no clear definition of recurrence of the stricture. As this is a major subject of dispute in urethral surgery, this issue should be addressed, at least in the discussion.
- The length of the stricture was not mentioned.
- Were these all primary strictures? Should be addressed.
- The first publication was in 2007. Yet, MMC injection is not implemented in clinical practice for prevention of urethral stricture. It should be discussed why this is the case.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Apr 2020

Andy Andy

Thank you for your review. We have revised our publication according to your comments and we will upload it as soon as possible. But some comments I would like to answer them

- The literature search was until September 2018. Why is an update missing?

We have searched with our search strategy and there are no updates until September 2018.

- The first publication was in 2007. Yet, MMC injection is not implemented in clinical practice for prevention of urethral stricture. It should be discussed why this is the case. It has been stated clearly that the evidence for MMC injections are not enough for it to be implemented in clinical practice. Therefore, we require further research.

We are open to any suggestion for improving this study, thank you

Competing Interests: No competing interests were disclosed.

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