Efficacy of mitomycin-C on anterior urethral stricture after internal urethrotomy: A systematic review and meta-analysis [version 2; peer review: 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, Sciedirect, 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 effect from every study was conducted in meta-analysis. Random effect 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 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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First published: 08 Aug 2019, 8:1390 https://doi.org/10.12688/f1000research.19704.1
Background

Urethral stricture often impairs quality of life and may result in a large economic burden. There are several procedures available for treating this condition, ranging from minimally invasive procedures like internal optical urethrotomy (IOUS) to invasive procedures such as urethroplasty, with or without grafting, and tissue engineering. 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. 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 fibroblasts.

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 Medicine. Our present study aims to determine whether mitomycin-C provides better efficacy compared to controls (without mitomycin-C) in adult patients with anterior urethral stricture after internal urethrotomy.

Inclusion and exclusion criteria

To be considered for inclusion, the included studies were required to be randomized controlled trials (RCTs) study investigating efficacy of mitomycin-C as the additional treatment to internal urethrotomy in anterior urethral stricture. We expanded the searching by including related studies suggested by the databases. Year of publishing was not considered as inclusion criterion. Any study until March 15th, 2020 was included. The primary outcome measures were efficacy of mitomycin-C administration, determined by risk ratio for proportion results and mean difference for continuous data. Animal studies, case series, case report, editorials, and book chapters were excluded.

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 stricutures, 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 stricutures, 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.

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 bias. Using Revman 5.3 software, recurrence number from all selected studies were analyzed. Data were analyzed using forest plots with calculation of random effect. 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 effect 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 six databases found 49 study articles. There were 29 articles eliminated after title and abstract screening. The remained 20 articles were reduced to six articles after eliminating duplicates, 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. 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. study used 0,1 mg of Mitomycin-C in 2 ml of distilled water injected in four quadrants. Ali et al. study used 0,1% Mitomycin-C injected in three quadrants, and Islam et al. study used 0,1 mg in 2 ml of distilled water.
in two quadrants. Moradi et al.\textsuperscript{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.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Average age (year)</th>
<th>Pre-intervention stricture site</th>
<th>Procedure of internal urethrotomy</th>
<th>Clinical feature</th>
<th>Cause of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moradi et al., 2016</td>
<td>54.55 ± 21.25</td>
<td>Anterior urethral stricture</td>
<td>Trans-urethral incision at 12 o’clock via cold knife urethrotomy</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ali et al., 2015</td>
<td>37.31 ± 10.1</td>
<td>Bulbar urethra: 84.6% Penile urethra: 15.4%</td>
<td>Internal Optic urethrotomy</td>
<td>Mitomycin-C group</td>
<td>Road traffic: 59% Iatrogenic: 30.8% Straddle: 9% Infective: 1.3%</td>
</tr>
<tr>
<td>Mazdak et al., 2007</td>
<td>29.8 (15–70)</td>
<td>Anterior urethral stricture</td>
<td>Trans-urethral incision at 12 o’clock via cold knife urethrotomy</td>
<td>N/A</td>
<td>Straddle injury or other blunt perineal trauma</td>
</tr>
<tr>
<td>Islam et al., 2019</td>
<td>49.43 ± 8.10</td>
<td>Anterior urethral stricture</td>
<td>Internal Optic Urethrotomy</td>
<td>N/A</td>
<td>Idiopathic, lichen sclerosus, urethritis, or unknown</td>
</tr>
</tbody>
</table>

[i] MMC, mitomycin C.
### Table 2. Summary and appraisal of the selected articles.

<table>
<thead>
<tr>
<th>Studies</th>
<th>LoE</th>
<th>Sample Size</th>
<th>Methods of mitomycin-C application</th>
<th>Timing of mitomycin-C application</th>
<th>Follow up endpoint</th>
<th>Validity</th>
<th>Relevance</th>
<th>Feasibility</th>
<th>Benefit Overweight the Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moradi et al., 2016</td>
<td>1b</td>
<td>40</td>
<td>Intraluminal injection of 0.8 mg mitomycin-C + propylene glycol through indwelling catheter</td>
<td>After Internal Urethrotomy</td>
<td>12 months</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali et al., 2015</td>
<td>1b</td>
<td>180</td>
<td>Submucosal injection of 0.1% mitomycin-C at three quadrants (1, 11, &amp; 12 o’clock position) using TLA needle</td>
<td>After Internal Urethrotomy</td>
<td>18 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mazdak et al., 2007</td>
<td>1b</td>
<td>40</td>
<td>Submucosal injection of 0.1 mg mitomycin-C in four quadrants (1,5,7, &amp; 11 o’clock position) using 22-Gauze cystoscopic needle</td>
<td>Before Internal Urethrotomy</td>
<td>6 months</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Islam et al., 2019</td>
<td>1b</td>
<td>80</td>
<td>Submucosal injection of 0.1 mg Mitomycin-C in two quadrants (11 &amp; 1 o’clock) using 21-gauge cystoscopic needle</td>
<td>After internal Urethrotomy</td>
<td>6 months</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

LoE, level of evidence; RR, relative risk; ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat.
Outcome measures

We included the studies in which recurrence was defined by a patient having obstructive symptoms, obvious stricture at retrograde urethrogram, or uroflowmetry with maximum flow rate less than 12 mL/s, and stricture was measured using retrograde urethrogram or ultrasonography of the urethra. The outcome that measured was recurrence rate (percentage).

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. From study characteristic that is quite different and small number of studies, we choose to use random-effect model in forest plot showed in Figure 2. 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.

Discussion

Urethral stricture is a serious complication in male patients, which causes great morbidity and considerable health-related costs. This condition often results in voiding dysfunction, which will affect quality of life. Moreover, this voiding dysfunction can trigger chain of events leading to renal failure. Majority of the recommended treatment methods have low success rate. A recent survey revealed that 86% of American urologists prefer internal urethrotomy when treating anterior urethral stricture. However, internal urethrotomy is associated with a high rate of urethral stricture recurrence, ranging from 20 to 60%. Despite several methods have been introduced to lower recurrence rate, including clean intermittent self-catheterization, numerous authors has labeled this a failure as it could not fully prevent recurrence of urethral stricture.

Despite unclear pathophysiology of urethral stricture, a pathophysiological mechanism suggested is fibrosis caused by excessive synthesis of collagen and altered extracellular matrix. Therefore, any drug or procedure which can delay fibrosis after internal urethrotomy would lead to an increase of surgical success rates and patient comfort, and therefore decrease treatment costs. Therefore, many studies have been performed to explore different molecules the can prevent fibrosis and urethral stricture recurrence.

Mitomycin-C is an alkylating antineoplastic antibiotic, produced by Streptomyces caespitosus. Mitomycin-C can inhibit DNA synthesis by linking adenine and guanine, resulting in DNA cross-linking. It can suppress cellular RNA and protein synthesis, and is not cell cycle specific. Therefore, it can delay the healing process by preventing replication of fibroblasts and epithelial cells, as well as inhibiting collagen synthesis. It has been shown that mitomycin-C can improve the success rates of trabeculotomy and myringotomy by preventing proliferation of fibroblasts and development of fibrosis.

The anti-fibroblast activity mechanism of mitomycin-C is unknown. Experts have suggested that the reduction of fibroblast activity may be mediated by myofibroblasts apoptosis. As the wound closes, apoptosis of myofibroblast and vascular cells increases, indicating that this is the mechanism by which granulation tissue will lead to scarring.

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. and Moradi et al. study stated their studies are randomized. But, the randomization procedure was not stated in the study method. On the other hand, although Ali et al. had randomized its subjects, age characteristics in the two groups were significantly different. Every stricture in this review is all primary stricture.

All studies support the use of mitomycin-C to prevent or delay anterior urethral stricture after internal urethrotomy. This was confirmed by a less rate of recurrence rate in Mitomycin-C patients; 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., Farrell et al., and Sourial et al. Mazdak et al. 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.

![Figure 2. 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%.](image-url)
Due to short period of follow up time in all studies, some authors concluded that the study of Mitomycin-C needed firm results regarding long term success. Mazdak et al. 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**

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.

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).

### References


Open Peer Review

Current Peer Review Status: 

Version 2

Reviewer Report 29 June 2020

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Farhad Shokraneh
King's College London, London, UK

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.

**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, Universitas Indonesia, Jakarta Pusat, Indonesia

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
University Medical Centre Utrecht, Utrecht, The Netherlands

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.

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, Universitas Indonesia, Jakarta Pusat, Indonesia

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.

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**Review: Version 1**

**Reviewer Report 17 February 2020**

https://doi.org/10.5256/f1000research.21610.r59109

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**Farhad Shokraneh**

King's College London, London, UK

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 RCT\textsuperscript{3}. 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

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

\textbf{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 state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 27 Apr 2020

\textbf{Andy Andy}, Indonesia University, Urology Department, Indonesia

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.
Laetitia M. O. de Kort
University Medical Centre Utrecht, Utrecht, The Netherlands

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**, Indonesia University, Urology Department, Indonesia

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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