

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Balloon dilation for the treatment of male urethral strictures: A Systematic Review and Meta-analysis
<b>AUTHORS</b>	Li, Xiaoyu; Xu, Chunru; Ji, Xing; Zhu, Zhenpeng; Cai, Tianyu; Guo, Zhenke; Lin, Jian

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Chan, Garson Saskatchewan Health
<b>REVIEW RETURNED</b>	04-Feb-2023

<b>GENERAL COMMENTS</b>	<p>Thank you for this interesting SR on the use of balloon dilation in urethral strictures in men.</p> <p>This is an important review as there is now more devices, medically coated balloons on the market that show benefit in urethral stricture disease.</p> <p>Please check general grammar: page 4 lines 57-58 intro Page 17, line 57 "dissection" Page 18, line 11-12</p> <p>Can you discuss or check effect of balloon vs other DVIU or regular dilation? How accurate can we be about the data when the included studies include both retrospective and prospective rather than only RCT? I have an issue with including abstract only articles from conferences as they are not subject to same scrutiny and peer review.</p> <p>I see patients were included with both anterior and posterior strictures/stenosis. Can the authors separate these into separate analysis, they sometimes behave differently in treatment response.</p> <p>What was the loss to follow up rate in the papers?</p> <p>Only 6 papers had other outcome measures like UFR, PVR and IPSS. Authors comment on critical timing of balloon dilation in conclusion, can they expand on this? not mentioned elsewhere.</p> <p>Given the difficulty having high quality RCT in the SR it is difficult to have a solid conclusion.</p>
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<b>REVIEWER</b>	Frankiewicz, Mikołaj Medical University of Gdansk
<b>REVIEW RETURNED</b>	25-Mar-2023

<b>GENERAL COMMENTS</b>	<p>This is an important, well-designed study presenting a systematic review and meta-analysis of the application of balloon dilation for the treatment of male urethral strictures.</p> <p>As commented by the authors – balloon dilatation may be an important intermediate choice for the treatment of male urethral stricture, yet until now the data is still lacking regarding the long-term outcomes of this method.</p> <p>The limitation of the study is the fact that the main outcomes that were analysed did not include the patient satisfaction from the procedure (this parameter can be measured by PROMs, such as USS-PROM which has been included in some of the studies).</p> <p>I would encourage the authors to highlight in the manuscript the important aspect of QoL and patient satisfaction after the procedure or if possible, provide further data on this topic regarding balloon dilatation.</p> <p>Furthermore, the authors state that Lichen sclerosus is the most prominent cause of idiopathic urethral strictures. This information is not clear, as in the literature most authors do not include LS to idiopathic strictures. Instead, aetiology of LS, despite not being fully elucidated, is thought to have an autoimmune origin and is often included into inflammatory strictures.</p>
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<b>REVIEWER</b>	Akhtar, Sohail Government College University Lahore, Statistics
<b>REVIEW RETURNED</b>	07-Aug-2023

<b>GENERAL COMMENTS</b>	<p>The statistical analysis is poorly described. There are no information about the publication bias, sensitive analysis, subgroup analysis and meta-regression models. PRISMA diagram must be updated to the new version 2020. So many forest plots are presneted. No funnel plot in the entire analysis.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1. Please check general grammar:

page 4 lines 57-58 intro

Page 17, line 57 "dissection"

Page 18, line 11-12

Response : Thank you for your suggestion. We have checked the corresponding sentences and revised them as follows. The original text is in black and the revised text is in blue.

**page 4 lines 57-58 intro**

"As is a well-tolerated minimally invasive endourology procedure widely used in the clinical management, balloon dilation may have higher accuracy and lower complication rates than simple dilation, and a longer recurrence-free time."

"Although balloon dilation is a well-tolerated minimally invasive endoluminal surgical procedure widely used in practice, its clinical significance has not been systematically and comprehensively reviewed."

**Page 17, line 57 "dissection"**

"One-year results from another RCT (ROBUST III trial) showed that Optilume DCB had a significantly higher dissection success rate at 6 months than the DVIU group (75% vs 27%,  $p < 0.001$ )."

"One-year results from another RCT (ROBUST III trial) showed that Optilume DCB had a significantly higher anatomical success rate at 6 months than the DVIU group (75% vs 27%,  $p < 0.001$ )."

**Page 18, line 11-12**

"Besides, beta-irradiation therapy with use of the rhenium-188 mercaptoacetyltriglycine-filled balloon is expected to prevent or delay stenosis recurrence in patients with recurrent urethral strictures, and the mean treatment interval increased from 2.2 months before balloon dilation to 10.7 months after treatment."

"Besides, Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation is expected to delay stenosis recurrence in patients with urethral strictures. A clinical report of five patients found that the mean treatment interval was prolonged from 2.2 months to 10.7 months after Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation."

2. Can you discuss or check effect of balloon vs other DVIU or regular dilation?

Response : Thank you for your suggestion. We performed a analysis of the only two currently reported studies that compared balloon dilation with DVIU and optical internal urethrotomy (OIU), finding no statistically significant difference. For the time being, there are no studies comparing the clinical outcomes of simple dilation versus balloon dilation. We further analyzed and compared balloon dilation with simple dilation and DVIU in the Discussion section.

Both balloon dilation and simple dilation are essentially dilatation, a tearing of scar tissue and scar remodeling at the site of the stricture. Balloon dilation applies a 360° circumferential radial force at the stricture site, providing a more uniform force than simple dilation. Meanwhile, for some harder scars that cannot be torn by simple dilation, the balloon can gradually increase the pressure to achieve the purpose of dilatation, which has a broader clinical indications.

DVIU is commonly used for posterior urethral strictures and is avoided in the penile urethra to prevent leakage of the cavernous penile veins to circumvent the risk of causing impotence. Balloon dilation

has no definitive stricture site limitations and can be effective in the dilatation of hard-textured scars that cannot be incised by DVIU.

3. How accurate can we be about the data when the included studies include both retrospective and prospective rather than only RCT? I have an issue with including abstract only articles from conferences as they are not subject to same scrutiny and peer review.

Response : Thank you for your suggestion. We further conducted a bias analysis of 14 non-randomized controlled trial studies using the ROBINS-I tool. We must confess that there is considerable risk of bias in this meta-analysis. Due to the limited quality of the current study, we had to synthesize the retrospective observational study. We tried our best to minimize the effect of these biases on the combined results using some statistical methods.

For the success rate of conventional balloon dilatation, we combined eight studies. All eight studies were retrospective. We excluded studies with sample sizes of less than 30 because this could result in a large selection bias.

Two prospective clinical trials involving drug-coated balloon dilation were analyzed separately.

Conference abstracts were also included in the analysis if they reported sufficient data and the reliability of the study was adequately assessed. One conference abstract was included in the analysis of the success rate of conventional balloon dilation. The results of the sensitivity analysis showed a success rate of 66.69% (95% CI: 53.81%-78.45%) after removal of this conference abstract. Compared to the pooled result of all studies, the deviation rate is 0.6%.

4. I see patients were included with both anterior and posterior strictures/stenosis. Can the authors separate these into separate analysis, they sometimes behave differently in treatment response.

Response : Thank you for your suggestion. We also fully recognize the impact of differences in anterior and posterior urethral strictures on balloon dilatation therapy. Most of the current studies have not further categorized comparisons of balloon dilation based on differences in stricture location, and cases with different stricture sites were analyzed together.

For the success rate of conventional balloon dilation, we performed a subgroup analysis based on the proportion of anterior urethral stricture sites in the study (Supplementary Figure 4). The combined results of studies dominated by anterior urethral strictures (70%-90%) indicated a success rate of 66.45% (95% CI: 47.58%-83.01%) for balloon dilation. Moreover, we combined data from two studies that performed subgroup analysis of stricture location and did not find any statistical difference in the efficacy of balloon dilatation between anterior and posterior urethral strictures (RR=0.9568, 95%CI: 0.6618-1.3832, p=0.814).

More studies on stricture location discussion are needed to further explore the efficacy of balloon dilatation.

5. What was the loss to follow up rate in the papers?

Response : Thank you for your suggestion. The loss to follow up rates for the 15 included studies are showed in the table below. Bias due to missing data has been assessed by using ROBINS-I.

Study	Number of patients lost to follow-up (for the success rate endpoint)	Total number of patients enrolled in study	Loss to follow up rate (for the success rate endpoint)
Virasoro, Ramon et al. 2022	10	53	18.87%
Elliott, S. P. et al. 2022	52	127	40.94%
Beeder, L. A. et al. 2022	0	91	0
Alibekov, M. M. et al. 2022	0	7	0
Yi, Y. A. et al. 2020	0	80	0
Kumano, Y. et al. 2019	0	22	0
Zhou, Y. et al. 2016	0	45	0
Yu, S. C. et al. 2016	6	62	9.7%
Chhabra, J. S. et al. 2016	10	144	6.9%
Ishii, Gen et al. 2015	0	10	0
Mao, D. et al. 2014	2	39	5.1%
Vyas, J. B. et al. 2013	0	120	0
Alguersuari, A. et al. 2012	0	65	0
MacDiarmid, S. A. et al. 2000	6	57	10.5%
Mohammed, S. H. et al. 1988	1	7	14.3%

6. Only 6 papers had other outcome measures like UFR, PVR and IPSS.

Authors comment on critical timing of balloon dilation in conclusion, can they expand on this? not mentioned elsewhere.

Response : Thank you for your suggestion. We added some indicators of patients' subjective perception of balloon dilation to enrich other outcome measures, such as Patient-Reported Outcome Measure for Urethral Stricture Surgery (USS-PROM), International Prostate Symptom Score - Quality of Life (IPSS QoL), and International Index of Erectile Function (IIEF).

The timing of balloon dilation is closely related to the location, length, and scar thickness of the stricture, and appropriate case selection is critical. Balloon dilation is particularly suitable for patients with urethral strictures <1 cm in length, especially bulbar urethral strictures. Balloon dilation may even be used as an initial therapeutic attempt in some patients with long segments of complex urethral strictures.

7. Given the difficulty having high quality RCT in the SR it is difficult to have a solid conclusion.

Response : Thank you for your suggestion. Interpretation of evidence from our meta-analysis needs to be approached with caution on account of the susceptibility to selection bias, recall bias, and exaggerated efficacy of balloon dilation. RCTs with better design, larger sample sizes, and more comparable control groups are needed to further illustrate the efficacy and safety of balloon dilation in the future.

Reviewer #2:

1. The limitation of the study is the fact that the main outcomes that were analysed did not include the patient satisfaction from the procedure (this parameter can be measured by PROMs, such as USS-PROM which has been included in some of the studies). I would encourage the authors to highlight in the manuscript the important aspect of QoL and patient satisfaction after the procedure or if possible, provide further data on this topic regarding balloon dilatation.

Response : Thank you for your suggestion. We added some indicators of patients' subjective perception of balloon dilation, such as USS-PROM, QoL, and International Index of Erectile Function (IIEF). The concrete results are summarized in Table 4.

2. Furthermore, the authors state that Lichen sclerosus is the most prominent cause of

idiopathic urethral strictures. This information is not clear, as in the literature most authors do not include LS to idiopathic strictures. Instead, aetiology of LS, despite not being fully elucidated, is thought to have an autoimmune origin and is often included into inflammatory strictures.

Response : Thanks for your correction. Lichen sclerosus is a specific cause of urethral strictures. We have corrected the relevant parts of the manuscript.

Reviewer #3:

1. The statistical analysis is poorly described. There are no information about the publication bias, sensitive analysis, subgroup analysis and meta-regression models.

Response : Thank you for your suggestion. We have provided a more detailed statistical analysis, adding aspects of publication bias, sensitive analysis, subgroup analysis and meta-regression models.

A funnel plot of eight studies included for the evaluation of conventional balloon dilation success rate was performed, and there is no evidence of publication bias (Egger test:  $t=-2.42$ ,  $p=0.052>0.05$ ). The recalculated results of sensitive analysis are shown in Supplementary Table 4. We further did meta-regression and found that factors such as location of the stricture ( $t=5.25$ ,  $p<0.05$ ), and length of the stenosis ( $t=7.97$ ,  $p<0.05$ ), age ( $t=7.97$ ,  $p<0.05$ ) may be associated with the high heterogeneity, and subgroup analyses of these factors were performed in the following contents of section 3.6.

2. PRISMA diagram must be updated to the new version 2020.

Response : Thank you for your suggestion. The PRISMA diagram has been updated to the new version 2020 (Supplementary Table 1. PRISMA 2020 checklist) .

3. So many forest plots are presneted.

Response : Thank you for your suggestion. We have streamlined the forest plots in the manuscript, and some forest plots will be used as supplementary material.

4. No funnel plot in the entire analysis.

Response : Thank you for your suggestion. We have added the funnel plot to the manuscript (Supplementary Figure 1).

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Chan, Garson Saskatchewan Health
<b>REVIEW RETURNED</b>	22-Nov-2023

<b>GENERAL COMMENTS</b>	<p>Thank you for your paper and SR of balloon dilation for urethral stricture disease.</p> <p>This is an interesting review paper and the introduction nicely summarizes the current literature.</p> <p>Please include Pang KH, Chapple CR, Chatters R, Downey AP, Harding CK, Hind D, Watkin N, Osman NI. A systematic review and meta-analysis of adjuncts to minimally invasive treatment of urethral stricture in men. <i>European Urology</i>. 2021 Oct 1;80(4):467-79.</p> <p>The above paper is the most recently published paper SR on the subject with balloon dilation with drug coated devices.</p> <p>Lumen N, Campos-Juanatey F, Greenwell T, Martins FE, Osman NI, Riechardt S, Waterloos M, Barratt R, Chan G, Esperto F, Ploumidis A. European Association of Urology guidelines on urethral stricture disease (part 1): management of male urethral stricture disease. <i>European Urology</i>. 2021 Aug 1;80(2):190-200.</p> <p>The overall success rate was quoted at 67% which is suprisingly high but as they mention, likely overestimated the success rate due to the selection criteria of the individual studies and the exclusion criteria of the SR. For the overall 67%, what was the follow up timing? Some studies had follow up of only 6 months and we know that strictures can recur long after that.</p> <p>There is typo/grammar in: 3.5.3 Assessment of patient's clinical symptomsThe requires spacing between</p> <p>Can the authors clarify or elaborate on why they found no statistically significant difference in efficacy between conventional balloon dilation and internal urethrotomy but subsequent listed studies in their text say that there actually was a significantly higher stricture-free survival in the balloon dilation group?</p> <p>There is typo/grammar in: 3.5.4 Comparison of balloon dilation with other endoluminal treatments We conducted a separate analysis of two studies compared</p> <p>In keeping with the literature, strictures &lt;1cm were more successful.</p> <p>I do have a concern about including the one study on self patient dilation with balloon as there is only 1 small study &lt;25 patients. Their exclusion criteria initially stated they excluded those &lt;30 patients. Please clarify.</p> <p>As there is no direct comparison between DVIU, simple dilation, and balloon, how does one choose?</p>
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	<p>They state that Balloon dilation is particularly suitable for patients with urethral strictures &lt;1 cm in length, especially bulbar urethral strictures, but these are the same ones recommended for simple dilation.</p> <p>Please include a conclusion.</p>
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<b>REVIEWER</b>	Frankiewicz, Mikołaj Medical University of Gdansk
<b>REVIEW RETURNED</b>	18-Nov-2023

<b>GENERAL COMMENTS</b>	<p>The paper systematically reviewed the principle, safety, and efficacy of balloon dilation, considering various influencing factors. The study is methodologically sound, adhering to established systematic review protocols and providing an extensive analysis of the available literature. Below, I suggest some additional information to be included in the manuscript:</p> <p>In the section "3.5.2 Drug coated balloon dilation success rate" I would suggest adding some information about the inclusion criteria and patient selection included in the mentioned studies.</p> <p>In section "3.7 Intermittent urethral balloon self-dilation" it's worth mentioning that there is no specific schedule of self-dilatation recommended. Or if any conclusions may be made, authors may provide data on that issue, as it is a valuable information for the readers. It may be written in the discussion- as in the discussion authors state that: "Balloon dilatation can also be used in conjunction with repeat simple dilation, endourethrotomy and urethroplasty, suggesting that it may be an important intermediate choice for the treatment of male urethral stricture."</p>
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## VERSION 2 – AUTHOR RESPONSE

Replies to the reviewers' comments:

Reviewer #2:

1. In the section "3.5.2 Drug coated balloon dilation success rate" I would suggest adding some information about the inclusion criteria and patient selection included in the mentioned studies.

Response : Thank you for your suggestion. We have added information about patient selection included in the mentioned studies to the manuscript.

"Both drug balloon studies were performed in patients with recurrent anterior urethral strictures who had received at least 1 prior endoscopic treatment. The patients had urethral strictures  $\leq 12F$ , all less

than 3 cm in length. The IPSS scores were greater than 11, and all the patients had urinary flow rates of at least 15 ml/s or less. These studies excluded patients with prior urethroplasty, lichen sclerosus, neurogenic bladder, bladder neck contracture, artificial urinary sphincter, or other confounding etiologies."

2. In section "3.7 Intermittent urethral balloon self-dilation" it's worth mentioning that there is no specific schedule of self-dilatation recommended. Or if any conclusions may be made, authors may provide data on that issue, as it is a valuable information for the readers. It may be written in the discussion- as in the discussion authors state that: "Balloon dilatation can also be used in conjunction with repeat simple dilation, endourethrotomy and urethroplasty, suggesting that it may be an important intermediate choice for the treatment of male urethral stricture."

Response : Thank you for your suggestion. We have added relevant content in the DISCUSSION section.

"Balloon dilation can also be used in conjunction with repeat simple dilation, endourethrotomy and urethroplasty. If urethroplasty is not feasible, patients can undergo intermittent self-dilation to stabilize the results after endoluminal therapy. Intermittent urethral balloon self-dilation may be an option, but its safety is difficult to ensure due to the lack of direct visualization control and difficulty in achieving the appropriate therapeutic pressure of the balloon. There is no standardized schedule for self-dilation, and the exact dilation schedule depends on the condition and the treatment recommended by the doctor. Patients are usually advised to start with more frequent dilation, even daily, and then gradually increase the interval. Intermittent self-dilation can continue for a fixed period of time or indefinitely. Nevertheless, intermittent self-dilation tends to stabilize the stricture and prolong recurrence rather than keep the patient stricture free [3]. The emergence of a new, safer, drug-coated balloon suitable for at-home use may prolong the patient self-dilation interval and bring new hope for future treatments."

Unfortunately, current evidence does not have a clear recommended timeline for patient self-dilation. Under the guidance of the doctor, patients can perform self-dilatation at different frequencies depending on their condition. Initially, patients were even able to dilate daily, and then the dilation intervals gradually stabilized to one month, six months, or even one year. Concern must be expressed that repeated dilation may have an adverse effect on urethral strictures. Intermittent self-dilation is only a means of stabilizing the efficacy of the treatment after endoluminal therapy, and patients should undergo urethroplasty when available.

Reviewer #1:

1. Please include Pang KH, Chapple CR, Chatters R, Downey AP, Harding CK, Hind D, Watkin N, Osman NI. A systematic review and meta-analysis of adjuncts to minimally invasive treatment of urethral stricture in men. *European Urology*. 2021 Oct 1;80(4):467-79.

The above paper is the most recently published paper SR on the subject with balloon dilation with drug coated devices.

Lumen N, Campos-Juanatey F, Greenwell T, Martins FE, Osman NI, Riechardt S, Waterloos M, Barratt R, Chan G, Esperto F, Ploumidis A. European Association of Urology guidelines on urethral stricture disease (part 1): management of male urethral stricture disease. *European Urology*. 2021 Aug 1;80(2):190-200.

Response : Thank you for your suggestion. We have included the above references in the manuscript.

[54] Pang KH, Chapple CR, Chatters R, Downey AP, Harding CK, Hind D, et al. A Systematic Review and Meta-analysis of Adjuncts to Minimally Invasive Treatment of Urethral Stricture in Men. *European urology*. 2021;80:467-79.

"To reduce the high recurrence rate after endoluminal treatment, intraurethral lesion injections of drugs such as steroids and mitomycin C are commonly used, and balloons are considered promising forms of drug delivery [54]. "

[3] Lumen N, Campos-Juanatey F, Greenwell T, Martins FE, Osman NI, Riechardt S, et al. European Association of Urology Guidelines on Urethral Stricture Disease (Part 1): Management of Male Urethral Stricture Disease. *Eur Urol*. 2021;80:190-200.

"Iatrogenic urethral injury is the most common type of urethral stricture in resource-rich countries, whereas urethral injuries caused by infection and trauma are more common in developing countries [3, 4]."

"Although urethroplasty has been recognized as a curative treatment for urethral strictures, dilation and direct visual internal urethrotomy (DVIU) are still widely used and effective for single bulbar urethral strictures < 2 cm, for which the success rate is 35-70% [3, 9]."

"Nevertheless, intermittent self-dilation tends to stabilize the stricture and prolong recurrence rather than keep the patient stricture free [3]."

2. The overall success rate was quoted at 67% which is surprisingly high but as they mention, likely overestimated the success rate due to the selection criteria of the individual studies and the exclusion

criteria of the SR. For the overall 67%, what was the follow up timing? Some studies had follow up of only 6 months and we know that strictures can recur long after that.

Response : Thank you for your suggestion. We recognized this problem as well, and have added some details to the manuscript. Reported success rates varied from 35.5% to 86.7%. Specific information on the eight studies included in the meta-analysis is presented in the table below. "Six of these studies reported follow-up, with a median pooled follow-up time of 13.50 months (95% CI: 12.86-14.14; heterogeneity:  $I^2=99.2\%$ ,  $P<0.05$ ). "

Study	Evaluable Patients (n)	Reported Success Rate (%)	Follow-up
Beeder, L. A. et al. 2022	91	50	12 months (3 - 40)
Yi, Y. A. et al. 2020	80	66.3	8.4 months (IQR, 3.9 - 22.5)
Zhou, Y. et al. 2016	45	86.7	6 - 24 months
Yu, S. C. et al. 2016	31	35.5	14.75 months (5 - 36)
Chhabra, J. S. et al. 2016	134	84.4	24 months (3 - 52)
Mao, D. et al. 2014	37	64.9	/
Vyas, J. B. et al. 2013	120	68	6 months (2 - 60)
Alguersuari, A. et al. 2012	65	69	/

"This result needs to be interpreted with caution and most likely overestimates the efficacy of balloon dilation. Clinical data obtained during long-term follow-up are lacking, and the real-world balloon dilation success rate should decline progressively with longer follow-up. Moreover, the assessment of the success rate of balloon dilation involves significant subjective factors that may exaggerate efficacy."

3. There is typo/grammar in:

3.5.3 Assessment of patient's clinical symptoms The

requires spacing between

Response : Thank you for your suggestion. We have revised the text accordingly.

4. Can the authors clarify or elaborate on why they found no statistically significant difference in efficacy between conventional balloon dilation and internal urethrotomy but subsequent listed studies in their text say that there actually was a significantly higher stricture-free survival in the balloon dilation group?

Response : Thank you for your suggestion. We have added details to the text. " Even though fewer comparative studies are currently available, the balloon dilation may have potentially favorable long-term results by virtue of its smaller shear force and uniform 360° circumferential dilation."

The conclusion that the efficacy of conventional balloon dilation versus internal urethrotomy is not statistically significant is based on the only 2 studies available. There are limited studies comparing balloon dilation with other endoluminal treatments, and it is difficult to derive reliable evidence. We hypothesized that balloon dilatation might have better efficacy based on its principles and our daily clinical experience. "The principle of balloon dilation is to apply radial force along the balloon span at the stricture site. While the principle of traditional optical internal urethrotomy is to achieve epithelial regeneration by incising scar tissue. Balloon dilation applies less shear force and causes less trauma, which can reduce the risk of cavernous fibrosis development and cause less discomfort. Balloon dilation can also cause the fibrous scar in the stricture to more evenly fracture, resulting in 360° annular expansion, thereby increasing the inner diameter of the stenotic segment; during the balloon dilation process, the urethral pressure gradually increases, and the balloon is slowly and gently expanded to minimize damage to blood vessels and urethral tissue. Balloon dilation tends to achieve extrusion molding in a single pass, and the high pressure of the balloon is effective in compressing the bleeding point. In addition, the smooth surface of balloon can prevent normal urethral mucosal damage." The pressure of the balloon is often immense, and this sustained pressure allows better contouring to be achieved in some of the harder scarring that cannot be resolved by DVIU and simple dilation. Therefore, balloon dilation may have higher stricture-free survival. Balloon dilation also showed better results in our ongoing single-center clinical study. More high-quality studies are needed to further evaluate the real-world efficacy of balloon dilatation.

5. There is typo/grammar in:

3.5.4 Comparison of balloon dilation with other endoluminal treatments

We conducted a separate analysis of two studies compared

Response : Thank you for your suggestion. We apologize for the poor language of our manuscript. We have revised the text accordingly and invited native English speakers to revise the language of the manuscript. In the "Manuscript-marked copy" document, the copyediting changes are shown in blue font and content changes are shown in red font.

6. I do have a concern about including the one study on self patient dilation with balloon as there is only 1 small study <25 patients. Their exclusion criteria initially stated they excluded those <30 patients. Please clarify.

Response : Thank you for your suggestion. As a specific form of balloon dilation, we also briefly reviewed the clinical evaluation of patient self-balloon dilation. Patient self-balloon dilation is not the subject part of this systematic review and meta-analysis. In the materials and methods section, we indicated that studies of patient self-dilation were excluded. These studies did not participate in the systematic review and meta-analysis, and served only as components of an additional supplementary brief review. The exclusion criteria for studies with a sample size of less than 30 were only for the meta-analysis of the success rate of conventional balloon dilation.

"2. Materials and methods"

"2.2 Eligibility criteria"

"Two researchers (X.L. and C.X.) screened and assessed the search results independently. The inclusion criteria were as follows: (1) studies with male patients diagnosed with urethral strictures; (2) studies in which balloon dilation was applied as the main intervention, not including patient self-dilation; (3) clinical studies, retrospective or prospective; (4) studies reporting the success and adverse event rates."

"3. Results"

"3.5 Clinical efficacy of balloon dilation for male urethral strictures"

"3.5.1 Conventional balloon dilation success rate"

"For studies with conventional balloon dilation, we defined success of balloon dilation as no recurrence or no further stricture treatment during the follow-up period, excluding studies with a sample size of less than 30 on account of the potentially greater selection bias and merging data from 8 studies published in 2012-2022 [31, 32, 34-36, 38-40]."

The reason why we have added the supplementary brief review on patient self-balloon dilatation in the manuscript is because this is really a point of concern in actual clinical practice. Endoluminal treatment of male urethral strictures should not focus solely on the surgical procedure, and management of the full postoperative cycle is critical. After endoluminal therapy, the patient must face the choice of which means to maintain the efficacy. Balloon dilation can be used not only as a surgical option, but also as a potentially convenient and patient-friendly means of postoperative maintenance. "If urethroplasty is not feasible, patients can undergo intermittent self-dilation to stabilize the results after endoluminal therapy. The emergence of a new, safer, drug-coated balloon suitable for at-home use may prolong the patient self-dilation interval and bring new hope for future treatments."

7. As there is no direct comparison between DVIU, simple dilation, and balloon, how does one choose? They state that Balloon dilation is particularly suitable for patients with urethral strictures <1

cm in length, especially bulbar urethral strictures, but these are the same ones recommended for simple dilation. Please include a conclusion.

Response : Thank you for your suggestion. We have added details to the text.

"Like simple dilation and DVIU, balloon dilation is indicated for patients with short-segment urethral strictures. Although balloon dilatation is currently not definitively superior to simple dilation or DVIU due to the lack of long-term follow-up studies, balloon dilation has the following advantages: (1) In principle, the balloon expands with less shear force, presenting a gradual uniform 360° circular dilation so as to minimize the non-therapeutic urethral injuries; (2) In the penile urethra where DVIU is not recommended, simple dilation and balloon dilation can be used; (3) As long as the guidewire can be passed, simple dilation and balloon dilation can be attempted in stenotic segments in which the endoscope of the DVIU cannot pass; (4) The balloon, with its high pressure, can dilate some urethras with harder scars that are difficult to dilate with simple dilation and DVIU; (5) The balloon can be used as a promising drug delivery tool and has achieved favourable clinical results. "

"5. Conclusion"

"Balloon dilation may be an intermediate step before urethroplasty and a promising alternative to simple dilation and DVIU. The balloon is a promising drug delivery tool, and paclitaxel drug-coated balloon dilation is effective in reducing retreatment rates in patients with recurrent anterior urethral strictures. Due to the low quality of the evidence, we have little confidence in our estimates of effects. Evidence for other comparisons and outcomes is also limited. The stricture etiology, stricture location, stricture length, and previous treatment may be associated with the efficacy of balloon dilation. However, additional high-quality studies are needed for further investigation."

#### VERSION 3 – REVIEW

<b>REVIEWER</b>	Chan, Garson Saskatchewan Health
<b>REVIEW RETURNED</b>	08-Jan-2024
<b>GENERAL COMMENTS</b>	Thank you for taking the time to respond to the comments and revisions. I have no further major concerns at this time for revision.