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Do previous urethral endoscopic procedures and preoperative self-dilatation increase the risk of stricture recurrence after urethroplasty?

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Abstract

Objective: To evaluate the relation between clinically relevant stricture recurrence after first urethroplasty and prior endoscopic treatments (dilatation and/or direct visual internal urethrotomy) or intermittent self-dilatation (ISD).

Methods: Patients with bulbar urethral strictures treated with first urethroplasty between 2011 and April 2019 were included in a prospectively gathered database with standardized follow-up. Stricture recurrence was defined as any need for reintervention. Primary outcome was the analysis of recurrence risk after first urethroplasty in relation with the number of prior endoscopic treatments or performance of ISD. Univariate and multivariate statistical analyses were performed.

Results: Overall, 106 patients were included with a median follow-up of 12 months (interquartile range 8-13]. Reintervention was necessary in 16 patients (15%). Recurrence was more prevalent in patients with ≥3 prior endoscopic treatments (28%, $P = .009$). No increased risk of recurrence was found in patients with 1 or 2 prior endoscopic treatments. The prevalence of prior ISD was twice as high in the stricture recurrence group (56% vs 26%, $P = .014$), and ISD was performed in 61% of the patients with ≥3 prior endoscopic treatments ($P < .001$). The number of prior endoscopic interventions and performance of ISD were no independent predictors for recurrence in the multivariable analysis.

Conclusions: This study shows that the risk of recurrence after first urethroplasty is increased in patients with ≥3 prior endoscopic treatments and in those who performed ISD. Patients performing ISD more often had ≥3 prior endoscopic treatments. Prior endoscopic treatment and performance of ISD were not independent predictors of stricture recurrence.

KEYWORDS
reconstructive surgical procedures, recurrence, therapy, treatment failure, urethral stricture

Abbreviations: BM, buccal mucosa; DVIU, direct visual internal urethrotomy; EPA, excision and primary anastomosis; ISD, intermittent self-dilatation; RUG, retrograde urethrography; VCUG, voiding cystourethrography.

1 | INTRODUCTION

Urethral strictures have an estimated prevalence of 0.6% in Western countries[1] and are caused by medical interventions, infection and inflammation, trauma, or may be idiopathic.[2] Strictures can be treated with dilatation, direct visual internal urethrotomy (DVIU), or urethroplasty. Treatment choice is dependent on patient age and comorbidities, stricture etiology, location and length, the number of strictures, risk of recurrence, and patient preference.[3] Urethroplasty with (transecting or non-transecting) anastomotic repair or free graft urethroplasty have emerged as the standard management for most strictures, offering high success rates (up to 90%).[4] Dilatation or DVIU are less invasive treatment options, but recurrence after these procedures is more common. Recurrence rate at 2 years after first DVIU is 30% to 60% and increases to 50% to 100% after second urethrotomy.[4] Therefore, open urethral reconstruction should be offered instead of repeated endoscopic management for recurrent anterior urethral strictures.[5] Furthermore, repeat transurethral manipulation of bulbar urethral strictures is associated with increased stricture complexity and prolonged disease duration, due to cumulative tissue injury resulting in amplified spongiofibrosis.[6] In addition, repetitive endoscopic treatment may impair the success rate of urethroplasty.[7,8] Also, for the same reason, intermittent self-dilatation (ISD), performed to delay or defer further intervention, might increase the risk of failure.[6]

Knowledge of factors contributing to treatment success has great importance for preoperative counseling and shared decision-making. The aim of this study is to evaluate the relation between clinically relevant stricture recurrence after first urethroplasty and the number of prior (repeated) endoscopic treatments or ISD.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

A total of 130 consecutive male patients of 18 years and older received a first anterior urethroplasty between 2011 and April 2019 in a tertiary referral center for urethral strictures. Only patients with penobulbar or bulbar strictures with short penile extension were included. Penobulbar strictures with penile approach during urethroplasty were excluded, as well as patients with a history of hypospadias and pelvic fracture urethral distraction injury. A total of 106 patients were included in this study. Ethical board approval was acquired for this study (18-353). Informed consent was not required.

2.2 | Data collection

The collected data consisted of patient age and medical history (including all prior urethral endoscopic procedures and ISD), stricture characteristics (etiology, location, and length), urethroplasty technique, and postoperative outcome parameters. Since 2011, all patients attending our hospital with urethral stricture disease have had a standardized preoperative work-up and postoperative follow-up, allowing prospectively gathered data to be collected from the electronic patient file system.

Preoperative diagnostic evaluation included data extraction on medical history and previous procedures from referral letters and questionnaires on medical history and stricture etiology, International Prostate Symptom Score, uroflowmetry and measurement of postvoid residual, retrograde urethrography (RUG), and 16F flexible cystoscopy. The latter two allowed preoperative identification of stricture location and estimation of stricture length. Stricture length was measured during urethroplasty and included in the operation report. Postoperatively, the transurethral catheter was removed after 3 weeks if voiding cystourethrography (VCUG) showed no leakage of contrast. In case of leakage, VCUG was repeated after 2 to 3 weeks prior to catheter removal (if no leakage).

The standardized follow-up was 1 year and included uroflowmetry at 3, 6, and 12 months, RUG at 6 months, and flexible cystoscopy (16F) at 12 months.

Stricture recurrence was defined as any need for reintervention based on patient symptoms (functional outcomes) combined with diagnostic findings during follow-up (anatomic outcomes), which was also described by the TURNS protocol.[9] Reintervention was described as any surgical procedure, including outpatient dilatation, endoscopic reintervention, and redo urethroplasty.

In case there were no signs of treatment failure after 12 months, patients were discharged from follow-up with the instruction to return in case of symptoms suggestive of stricture recurrence.

2.3 | Surgical technique

The surgical technique was based on the peroperative clinical judgment and expertise of the three reconstructive urologists of our center. If technically feasible, excision and primary anastomosis (EPA) was performed. In case of a long defect, in general more than 2 cm, dorsal onlay buccal mucosa (BM) graft urethroplasty was performed.

2.4 | Statistical analyses

Groups were compared using the χ^2 test for categorical data. For a statistically significant χ^2 test with three or more groups, post hoc analysis with adjusted *z* scores and Bonferoni adjusted *P* value for significance was performed. Our data were not normally distributed. Therefore, the difference in continuous variables was evaluated with the Mann-Whitney *U* test (two categories) and Kruskal-Wallis test (>2 categories). Multivariable logistic regression analysis was performed with all significant univariate variables to identify independent predictors. A *P* value <.05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics 25.

3 | RESULTS

In total, 106 patients were included in this study. Seventeen (16%) patients had no prior endoscopic procedure, 28 (26%) had one,

25 (24%) had two, and 36 (34%) had three or more. There were 32 patients (30%) who routinely performed ISD before anterior urethroplasty. Median follow-up was 12 (interquartile range [IQR] 8-13) months, median age at surgery was 42 (IQR 31-53) years, and median peroperative stricture length was 2.0 (IQR 1.5-3.5) cm. EPA was performed in 85 (80%) of the included patients with a median peroperative stricture length of 2.0 (IQR 1.2-2.0) cm. The other 21 (20%) were treated with dorsal onlay BM graft urethroplasty, and these patients had a longer median peroperative stricture length of 4.8 (IQR 4.0-5.3) cm ($P \leq .001$).

From all 106 included patients, 90 (85%) showed no recurrence during follow-up (Table 1). Sixteen patients had a reintervention after the first urethroplasty, of whom 8 (7.5%) were treated endoscopically (dilatation or DVIU) and 8 (7.5%) with redo urethroplasty.

There was a significant relation between number of prior endoscopic procedures and stricture recurrence after the first anterior urethroplasty ($P = .021$): Specifically, recurrence was more prevalent after three or more prior endoscopic treatments (28%, $P = .009$). The prevalence of prior ISD was higher in the stricture recurrence group (56% vs 26%, $P = .014$). Also, we found a relation between stricture etiology and recurrence. Patients with idiopathic etiology less often had a recurrence (6%, $P = .019$). No difference was found in median age, stricture length, stricture location, and urethroplasty technique in patients with and without recurrence.

The relation between number of prior endoscopic treatments and other parameters was compared (Table 2). There was no difference in median age at surgery, median peroperative stricture length, stricture etiology and location, and urethroplasty technique between patients with various numbers of prior endoscopic treatments. Patients with repeated transurethral procedures tended to be older (not significant).

Patients who performed ISD were older than patients who did not perform ISD (48 vs 38 years, $P = .009$, Table 3). Furthermore, 61% of patients with three or more prior endoscopic procedures performed ISD prior to primary urethroplasty, which is more prevalent than in patients with 0 to 2 prior endoscopic treatments ($P < .001$).

There was no difference in median peroperative stricture length, stricture etiology and location, and urethroplasty technique between patients who did or did not perform preoperative ISD.

The variables etiology, preoperative ISD, and number of prior endoscopic interventions were included in a multivariable logistic regression

TABLE 1 Overall results. Patient and stricture characteristics in patients without and with recurrence after first urethroplasty

Patient characteristics	No recurrence n = 90 (85%)	Recurrence n = 16 (15%)	*P* value
Median age at surgery, years [IQR]	41 [31-50]	53 [28-67]	.202[a]
Median time of follow-up, months [IQR]	12 [9-13]	9 [5-27]	.582[a]
Stricture etiology:			.019[b]
• Idiopathic	48 (94%)	3 (6%)	
• Iatrogenic	11 (65%)	6 (35%)	
• Lichen sclerosis	3 (100%)	0 (0%)	
• Straddle injury	28 (80%)	7 (20%)	
Stricture location:			.912[b]
• Bulbar	85 (85%)	15 (15%)	
• Penobulbar	5 (83%)	1 (17%)	
Prior endoscopic treatments (dilatation, DVIU):			.021[b]
• 0	14 (82%)	3 (18%)	
• 1	28 (100%)	0 (0%)	
• 2	22 (88%)	3 (12%)	
• ≥3	26 (72%)	10 (28%)	
Prior ISD			.014[b]
• Yes	23 (72%)	9 (28%)	
• No	67 (91%)	7 (9%)	
Technique			.908[b]
• EPA	72 (85%)	13 (15%)	
• BM dorsal onlay	18 (86%)	3 (14%)	
Median stricture length in cm [IQR]	2.0 [1.5-3.0]	1.8 [1.0-3.3]	.496[a]
• EPA	2.0 [1.5-2.0]	1.5 [1.0-2.0]	
• BM dorsal onlay	5.0 [4.0-5.0]	4.5 [4.0-4.5]	

Abbreviations: BM, buccal mucosa; DVIU, direct visual internal urethrotomy; EPA, excision and primary anastomosis; IQR, interquartile range; ISD, intermittent self-dilatation.

[a]Kruskal-Wallis test.

[b]Chi-square test.

TABLE 2 Patient and stricture characteristics in patients with 0, 1, 2, and ≥3 prior endoscopic treatments

	0 n = 17 (16%)	1 n = 28 (26%)	2 n = 25 (24%)	>3 n = 36 (34%)	*P* value
Median age at surgery, years [IQR]	32 [24-43]	40 [30-50]	42 [37-52]	45 [33-58]	.091[a]
Median stricture length, cm [IQR]	1.5 [1.0-3.0]	2.0 [1.5-3.0]	2.0 [1.0-4.3]	2.0 [1.5-4.0]	.255[a]
Stricture etiology:					.096[b]
• Idiopathic	7 (41%)	17 (61%)	12 (48%)	15 (42%)	
• Iatrogenic	2 (12%)	2 (7%)	3 (12%)	10 (28%)	
• Lichen sclerosis	0 (0%)	0 (0%)	0 (0%)	3 (8%)	
• Straddle injury	8 (47%)	9 (32%)	10 (40%)	8 (22%)	
Stricture location:					.552[b]
• Bulbar	16 (94%)	26 (93%)	25 (100%)	33 (92%)	
• Penobulbar	1 (6%)	2 (7%)	0 (0%)	3 (8%)	
Technique					.156[b]
• EPA	16 (94%)	24 (86%)	20 (80%)	25 (69%)	
• BM dorsal onlay	1 (6%)	4 (14%)	5 (20%)	11 (31%)	

Abbreviations: BM, buccal mucosa; EPA, excision and primary anastomosis; IQR, interquartile range.
[a]Kruskal-Wallis test.
[b]Chi-square test.

TABLE 3 Patient and stricture characteristics of patients with and without prior intermittent self-dilatation

	Prior ISDn = 32 (30%)	No prior ISDn = 74 (70%)	*P* value
Median age, years [IQR]	48 [38-59]	38 [27-49]	.009[a]
Prior endoscopic interventions (%):			<.001[b]
• 0	1 (6%)	16 (94%)	
• 1	4 (14%)	24 (86%)	
• 2	5 (20%)	20 (80%)	
• ≥3	22 (61%)	14 (39%)	
Stricture etiology (%):			.265[b]
• Idiopathic	12 (24%)	39 (76%)	
• Iatrogenic	7 (41%)	10 (59%)	
• Lichen sclerosis	2 (67%)	1 (33%)	
• Straddle injury	11 (31%)	24 (69%)	
Stricture location (%):			.863[b]
• Bulbar	30 (30%)	70 (70%)	
• Penobulbar	2 (33%)	4 (67%)	
Technique (%)			.052[b]
• EPA	22 (26%)	63 (74%)	
• BM dorsal onlay	10 (48%)	11 (52%)	
Median stricture length, cm [IQR]	2.0 [1.5-4.0]	2.0 [1.5-3.0]	.075[a]

Abbreviations: BM, buccal mucosa; EPA, excision and primary anastomosis; IQR, interquartile range; ISD, intermittent self-dilatation.
[a]Mann-Whitney *U* test.
[b]Chi-square test.

model. The results are presented in Table 4. In this multivariable model the number of previous endoscopic interventions and ISD did not remain as independent predictors for stricture recurrence after the first anterior urethroplasty. Only iatrogenic strictures (odds ratio [OR] 5.7, $P = .035$) remained as an independent predictor for stricture recurrence with idiopathic strictures as reference.

4 | DISCUSSION

The overall success rate of urethroplasty in our studied cohort was 85%. An increased risk of recurrence was found in patients with three or more endoscopic interventions and in patients who performed ISD prior to first urethroplasty.

TABLE 4 Multivariable logistic regression analysis for the prediction of recurrence after first bulbar urethroplasty

Variable	OR (95% CI)	*P* value
Etiology:		
• Idiopathic	Reference	-
• Iatrogenic	5.7 (1.1-29.0)	.035
• Lichen sclerosis	NA	NA
• Straddle injury	4.1 (0.9-19.3)	.070
Number of prior endoscopic interventions:		
• 0	Reference	-
• 1	NA	NA
• 2	0.6 (0.1-3.6)	.572
• ≥3	1.3 (0.2-7.8)	.763
Prior ISD	2.3 (0.6-9.2)	.231

Note: All significant ($P < .005$) univariate variables are included in the analysis.
Abbreviations: ISD, intermittent self-dilatation; NA, not applicable (there was no recurrence); OR, odds ratio.

There was no difference in recurrence risk in patients without and with one or two prior endoscopic treatments.

Our results show a difference in recurrence rate in patients who performed ISD prior to urethroplasty (28%) compared to patients who did not (9%). We also found a strong relation between number of previous endoscopic procedures and performance of ISD. It is plausible that patients were advised to start with ISD after repeated endoscopic treatment because of the high risk of recurrence (>50%).[10] This may explain why preoperative ISD and number of preoperative endoscopic treatments were not identified as independent risk factors in the multivariable analysis.

The lower recurrence rate in patients with one prior endoscopic procedure compared to no previous endoscopic treatment might be explained by the etiology of the strictures. The recurrence rate in patients with idiopathic strictures was only 6%. Remarkably, 61% of patients with one prior endoscopic procedure had an idiopathic stricture, compared to 41% of patients with no prior endoscopic procedure. More iatrogenic strictures and straddle injuries were found in the latter group. Iatrogenic stricture etiology was identified as an independent risk factor for recurrence in our multivariable analysis (OR 5.7), with idiopathic etiology as reference. A larger study of Kinnaird et al[11] identified iatrogenic etiology as independent risk factor in multivariate regression analysis as well. Iatrogenic strictures are mainly found after urethral instrumentation in the context of treatment for benign prostatic hyperplasia, urothelial cell carcinoma, and urolithiasis. It is unknown why urethral instrumentation other than stricture treatment predisposes for stricture recurrence. Factors such as use of electrocoagulation and laser may play a role. Another explanation is that, although not identified in our study, patients with iatrogenic strictures may have other age-related or metabolic characteristics compared with patients with idiopathic or traumatic strictures.

We did not find a longer median stricture length in patients with prior repeated endoscopic interventions or in patients with ISD. Furthermore, stricture length was not associated with stricture recurrence. This is in contrast with some previous studies, which reported increased stricture length in patients with repeated transurethral manipulation[6] and increased recurrence risk with longer strictures.[11-13]

In our series, 31% of the patients with ≥3 prior endoscopic treatments were treated with BM dorsal onlay urethroplasty compared to 6% without prior endoscopic treatment, although these numbers were not significant.

It is widely accepted that recurrence rate after onlay urethroplasty is higher than after EPA, which was not found in our series. In a recent study by Barbagli et al with inclusion of 1242 bulbar urethroplasties, success rate after EPA was 85.9%. The success rate after BM urethroplasty was dependent on the used technique (68%-87.5%).[13] A similar success rate with BM and EPA urethroplasty was found in other studies,[14,15] and these success rates are comparable to our series. The variation between studies may be explained by differences in experience, used techniques, and definition of success or recurrence.

There is some inconsistency in the literature concerning prior repeated endoscopic interventions as a risk factor for failure after urethroplasty.[6-8,12]

In the study of Breyer et al,[8] with inclusion of 443 patients, an increased risk of recurrence was found with prior DVIU in a multivariate analysis (hazard ratio [HR] 1.7, $P = .04$), but previous dilatation was not identified as risk factor (HR 0.8, $P = .48$). In this study, the number of DVIU was not specified. In the study of Kessler et al,[7] with inclusion of 267 patients, two or more previous DVIU was found as risk factor for recurrent strictures after urethroplasty (HR 2.25; 95% CI, 1.05-4.8). In a more recent study by Chapman et al,[12] who analyzed 596 patients, the number of previous failed endoscopic procedures did not affect the stricture recurrence rate after urethroplasty. Barbagli et al,[13] with inclusion of 1242 bulbar urethral strictures, did not find increased recurrence rates with any previous dilatation or DVIU either.

It should be mentioned that the patients in these studies were less homogenous compared to our cohort due to differences in inclusion criteria, such as stricture location,[7,8] inclusion of redo urethroplasty,[7,8,12] inclusion of traumatic strictures without further specification,[7,8,12,13] and history of hypospadias repair.[7,8,12]

A more similar study by Hudak et al,[6] with inclusion of 101 bulbar urethroplasties divided their cohort in two groups: 0 to 1 and >2 transurethral manipulations, including any dilatations (operative, in office, or self-dilatation at home). More failures were found during follow-up in patients with >2 transurethral manipulations before urethroplasty compared to 0 to 1 previous treatments, though not statistically significant (12% vs 2%, $P = .110$). This study concluded that repeat transurethral manipulations were associated with increased stricture complexity and prolonged disease duration.

The results of the OPEN trial have been recently published, a randomized controlled trial where 159 patients with recurrence of bulbar

stricture after prior DIVU were allocated for open urethroplasty vs repeated DVIU.[16] Patients were followed for up to 4 years: 15 men allocated for urethroplasty needed reintervention compared to 29 allocated for DVIU (HR 0.52 [0.31-0.89], $P = .017$). An increased risk of recurrence after repeated DVIU was found. However, both intervention groups had a similar improvement in symptom scores at 24 months of follow-up and similar adverse events, despite the increased recurrence rate with repeated DVIU. Therefore, the OPEN trial suggests that both options should be available for recurrent bulbar strictures as both procedures are likely to improve symptoms. Nevertheless, there is a longer duration of benefits with urethroplasty.

The OPEN trial[16] did not differentiate in the number of previous endoscopic treatments and did not analyze the risk of recurrence after the first urethroplasty with multiple prior endoscopic treatments. The homogenous patient cohort and the analysis of four groups with different numbers of prior endoscopic treatment in our study provide relevant and new information for the treatment of recurrent bulbar strictures. We found no difference in recurrence rate in patients with one or two prior endoscopic treatments before first urethroplasty. Three or more prior endoscopic treatments, on the other hand, led to an increased risk of recurrence after the first urethroplasty.

The findings from our study and from previous literature suggest that a second endoscopic treatment of a recurrent bulbar stricture could be a valid treatment option, next to urethroplasty. Patients should be well informed about the recurrence risk with second endoscopic treatment. Our data show an increased recurrence risk after the first urethroplasty with ≥3 prior endoscopic treatments. We would therefore advise against a third (or more) endoscopic treatment for recurrent bulbar strictures and would strongly advise a patient to choose urethroplasty if a curative treatment is desired.

Also, a relation between ISD and ≥3 previous endoscopic treatments was found. Multivariate analysis of our data shows that those factors were no independent predictors, suggesting that ISD is often advised in patients with repeated endoscopic procedures.

The retrospective data collection limits the strength of this study although the work-up, treatment, and follow-up in this homogenous cohort were standardized and thorough. It is possible that with a larger cohort more significant differences would have been found.

It is important to note that stricture recurrence was defined as any need for reintervention, based on patient symptoms and diagnostic findings. If cystoscopy showed limited scarring at the operation site, without patient symptoms and passage of the cystoscope, no reintervention was performed, and patients were kept in follow-up.

The purpose of this study was to analyze a homogenous cohort of (peno)bulbar strictures with no history of previous urethroplasty. We have chosen to specify the number of previous endo-urological procedures in four categories, thereby analyzing a relation between stricture recurrence rate and the number of repeated endoscopic treatments (three or more). Furthermore, this study analyzed ISD as an univariable risk factor for stricture recurrence after urethroplasty. To our knowledge, these findings have thus not been reported before.

5 | CONCLUSION

This study shows that ≥3 prior endoscopic treatments and preoperative self-dilatation in patients with (peno)bulbar urethral strictures are associated with increased stricture recurrence rates after the first urethroplasty. These parameters were not identified as independent predictors in multivariate analysis since a strong relation between previous endoscopic procedures and self-dilatation was found.

A second endoscopic treatment did not increase recurrence risk after the first urethroplasty and could therefore be proposed as an alternative to urethroplasty in bulbar urethral strictures, thereby counseling patients for the high recurrence risk of a second endoscopic treatment (>50%). It is important that patients are referred in time for urethroplasty for (peno)bulbar strictures to avoid stricture recurrences and unnecessary prolonged disease duration.

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All authors contributed to the methodology and idea formulation. H. Yildirim performed the data analysis and manuscript writing. Prof de Kort, Dr Wyndaele, and Dr Hennus contributed equally to the manuscript review and revision of this paper.

DISCLOSURE

The authors declare that they have no conflict of interest. There was no project funding.

ETHICS STATEMENT

This study was approved by the medical ethical review board of the University Medical Center Utrecht and is in accordance with the 1964 Helsinki Declaration and its later amendments.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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