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Original Article

Long-term outcomes of urethral balloon dilation for anterior urethral stricture: A prospective cohort study

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KEYWORDS
Balloon dilation;
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Self-calibration;
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Abstract *Objective:* To prospectively follow up a cohort of anterior urethral stricture disease patients managed with balloon dilation (BD) for 3 years to evaluate the long-term outcomes and to study factors that contribute to recurrence.
Methods: This study included men who had urethral BD for significant anterior urethral stricture disease between January 2017 and March 2019. Data about the patient age, stricture characteristics, and recurrence date were recorded, along with information on postoperative indwelling catheter use and operative complications. Furthermore, information about the self-calibration procedure was collected and where available, free flow (FF) measurements during the follow-up period were recorded and analyzed. Success was defined as a lack of symptoms and acceptable FF rates (maximum flow rate>12 mL/s).
Results: The final analysis was conducted on 187 patients. The mean follow-up period was 37 months. The long-term overall success rate at the end of our study was 66.8%. Our recurrence rate was 7.4% at 12 months, 24.7% at 24 months, and reached 33.2% at the end of our study. The time to recurrence ranged from 91 days to 1635 days, with a mean of 670 days. The stricture-free survival was significantly shorter with lengthy peno-bulbar ($p=0.031$) and multiple strictures ($p=0.015$), and in the group of patients who were not committed to self-calibration protocol ($p<0.011$). However, post-procedural self-calibration was the most important factor that may have decreased the incidence of recurrence (odds ratio=5.85). Adjuvant self-calibration after BD not only reduced the recurrence rate from 85.4% in the non-self-calibration group to 15.1% in the self-calibration one ($p<0.001$), but also improved the overall stricture-free survival and FF parameters.

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Conclusion: Urethral BD has a high recurrence rate in the long-term, especially with long and multiple strictures. Adjuvant self-calibration has proven to reduce the recurrence risk and the need for re-intervention.

1. Introduction

Male urethral stricture disease (USD) is one of the oldest and most common health issues in urology [1]. In India, its true burden has not been reported [2].

Despite that open formal urethroplasty is regarded as the gold standard treatment for USD, it requires a higher surgical experience compared to the minimal invasive endoscopic procedures; direct visual internal urethrotomy (D-VIU) and balloon dilation (BD), which are less morbid and easier to perform, need minimal resources, and do not need a higher learning curve. Besides, they can be performed as a day procedure since they require minimal recovery time and has a lower cost burden [3].

While D-VIU requires an incision of the stricture segment leading to bleeding and extravasation that might aggravate spongiofibrosis [4], BD, on the other hand, works by applying radial forces against the stricture walls, reducing trauma and the potential for spongiofibrosis [5].

Most of the studies conducted on urethral BD are retrospective and lack the long-term follow-up (FU). In this work, we aimed to prospectively follow up a cohort of USD patients managed with BD for at least 3 years to evaluate the long-term outcomes and to study factors that may have contributed to recurrence.

2. Patients and methods

2.1. Study design

This is an observational prospective study conducted in a tertiary care center (Muljibhai Patel Urological Hospital, Nadiad, India).

2.2. Study population

All men who had urethral BD for significant (Grades 2–4 as per European Association of Urology classification of urethral narrowing [6]) anterior USD between January 2017 and March 2019 were eligible for inclusion. Patients with bladder neck contracture, meatal stenosis, complex strictures (pan-anterior, obliterative Grade 5 strictures or those with dense strictures), or patients on clean intermittent catheterization for other emptying lower urinary tract symptoms were excluded from the study.

2.3. Intervention and outcome measures

All our procedures were performed under antibiotic coverage and short sedation with the patients in the lithotomy position, using the NephroMax™ balloon catheter set (Boston Scientific Corporation, Marlborough, MA, USA) that consists of a 7-Fr open-tip catheter, which has an 8-cm balloon that inflates fully to 24 Fr at maximum inflation, using a high-pressure stopcock device. After an on-table retrograde urethrography, a glide wire (0.038-inch; 1 inch = 2.54 cm) is passed into the urinary bladder. The urethra is then coaxially dilated over the wire, initially with fascial dilators (up to 12 Fr) and then with a balloon for 5 min at 8 atmospheric pressure. The balloon was placed across the stricture with the help of radio-opaque markings on either end. The dilation was confirmed on a fluoroscope screen by the disappearance of wasting. Then, the lower urinary tract was inspected with a 21-Fr cystoscope and cases with soft passable narrowing were included whereas those with dense strictures (inferred by urethral induration, which is often indicative of severe spongiofibrosis [7]) were ruled out. A 16-Fr urethral catheter was then inserted.

After catheter removal, the patients were given a trial to void and taught how to do self-calibration with the 14- or 16-Fr Tiemann catheter (Advin Health Care, Ahmedabad, Gujarat, India). Patients were then discharged on oral antibiotic for 4 weeks (the time of the first FU visit) and instructed to undergo self-calibration initially once daily for 3 months, then every alternate day for the next 3 months, then weekly for 3 months, and biweekly after that.

Given that most stricture recurrences commonly take place within 3 years [8], eligible patients were followed for at least 3 years, and patients who did not complete the 3 years were ruled out. The timing of FU was at 1 month to assess the compliance with self-calibration, every 3 months during the first year and bi-annually after that. At each visit, patients were asked for any lower urinary tract symptoms and for self-calibration. They were also calibrated with the 16-Fr catheter. If a patient complains of lower urinary tract symptoms or there was any issue with the calibration at visits, a free flow (FF) study was conducted.

Data about the patient age, stricture characteristics (etiology, number [single or multiple], location, primary or recurrent, and grade), and recurrence date were collected, along with information on postoperative indwelling catheter use and operative complications. Furthermore, information about the self-calibration procedure was collected and where available, FF measurements during the FU period were recorded and analyzed.

Success was defined as lack of symptoms and acceptable FF rates (maximum flow rate [Q_{max}] >12 mL/s) [2].

2.4. Sample size and statistical analyses

An online statistical calculator (https://statulator.com/SampleSize/ss1P.html) was used to estimate the sample size considering the following factors: assuming that 12% of the participants in the population suffer from significant anterior USD, with a 5% absolute precision and

95% confidence interval. Allowing for a 10% dropout rate, a total sample size of 187 patients was estimated.

Data were tabulated and analyzed using the SPSS® package 25 (IBM Corp, Armonk, NY, USA). Univariate analyses of continuous and categorical variables were done using the independent sample *t*-test and Chi-square test, respectively, with statistical significance considered at $p<0.05$. The significance of associations between peri-operative categorical variables with outcomes was analyzed using the Chi-square test. The Kaplan–Meier survival analysis was performed to evaluate the time to recurrence, and the log-rank test was applied to check for significance.

2.5. Ethical approval

Informed consents were obtained from all participants in the study, and the protocol for this research project was approved by our ethical committee (Muljibhai Patel Society for Research in Nephro-Urology) under Institutional Review Board (IRB/18/2022).

3. Results

Out of 294 patients who underwent urethral BD between January 2017 and March 2019, 59 were ruled out (17 had bladder neck contracture; 14 had meatal stenosis; 10 had pan-anterior urethral stricture with meatal stenosis; 10 had dense strictures; eight had functional neurogenic detrusor underactivity), and 48 were lost during the FU.

The final analysis was performed on 187 patients. The patients' ages ranged from 10 years to 87 years with a mean of 51 years. The pre-operative stricture characteristics (etiology, location, number, grade, and whether primary or recurrent) are shown in Table 1. The mean pre-procedural FF parameters of Q_{max}, voided volume (VV), and post-void residual (PVR) urine volume were 4.95 mL/s, 190.59 mL, and 74.53 mL, respectively (Table 2). All procedures went uneventful except for one patient who developed fever on post-operative Day 1. The median length of catheter stay post-operatively was 2 days and all patients voided freely after catheter removal.

At 1 month, the timing of first FU visit, the mean FF parameters of Q_{max}, VV, and PVR showed significant improvement with 23.23 mL/s, 306.35 mL, and 30.81 mL, respectively (Table 2). Nine patients failed to achieve Q_{max} of >12 mL/s; they were considered a primary procedural failure. Their Q_{max} ranged from 8.3 mL/s to 11.1 mL/s (mean 9.5 mL/s). They were instructed to continue self-calibration and none of them needed immediate reintervention. Self-calibration, as per our protocol, was performed by 74.3% ($n=139$) of our patients while 25.7% ($n=48$) did not.

The mean FU of our patients was 37 months. The recurrence rate in this study was 7.4% at 12 months, 24.7% at 24 months, and 33.2% by the end of the study. The mean FF parameters of Q_{max}, VV, and PVR of our patients at the end of FU period were 16.11 mL/s, 277.76 mL, and 41.49 mL, respectively (Table 2). The long-term overall success rate of BD at the end of our study was 66.8%.

The Kaplan–Meier stricture-free analysis was significantly shorter in patients with longer peno-bulbar strictures compared to focal penile and bulbar ones ($p=0.031$) (Fig. 1). It was also significantly shorter in patients with multiple strictures ($p=0.015$) (Fig. 2), and in the non-self-calibration group compared to self-calibration one ($p<0.011$) (Fig. 3). However, the log-rank test demonstrated that the time to recurrence was not affected by being primary or recurrent ($p=0.796$) or by the stricture etiology ($p=0.312$). The mean time to recurrence in our study was 670 days. Auxiliary procedures were required in 47 (25.1%) cases during the FU period: 32 were treated with

Table 1 Baseline (patient and stricture) characteristics, and overall procedural outcomes.

Variable	Value
Patient, *n*	187
Age, mean (range), year	51 (10–87)
Etiology, *n* (%)	
Iatrogenic	80 (42.8)
Post-TURP	44 (23.5)
Post-urethroplasty anastomotic stricture	15 (8.0)
Post-panendoscopy	16 (8.6)
Post-catheterization	5 (2.7)
Inflammatory	5 (2.7)
Traumatic	3 (1.6)
Unspecified (idiopathic)	99 (52.9)
Location, *n* (%)	
Bulbar	151 (80.7)
Penile	13 (7.0)
Peno-bulbar	23 (12.3)
Number, *n* (%)	
Single	173 (92.5)
Multiple	14 (7.5)
Primary or recurrent, *n* (%)	
Primary	172 (92.0)
Recurrent	15 (8.0)
Stricture grade, *n* (%)	
2	3 (1.6)
3	115 (61.5)
4	69 (36.9)
Length of catheter stay post-operatively, median (range), day	2 (1–3)
Self-calibration, *n* (%)	
Yes	139 (74.3)
No	48 (25.7)
Procedural failure, *n* (%)	
Primary	9 (4.8)
Overall	62 (33.2)
Need for auxiliary procedure, *n* (%)	47 (25.1)
BD	32 (17.1)
BD and D-VIU	5 (2.7)
Urethroplasty	10 (5.3)
FU, mean±SD, day	1127.95±467.69
Time to recurrence, mean (SD; range), day	670 (392; 91–1635)

BD, balloon dilation; FU, follow-up; SD, standard deviation; TURP, transurethral resection of the prostate; D-VIU, direct visual internal urethrotomy.

Table 2 FF parameters.

FF parameter	Pre-procedure	At 1 month after procedure	At the end of FU period
Q_{max}, mL/s	4.95±2.35	23.23±8.71	16.11±7.33
VV, mL	190.59±122.49	306.35±148.49	277.76±140.71
PVR urine volume, mL	74.53±70.07	30.81±22.14	41.49±38.01

FF, free flow; FU, follow-up; PVR, post-void residual; Q_{max}, maximum flow rate; VV, voided volume.
Note: values are presented as mean±standard deviation.

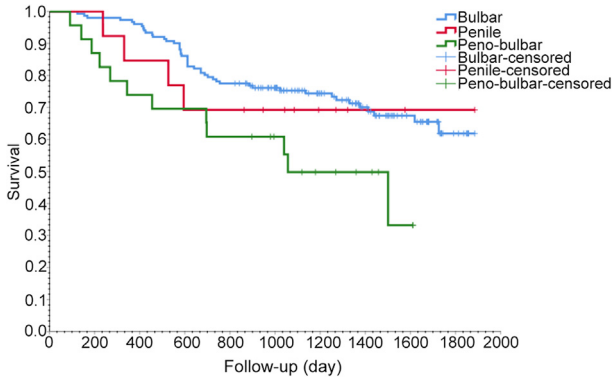

Figure 1 Kaplan–Meier curves predicting the time to recurrence by stricture locations. $p=0.031$ (log-rank [Mantel–Cox] test).

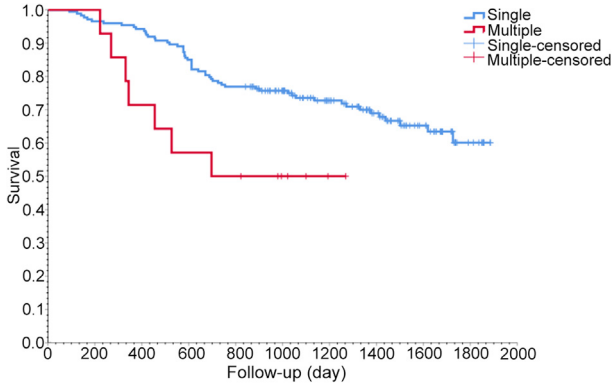

Figure 2 Kaplan–Meier curves predicting the time to recurrence by number of strictures. $p=0.015$ (log-rank [Mantel–Cox] test).

repeat BD; five had BD and D-VIU; and 10 underwent urethroplasty.

For the sake of further analysis, we evaluated all factors that may have contributed to stricture recurrence including baseline stricture characteristics and post-procedural self-calibration (Table 3). All were statistically insignificant except for self-calibration ($p<0.001$; odds ratio [OR] 5.85 [95% confidence interval 2.63–13.06]). The recurrence rate within the period of our study was 15.1% in the self-calibration group and 85.4% in the non-self-calibration one ($p<0.001$). Also, the mean Q_{max} at the end of the FU period was statistically in favor of the self-calibration group (18.21 mL/s) compared to 10.06 mL/s in the non-self-calibration one ($p<0.001$). The mean FU was significantly longer for the

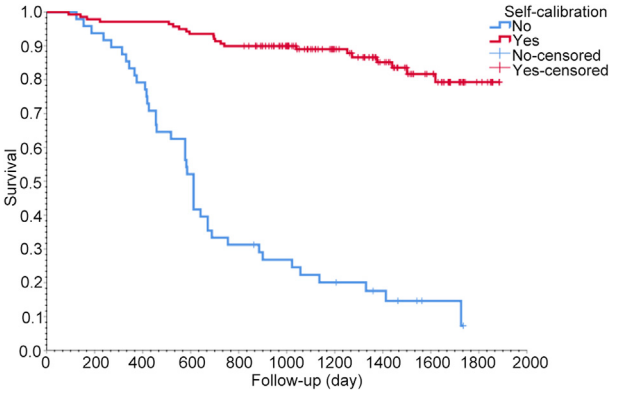

Figure 3 Kaplan–Meier curves predicting the time to recurrence by the treatment group. $p<0.011$ (log-rank [Mantel–Cox] test).

Table 3 Peri-operative categorical variables tested against the risk of recurrence.

Variable	Failure, *n*		Total, *n*	*p*-Value
	No	Yes		
Etiology				0.279
Iatrogenic	58	22	80	
Inflammatory	2	3	5	
Traumatic	2	1	3	
Unspecified	61	38	99	
Site				0.153
Bulbar	103	48	151	
Penile	9	4	13	
Peno-bulbar	11	12	23	
Single or multiple				0.196
Single	116	57	173	
Multiple	7	7	14	
Primary or recurrent				0.521
Primary	112	60	172	
Recurrence	11	4	15	
Stricture grade				0.581
2	2	1	3	
3	78	37	115	
4	42	27	69	
Self-calibration				<0.001
No	7	41	48	
Yes	116	23	139	

self-calibration group compared to that in the non-self-calibration group (1266.8 [standard deviation 396.1] days *vs.* 725.9 [standard deviation 433.1] days; $p<0.001$).

4. Discussion

Male anterior USD results from a number of etiologies. While inflammation once accounted for the majority of USD, these have now become infrequent, and idiopathic and iatrogenic now account for most strictures [9,10]. In our sample, inflammatory strictures accounted for only 2.7% whereas idiopathic and iatrogenic ones accounted for 52.9% and 42.8%, respectively. Post-transurethral resection of the prostate USD was the most culprit ($n=44$) among all iatrogenic causes ($n=80$). Since the etiology of stricture directly impacts the treatment outcomes, the time to recurrence in our study was tested against different etiologies; it was the shortest for inflammatory (906.7 days) compared to 1205 days for traumatic, 1424 days for idiopathic, and 1501 days for iatrogenic. However, this difference was not statistically significant ($p=0.312$).

Regarding the stricture location, the bulbar site was by far the most common (80.7%) in our study, which was in accordance with two previous reports on the Indian population [10,11].

USD is considered an ongoing disease that carries the risk of life-long recurrence; hence, a long-term FU is mandatory. This is of paramount importance after minimally invasive endoscopic procedures, which, despite being simple and less morbid, have higher recurrence and reintervention rates when compared to formal urethroplasty [3,12]. Earlier reports have demonstrated that these procedures are equally effective as the first-line treatment for USD [13], with a stricture recurrence rate of 40%–50% at 12 months. However, the success rate drops to 32% on the long-term FU, and success decreases even more with repeated minimally invasive treatment [14]. Hence, further interventions were proposed to improve stricture-free survival like post-procedural self-calibration, intralesional injection of various pharmaceutical agents, and the use of Optilume® drug-coated balloons (Urotronic Inc., Plymouth, MN, USA) [15].

In two earlier reports, we presented our short- and intermediate-term outcomes of patients who underwent BD in a retrospective fashion [16,17]. In the present study, however, a separate cohort of patients was prospectively observed for at least 3 years to look for long-term outcomes and for possible predictors of recurrence. We have chosen 3 years for the FU because most strictures recurrences usually occur within this period [8]. Besides, all patients were taught how to perform self-calibration, as an adjuvant to BD, and instructed to do it after that.

The recurrence rate in this study was 7.4% at 12 months, 24.7% at 24 months, and reached 33.2% at end of our study. The time to recurrence ranged from 91 days to 1635 days, with a mean of 670 days. The stricture-free survival was significantly shorter with lengthy peno-bulbar ($p=0.031$) and multiple strictures ($p=0.015$), and in the group of patients who were not committed to the self-calibration protocol ($p<0.011$).

However, post-procedural self-calibration was the most important factor that may have decreased the incidence of recurrence (OR=5.85). Adjuvant self-calibration after BD not only reduced the recurrence rate from 85.4% in the non-self-calibration group to 15.1% in the self-calibration one ($p<0.001$), but also improved the overall stricture-free survival and FF parameters. These data are in accordance with earlier studies showing that the recurrence risk after endoscopic urethral procedures is less than one-tenth in patients performing self-calibration post-operatively compared with about half in those not practicing self-calibration [8,18].

5. Conclusion

Urethral BD has a high recurrence rate in the long-term, especially with long and multiple strictures. Adjuvant self-calibration has proven to reduce the recurrence risk (OR=5.85) and the need for re-intervention.

Author contributions

Study concept and design: Abhijit Patil, Ravindra B. Sabnis.
Data acquisition: Ahmed M. Abdel Gawad.
Data analysis: Ahmed M. Abdel Gawad, Abhijit Patil, Ravindra B. Sabnis.
Drafting of manuscript: Ahmed M. Abdel Gawad, Abhijit Patil.
Critical revision of the manuscript: Ahmed M. Abdel Gawad, Abhijit Patil, Abhishek Singh, Arvind P. Ganpule, Ravindra B. Sabnis, Mahesh R. Desai.

Conflicts of interest

The authors declare no conflict of interest.

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