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Outcome Predictors of Augmentation Urethroplasty Using Dorsal Onlay Buccal Mucosal Graft

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ABSTRACT

Background: The incidence and timing of stricture recurrence and factors affecting urethroplasty outcomes remains incompletely characterized. **Objective:** To evaluate and determine the factors predicting the outcome of dorsal onlay buccal mucosal graft (BMG) urethroplasty. **Patients and Methods:** We analyzed the records of 115 patients underwent dorsal onlay BMG urethroplasty at Al-Azhar University Hospitals in Cairo, Egypt, from January 2015 to April 2018, with a minimum of 12 months of followup. The risk factors examined were patient age, stricture etiology, site, length, width, diabetes, hypertension, smoking, obesity, previous visual internal urethrotomy (VIU) and urethroplasty, early postoperative complications, extravasation at first periurethral ascending cystourethrogram (ACUG) and stricture width.

Results: Average patients age was 38 years. Stricture free rate was 90.4% and mean followup period was 47.5 months (range 12 to 67). Average stricture length was 5.9 cm, average stricture width was 6.3 mm, 63.4% of patients were with previous VIU, and 9.5% were with previous urethroplasty. On univariate analysis, etiology, site of stricture, previous four or more times VIU, DM, obesity, stricture length, postoperative (post op.). wound infection and leakage at first periurethral ACUG were associated with stricture recurrence. On multivariate analysis panurethral stricture (HR 280.6, 95% CI 9.1-8622.8, p =0.001), traumatic stricture (HR 17.1, 95% CI 2.4-123.4, p =0.005) were independent predictors of stricture recurrence. Stricture width, previous urethroplasty, the number of failed endoscopic procedures less than 4 times, smoking, HTN and patient age did not affect the recurrent stricture rate.

Conclusion: panurethral and traumatic strictures were independent predictors of stricture recurrence.

Keywords: Dorsal onlay urethroplasty, predictors of urethroplasty failure, stricture length.

INTRODUCTION

The urethra is a unique tube of epithelium and there is no better tissue than the urethra to replace. However, in the case of a narrowing of the long frontal urethra, the process of circumcision and primary anastomosis (EPA) is impossible. Skin flaps and dermis have been used to rebuild these long restrictions. However, the skin of the penis is not suitable for all cases, especially lactus sclerosis (LS) or recurrent cases that do not contain sufficient skin. BMG gained much interest because of its excellent short and long-term results, low postoperative complication rate and relative ease of use [(1)].

BMGs were used in penile, bulbar and even panurethral strictures using different techniques with a high success rate [(2-4)]. Stricture recurrence remains a reality. The incidence and timing of stricture recurrence after definitive urethral reconstruction remains incompletely characterized. A review of the literature reports recurrence rates ranging from 8.3% to 18.7%, with wide variation in incidence likely related to differences in stricture and patient characteristics, surgical approach and technique, length of follow-up, and method of surveillance [(5)].

There is inconsistency in the literature regarding which factors are associated with stricture recurrence after urethroplasty in studies with univariate as well as multivariate analysis. These inconsistencies could be related to the surgeon preference of urethroplasty technique, discrepancies in stricture etiology, inhomogeneity of urethroplasty populations, duration of follow up, stricture location and small cohort size. These factors make it difficult to draw meaningful conclusions from the existing literature. Some of the inconsistency can be explained by the fact that to our knowledge no group has examined a comprehensive list of all known potential confounding variables. This increases the risk of underestimating or overestimating the association between a given variable and the treatment outcome. Factors most often associated with stricture recurrence after urethroplasty in general are stricture length, prior failed procedures (urethroplastic or endoscopic), smoking and lichen sclerosis. Other occasionally identified factors include diabetes, stricture etiologies, preoperative uroflowmetry findings and surgeon experience [(6)].

In this series we studied factors most often associated with stricture recurrence after urethroplasty such as stricture etiology, stricture length, history of previous intervention, overall comorbidity and obesity, in addition to a new non studied variable; stricture width.

AIM OF THE WORK

To evaluate and determine the factors predicting the outcome of dorsal onlay BMG urethroplasty.

PATIENT AND METHODS

This observational retrospective and prospective study included all patients who underwent dorsal onlay buccal mucosal graft urethroplasty at Al-Azhar University Hospitals (Al-Hussein and Sayed Galal), Cairo, Egypt, during the period from January 2015 to April 2018.

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Patients with history of urethral dilatation or optical urethrotomy within 3 months before planned urethroplasty, short segment strictures amenable for EPA, active urinary tract infection, infectious disease affecting the mouth (such as Candida or herpes virus) and other oral pathology and patients who had previous surgery in the mandibular arch that prevents the mouth from being opened wide were excluded. One hundred and fifteen men were eligible for inclusion.

Ethical approval:

The Research Ethics Committee of our institution approved the study protocol and all participants provided an informed written consent before inclusion.

Data collection:

The patients' medical records were reviewed for:

Preoperative data: The age of patients, main presenting symptoms, stricture etiology, stricture site, associated medical comorbidities, previous history of failed endoscopic or open reconstruction interventions, preoperative uroflowmetry, ultrasound with measured P.V.R.U, retrograde and voiding cystourethrography.

Operative data: stricture length, width, estimated blood loss, catheter size. Postoperative: complications and stricture free status. Stricture free rate was evaluated at a time point at least 12 months postoperatively. A successful outcome was defined as normal voiding pattern without any postoperative intervention. Failure was the need for subsequent urethral procedures including dilation.

Data Analysis

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 24. Numerical data were summarized using means and standard deviations or medians and ranges. Data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Categorical data were summarized as percentages. Comparisons between the 2 groups with respect to normally distributed numeric variables were done using the independent t-test and repeated by Mann-Whitney test. For categorical variables, differences were analyzed with χ^2 (chi square) test and Fisher's exact test when appropriate. Logistic regression was done to detect independent factors that responsible for failure. All p-values are two-sided. P-values ≤ 0.05 were considered significant.

RESULTS

A total of 115 patients met the inclusion criteria. The mean age was 38.0±15.6 years, 42, 30, 30, and 13 patients had iatrogenic, idiopathic, traumatic and inflammatory stricture respectively, seventeen patients with DM, 17 with HTN, 10 were obese (BMI > 30) and 16 were smokers. Seventy-four patients had a previous history of intervention, 63 had previous history of dilatation, 1 had previous history of urethroplasty, 10 had previous history of both. 59, 40, 11 and 5 had bulbar, bulbo-penile, penile and panurethral stricture respectively (Table 1). The mean follow-up period was 47.85±17.55 months. Early postoperative complications demonstrated, 23 developed wound infection, 8 developed hematoma, 8 developed epididymo-orchitis, all complications were managed conservatively.

Table 1: Demographic data in studied 115 patients

Items		No.	%
Main presenting symptoms:	• Weak stream	72	68.6
	• Fixed suprapubic catheter	32	27.8
	• Incontinence with overflow	4	3.5
Etiology:	• Iatrogenic	42	36.5
	• Idiopathic	30	26.1
	• Traumatic	30	26.1
	• Inflammatory	13	11.3
Medical comorbidities:	• DM	17	14.8
	• HTN	17	14.8
	• Obesity	10	8.7
	• Smoking	16	13.9
Previous failed interventions (74 patients):	• VIU ± Dilation	63	85.1
	• Open reconstruction	1	1.4
	• Both VIU + Open	10	13.5
Site of stricture:	• Bulbar	59	51.3
	• Bulbo-penile	40	34.8
	• Penile	11	9.6
	• Pan anterior urethral stricture	5	4.3

We demonstrated 90.4 % success rate. Univariate analysis identified that traumatic etiology of stricture, panurethral stricture, previous (prev.) VIU four or more times, DM, obesity, stricture length, post op. wound infection and leakage at first periurethral ACUG were associated with stricture recurrence after urethroplasty (Tables 2 and 3).

Table 2: analysis of factors in relation to recurrent stricture after urethroplasty.

	Success (t =104)		Failure (t =11)		p value
	Count	%	Count	%	
Etiology					
iatrogenic	41	39.4	1	9.1	0.047
Idiopathic	29	27.0	1	9.1	0.177
Inflammatory	12	11.5	1	9.1	0.807
traumatic	22	21.1	8	72.7	< 0.001
Site					
bulbar	54	51.9	5	45.5	0.683
Bulbo-penile	39	37.5	1	9.1	0.060
penile	9	8.7	2	18.2	0.307
Pan-urethral	3	2.9	2	18.2	< 0.001
Comorbidities					
DM	14	13.5	4	36.4	0.047
HTN	14	13.5	3	27.3	0.220
Obesity	7	6.7	3	27.3	0.021
Smoking	13	12.5	3	27.3	0.178
Previous interventions					
Prev. VIU(1)	29	27.9	4	36.4	0.554
Prev. VIU(2)	20	19.2	2	18.2	0.933
Prev. VIU(3)	9	8.7	0	0.0	0.310
Prev. VIU(4)	4	3.8	3	27.3	0.002
Complication					
Wound infection	18	17.3	5	45.5	0.026
Hematoma	6	5.8	2	18.2	0.124
Leakage	18	17.3	6	54.5	0.004

Table 3: The relation between the stricture length, width and the success rate:

	success	Count	Mean	SD	P value
length	Yes	104	57	28	<0.014
	No	11	80	41	
width	Yes	104	6	2	<0.274
	No	11	7	2	

SD: standard deviation.

On multivariate regression analysis panurethral site and traumatic etiology were independent predictors of stricture recurrence (Table 4).

Table. 4: Multivariate analysis to detect independent factors for failure:

	B	S.E.	P value	OR	95% CI for OR	
					Lower	Upper
Pan-urethra	5.64	1.75	0.001	280.6	9.1	8622.8
Traumatic	2.84	1.01	0.005	17.1	2.4	123.4
VIU (4)	3.59	2.11	0.089	36.1	0.6	2257.3
Constant	-34.8	11.42	0.002	0		

B=Regression coefficients, SE=Standard error of the coefficient, OR=Odds Ratio, 95% CI for OR = 95% confidence interval for the =Odds Ratio. P-value≤0.05 is considered significant.

DISSCUSION

In all reviewed articles we found most factors that predict for recurrence after urethroplasty were stricture etiology, site, length, previous failed interventions, overall comorbidities; DM, HTN, obesity and smoking, early postoperative complications and leakage with periurethral ACUG. We will discuss every factor in details.

Site of stricture:

Our success rate for bulbar, penile, bulbo-penile and panurethra stricture was 91.5%, 81.8%, 97.5% and 60% respectively. Panurethral site was predictive for failure in univariate and multivariate analysis according to our results. Some reported success rate for bulbar, penile, bulbo-penile and panurethra stricture was 92%, 80%, 63% and 42% respectively [7]. Other reported success rate for bulbar and penile urethral stricture, 87.9% and 74.2% respectively. Penile site was predictive for failure in univariate and multivariate analysis according to his results [8]. Other series reported success rate for bulbar urethral stricture, 93.3% [6]. Some authors in a retrospective review showed comparable results between penile and bulbar urethroplasty [9]. Penile urethroplasty can be a simple procedure in the case of a normal penis, but its treatment can be challenging and can have higher risks of failure in men presenting with failed hypospadias repair and severe balanitis xerotica obliterans (BXO).

Etiology of stricture:

Our success rate for iatrogenic, idiopathic, inflammatory and traumatic stricture was 96.6%, 96%, 92% and 73% respectively. Traumatic cause was predictive for failure in univariate and multivariate analysis according to our results. Other series reported that iatrogenic stricture was associated with higher failure rate from 43% to 50% [10, 11, 12]. Others showed that iatrogenic stricture significantly predict failure (p= 0.03) [9]. Infectious stricture was independently associated with stricture recurrence [6]. Some authors showed comparable results between all etiologies [13, 14]. These differences may have related to number of patients in each group and degree of spongiofibrosis associated with each etiology. As regard infectious strictures, often secondary to urethral abscess, urethritis or necrotizing fasciitis, where significant tissue inflammation and necrosis may develop. This inflammatory response and tissue necrosis lead to fibrosis with poor recipient vascularity, which likely has a key role in deficient wound healing threatening urethroplasty success.

Stricture length:

In our series stricture length was found to correlate with the outcomes of treatment and similar outcomes have been demonstrated in other series. Similar conclusions in a large retrospective review of 604 patients treated for anterior and posterior urethral strictures in which stricture > 5 cm were associated with higher stricture recurrence rates [16]. Some showed that those with long strictures particularly strictures ≥5 cm were associated with higher stricture recurrence rates [10]. **Breyer *et al.*** [11] showed in their retrospective series of 443 patients that stricture length >4 cm was associated with recurrence. **Meeks *et al.*** [5] demonstrated in a systematic review that there was a significant difference in failure rate (12.4% *vs.* 16.6%) between strictures shorter than and longer than 5 cm. **Liu *et al.*** [9] in their series reported that earlier stricture recurrence were associated with longer stricture length, reaching statistical significance when comparing cases recurring before and after 6 months (median stricture lengths 5.5 cm and 4.0 cm, respectively [$P = 0.009$]. the shortest strictures tended to recur later. Similar conclusions in a large retrospective review of 596 patients treated for isolated bulbar urethral strictures in which increased stricture length associated with increase of the rate of recurrence, the rate of stricture recurrence was 4.9%, 7.4%, 13.4%, 19.2% and 28.6% when stricture length was ≤2, >2, >4, >6 and >8 cm respectively [$P < 0.001$] [6]. **Spilotros *et al.*** [14] reported similar conclusions in a retrospective review of 128 patients, the rate of stricture recurrence was 7.4%, 20.5% and 34% when stricture length was ≤4, 4.1-8 and >8 cm respectively [$P < 0.05$].

Stricture length plays a key role in predicting urethroplasty outcomes. Short strictures are most amendable to anastomotic urethroplasty but as stricture length increases so does the need for tissue transfer as buccal mucosa grafts or flaps. As stricture length increases, so does the surface area required for successful graft take. In turn this increases the risk of ischemic contracture, thus increasing the rate of stricture recurrence. Further strategies to improve graft take, such as incorporating biological promoters of wound healing, may be an interesting avenue to explore and may further optimize urethroplasty success [6, 15].

Stricture width

Is a very important factors to predict urethroplasty failure as it correlates with the urethral plate. This factor never discussed in all reviewed articles. In our series this factor tended to predict urethroplasty failure but not didn't reach significant results (p = 208).

Previous urethroplasty and endoscopic treatments

Some groups have identified previous urethroplasty or failed endoscopic procedures as having an adverse impact on stricture recurrence following urethroplasty [16, 17,18]. In Nigerian urology practice some authors reported that patients who had prior dilatations or

urethrotomies have significantly greater odds of developing a posturethroplasty recurrence [10]. In our series revision urethroplasty was not associated with stricture recurrence. But previous direct vision internal urethrotomy or dilation tended to contribute to urethroplasty failure mainly with multiple intervention, and became statistically significant with 4 or more repeated dilatations. **Liu *et al.*** [9] reached similar conclusions to our results. **Chapman *et al.*** [6] **Soave *et al.*** [12] **and Spilotros *et al.*** [14] reported that revision urethroplasty was not associated with stricture recurrence. Also previous urethral manipulation in the form of direct vision internal urethrotomy or dilation did not contribute to urethroplasty failure. This difference in literatures may contribute to difference in studied populations characteristics, number of studied patients, surgical techniques, associated other comorbidities, degree of healthy urethral plate result from previous interventions.

Obesity:

We found that obesity predicted for urethral stricture recurrence [p = 0.021]. Obesity is rarely included in other studies of urethroplasty failure. **Chapman *et al.*** [6] reported similar conclusions [p = 0.01]. **Rapp *et al.*** [13] in their series on 137 patients studying the effect of BMI on urethroplasty outcome, reported a recurrence rate of 17%. The recurrence rates stratified by BMI cohort were: 20% (<25 kg/m^2), 9% (25–30 kg/m^2), 19% (>30 kg/m^2). The mean BMI in patients with versus without recurrence was 28.9 (±7.2) and 30.4 (±10.2) kg/m^2, respectively (P=0.40), and reached conclusion that BMI did not independently predict for stricture recurrence following urethroplasty [19]. Obesity is associated with relative vascular insufficiency, chronic low grade inflammation, impaired collagen synthesis, and micromolecular and macromolecular deficiency. In addition to these biological factors, obesity likely impairs surgical exposure, particularly in the bulbar urethra, where exposure of the most proximal bulbar stricture can occasionally be difficult [6].

Diabetes, HTN and smoking:

In our series DM predict for urethroplasty failure [p = 0.047], however HTN and smoking did not. **Liu *et al.*** [9] reported that DM and HTN did not predict for urethroplasty failure. **Breyer *et al.*** [11] reported that smoking and DM are predictive for urethroplasty outcome. **Chapman *et al.*** [6] concluded that smoking and diabetes were not significant contributors to recurrent stricture in our series despite their known adverse effect on vasculature and wound healing. DM, HTN and smoking were individually associated with urethroplasty failure in other series [15,18]. These findings, in particular tobacco use, may be viewed as controversial. The same studies that found smoking to be a risk factor did not find smoking related comorbidities, such as chronic obstructive pulmonary disease, peripheral vascular and coronary artery disease, to be associated with stricture recurrence or they did not examine possible confounding associations [6, 19]. Regardless of the association with urethroplasty failure, there is strong evidence that smoking cessation at least 1 month prior to all surgeries significantly decreased wound and overall complication rates, and as such should be advocated in all patients preoperatively [20]. On balance it appears that individual comorbid conditions may not predispose to recurrent stricture but a combination of these comorbidities likely has a larger role. Given that strictures are more common in older patients; it is important to explore how aging affects the urethroplasty outcome. We found no correlation of age with urethroplasty failure, this result was similar to most reviewed articles. This is in agreement with descriptive studies showing that urethroplasty is an effective strategy in elderly patients and other studies that did not show an association of urethroplasty failure with patient age [11, 15].

Early postoperative complications:

In our series postoperative wound infection was significantly associated with higher rate of recurrence [p = 0.026], no data available in most reviewed articles correlate between postoperative wound infection and urethroplasty outcome.

Leakage at first periurethral ACUG (after 3 weeks):

Leakage at first periurethral ACUG is rarely included in other studies of urethroplasty failure. In our series postoperative leakage at first periurethral ACUG was significantly associated with higher rate of recurrence [p = 0.004]. Other series showed similar conclusions. **Verla *et al.*** [21] in their series on 474 patients found that only extravasation at first urethrography is independent risk factor for urethroplasty failure and is associated with earlier recurrence than other failed urethroplasties cases [p = 0.004]. Presence of extravasation at first pericatheter urethrogram may indicate delayed wound healing, bad graft positioning, graft hematoma, these factors affect overall graft take.

CONCLUSION

BMG urethroplasty represents a reliable therapeutic option for patient with urethral strictures with a success rate of 90.4%. Etiology of stricture, site of stricture, stricture length, prev. multiple VIU four times or more, DM, obesity, post op. wound infection and leakage at first periurethral ACUG were predictors for urethroplasty failure. On multivariate analysis panurethral

site and traumatic etiology were the only independent predictors for stricture recurrence.

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