Original Article

The use of amniotic membrane injection as an adjunct in endoscopic urethral stricture management

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ABSTRACT

Introduction: Endoscopic urethral stricture treatment has high recurrence rates. Due to research supporting amniotic membrane's (AMs) anti-inflammatory and anti-fibrotic properties reducing scar tissue formation, AM has generated interest in reconstructive urethral surgery. To the best of our knowledge, we performed the first investigation of the success rate of urethral dilation when combined with micronized AM injection for the treatment of urethral stricture.
Methods: Eligible patients were adult males with anterior strictures meeting strict criteria for diameter, length, International Prostate Symptom Score (IPSS), and flow rate. Micronized AM was injected in the stricture region during urethral dilation. The primary study endpoint was an anatomical success (≥14Fr) at 6 months. Secondary endpoints were evaluated with the IPSS, urethral stricture surgery – patient-related outcome measure, International Index of Erectile Function, flow rate, and postvoid residual. Outcomes were assessed at baseline and multiple points postinjection. Injection safety was analyzed.
Results: Ten men with a mean age of 52 years were included in the study. At 6 months, 7 of 10 patients demonstrated recurrence of the urethral stricture on cystoscopy. Improvements in secondary endpoints were noted in 10 of 10 patients at 3 months and 3 of 10 patients at 6 months. No adverse events were observed.
Conclusions: To the best of our knowledge, this is the first study evaluating micronized AM injection as an adjunct treatment at the time of urethral dilation. The urethral stricture recurrence rate did not improve with the injection of AM despite the hypothesized benefits of anti-fibrotic and anti-inflammatory properties.

INTRODUCTION

Management of urethral stricture disease (USD) depends on stricture etiology, localization, length of stricture, degree of spongiofibrosis, history of previous treatment, and patient's age. While primary USD is often initially managed with minimally invasive endoscopic techniques, such as urethrotomy and urethral dilation, the failure rates of these minimally invasive strategies are well documented.[1] In an effort to reduce the rate of recurrence, several injectable agents, including intralesional injection with steroids, mitomycin C, captopril, platelet-rich plasma, hyaluronidase, and tamoxifen have been explored as an adjunct to traditional endoscopic procedures.[2-4]

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_88_24

The characteristic pathological finding in USD, regardless of etiology, is ischemic spongiofibrosis. This typically manifests as scar tissue in the corpus spongiosum.[5,6] A urethral stricture is formed when the spongiosal tissue is replaced by dense nonelastic collagen fibers interspersed with fibroblasts.[7] As the spongiosum provides the vascular supply to the urethra, the degree of fibrosis in the corpus spongiosum relates directly to the extent and severity of the stricture.[8] The capability of the urethra to heal after endoscopic treatment, without reforming a stricture, is reliant on an adequate underlying blood supply, which is challenging when there is also underlying spongiofibrosis.[9]

Received: 03.03.2024, **Revised:** 06.07.2024,

Accepted: 13.08.2024, **Published:** 01.10.2024

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Amniotic membrane (AM) is known to possess anti-inflammatory and anti-scarring properties and has been shown to promote wound healing without scar formation.[10] AM has been extensively studied in animal models and has been used in human subjects for over 100 years.[11] While, historically, AM has been used primarily in ophthalmology, it has also been shown to decrease the recurrence rate of USD when applied after the surgical excision of long ureteral strictures.[12] Furthermore, studies have shown that AM provides a healthy substrate to promote wound healing without stricture reformation after resecting the affected scarred or infected tissue.[13-15] Nonetheless, the evaluation of AM with minimally invasive management, for example., urethral dilation of USD has not been fully established. We performed the first investigation into the use of injectable micronized AM as an adjunct to urethral dilation for the treatment of USD. We hypothesized that the use of injectable micronized AM as an adjunct to endoscopic urethral stricture management could help prevent or delay urethral stricture recurrence.

MATERIALS AND METHODS

This study was a single institution, prospective study. Approval was obtained from the local institutional review board committee. Eligible patients were adult males with anterior strictures ≤12Fr in diameter and ≤1.5 cm in length, International Prostate Symptom Score (IPSS) ≥11, and maximum flowrate <15 mL/s. Due to limited referral options for reconstruction, a maximum stricture length of ≤1.5 cm was chosen, understanding some of the strictures managed endoscopically may have been better managed with urethroplasty. We excluded patients with prior pelvic radiotherapy, intravesical stones, radical prostatectomy, lichen sclerosus, penile prosthesis or artificial urinary sphincter, stricture length of >1.5 cm on urethrography, obstructive benign prostate hypertrophy, posterior urethral stricture, and a history of any previous therapeutic procedure.

Evaluation at baseline included history, physical examination, urine culture, retrograde urethrography, cystoscopy, uroflow, and postvoid residual (PVR). Symptom assessments were measured at baseline using questionnaires including the IPSS, urethral stricture surgery patient-reported outcome measures (USS-PROM), and International Index of Erectile Function (IIEF).

Under general anesthesia, a retrograde urethrogram was performed, followed by placement of a guidewire and dilation using cook urethral dilators sequentially up to 24Fr. Commercially produced reconstituted 100 mg micronized AM (Clarix Flo; BioTissue, Miami, FL) was injected with a transurethral injection needle in the stricture region at the 5, 7, and 12 o'clock sites at the time of urethral dilation. In accordance with the personal practice of the surgeon in this single surgeon series, a 22Fr catheter was placed for 72 h. The primary study end point was an anatomical success (≥14Fr by cystoscopy) at 6 months. Key secondary endpoints were evaluated with the IPSS, USS-PROM, and IIEF questionnaires, as well as measurements of flow rate and PVR. These outcomes were assessed at baseline and 5 days, 14 days, 3 months, and 6 months postinjection. Cystoscopy was performed at 6 months or as soon as patients complained of obstructive voiding symptoms. The safety of injections was assessed by monitoring patients for local and systemic reactions in both the immediate and follow-up settings. Patients were also monitored for UTIs at subsequent visits.

RESULTS

Ten men with a mean age of 52 ± 15 years were included in the study with a mean stricture length as measured on retrograde urethrography of 0.9 cm (range: 0.8–1.2 cm). All strictures were in the bulbar urethra. Follow-up data were available for all patients with a mean follow-up period of 8 months (range: 6–10 mo). At 6 months, 7 of 10 patients demonstrated recurrence of the urethral stricture on cystoscopy. Improvements in flow rate, PVR, IPSS, and USS-PROM symptom scores were noted in 10 of 10 patients at 3 months and 3 of 10 patients at 6 months [Table 1]. No adverse events were observed. In those men who had a recurrence of stricture, all were offered urethroplasties. Two patients chose Optilume dilation over urethroplasty and the rest received urethroplasty.

DISCUSSION

The aim of urethral dilation is to dynamically stretch the scar. If scarring is limited to the epithelial layer, then dilation could, in theory, cure the patient, provided the scar does not reform. The urethral mucosa is enveloped by corpus spongiosum, a blood-rich erectile tissue that surrounds the urethra from the meatus to the bulbar urethra and provides the vascular supply to the urethra. Often, a urethral stricture is a narrowing of the urethral lumen because of ischemic spongiofibrosis. The severity of a urethral stricture is often related to the degree of fibrosis in the corpus spongiosum, the investing vascular layer of the urethra.[8] While the anti-inflammatory and anti-scarring properties of AM have been supported by *in vitro* and *in vivo* studies,[10] our pilot study suggests AM injected into the scar tissue at the site of stricture area after urethral dilation does not significantly change the rate of USD recurrence nor does it postpone the recurrence of urethral stricture following urethral dilation.

Table 1: Mean±standard deviation of questionnaire and uroflowmetry measurements before and after dilation with amniotic membrane injection (*n*=10)

	Pre	5 days	14 days	3 months	6 months
IPSS	26.3±1.7	8.7±0.9	8.9±1.3	8.6±1.4	22.1±3.4
USS-PROM	16.3±1.5	6.1±1.3	6.1±1.5	7±1.7	12.8±3.2
IIEF	7±0.7	7.6±0.5	7.6±0.5	7.6±0.8	7.6±0.6
Q_{max}	4.9±1.1	17.3±1.1	16.7±1.2	16.7±0.8	8.2±4.1
PVR	170±38	33.6±8.5	36.3±11	34.4±10	136±50

IPSS=International Prostate Symptom Score, IIEF=International Index of Erectile Function, PVR=Postvoid residual, USS-PROM=Urethral stricture surgery patient reported outcome measures, SD=Standard deviation

AM is the innermost layer of the placenta and has been used therapeutically for almost a century. The therapeutic applications of AM are diverse, and the mechanism of action for each one is different. The anti-scarring and anti-inflammatory qualities of AM are well established. The anti-scarring effect stems from preventing the expression of α-smooth muscle actin by pro-scarring myofibroblasts through suppressing transforming growth factor-β1 (TGF-β1) promoter activity and preventing canonical TGF-β signaling.[16] Recent studies have shown the key component within AM, i.e., HC-HA/PTX3, can reprogram and de-differentiate the pro-scarring myofibroblasts, which were mediated by SDF1-CXCR4 signaling followed by activation of canonical bone morphogenic protein (BMP) signaling.[17] Using a single substance to try to inhibit scar reformation is often insufficient. While AM can suppress the pathological generation of fibrotic tissue at different levels and can result in the reduction or absence of scarring and the preservation of tissue architecture and functionality, this utility appears to be limited to preventing scar formation as opposed to treating preexisting scars.[18]

USD is thought to involve scar tissue that commonly extends into the underlying corpus spongiosum. Some studies have shown periurethral scarring in ~40% and moderate spongiofibrosis in up to 81% of USD patients.[19,20] Although not specifically assessed in our study, the preexisting spongiofibrosis may help explain the high rate of stricture reformation in our cohort. To our knowledge, this is the first study evaluating AM as an adjunct treatment at the time of urethral dilation. The urethral stricture rate of recurrence did not improve with the injection of AM despite the hypothesized benefits of anti-inflammatory and anti-scarring properties, most likely due to the persistence of underlying spongiofibrosis. Similarly to other endoscopic treatment modalities for urethral strictures, AM injections are unreliable at producing a lasting effect for the treatment of urethral strictures. Our limitations include the small sample size, the lack of a control/sham arm, and the nonrandomization of the study design.

CONCLUSIONS

The injection of AM into USD at the time of dilation may not produce results better than dilation alone. This may be due to underlying spongiofibrosis that is not addressed by injection of AM. Furthermore, thorough research into new indications developed by medical technology companies for their existing drugs is necessary to ensure that we are practicing evidence-based medicine.

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How to cite this article: Pryde N, Vercnocke J, Lutchka J, Liaw A, Sessine M, Dhar N. The use of amniotic membrane injection as an adjunct in endoscopic urethral stricture management. Indian J Urol 2024;40:256-8.