Redo pelvic fracture urethral injury repair: The case for tadalafil

Pankaj M. Joshi, Devang Desai, Seichi Fuziwara, Sheliyan Raveenthiran, Mohammed Nafea, Sanjay B. Kulkarni

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ABSTRACT

Objective: To define the role of tadalafil in improving outcomes of redo urethroplasty for pelvic fracture urethral injury (PFUI). PFUI is common in developing countries, invariably as a result of road traffic trauma. Repair is complex, and redo cases are even more challenging.

Material and methods: This was a longitudinal prospective nonrandomized study between 2017 and 2019. Men undergoing redo-urethroplasty were nonrandomized into two groups. Group 1 received tadalafil 5 mg the next day after surgery and continued for 3 months, and group 2 did not receive tadalafil. Inclusion criteria were patients undergoing redo-urethroplasty willing to trial low-dose tadalafil post-operatively. Exclusion criteria were <18 years, females, primary cases, and complex cases such as recto-urethral fistula. Average follow-up was 19.5 months.

Results: Sixty patients were enrolled (29 in group 1 and 31 in group 2). Mean age was 31 years. These patients had 1-3 prior failed urethroplasties. Most required step 3 anastomotic urethroplasty (68.3%). Success was defined as absence of symptoms and no need for surgical intervention. Failure was defined as redo urethroplasty or >1 endoscopic intervention. Primary success was 83.3%. Success with tadalafil was 96.6%, compared to 71.0% in the non-Tadalafil group ($P = .0008$). Only one patient on tadalafil failed, compared with nine in the non-tadalafil group. Secondary success rate was defined as the need for a single subsequent endoscopic intervention and was 93.3%.

Conclusion: In our series, there was improved outcome with using tadalafil in patients having redo urethroplasty for PFUI. Further trials should be done to evaluate the use in all PFUI cases.

Keywords: Anastomotic urethroplasty; PFUI; pubectomy; tadalafil; urethroplasty.

Introduction

The incidence of pelvic fracture related urethral injury (PFUI) varies from 0.32 to 5/100,000 in men and 0.46-7.25/100,000 in women.[1–4] Progressive perineal anastomotic urethroplasty is the standard of care, performed by those well trained in the field. The overall success of urethroplasty in all PFUI cases depending on the definition of surgical success is 77-95%[5,6] even in well experienced centers. In uncomplicated cases, this can be as high as 90-98%,[2] and in redo cases, success rate can range from 77.7% to 84%.[6–8] In a previously published article, we discussed the three common factors, which result in failure of posterior urethroplasty in PFUI cases: inadequate mobilization of the bulbar urethra, inadequate scar tissue excision, and anastomosis of well vascularized urethral ends.[7]

In PFUI, the severed ends of the urethra are distracted, and the gap is replaced by fibrotic scar after the inflammatory process subsides. After initial tissue injury, wound healing involves hemostasis, inflammation, tissue proliferation, and remodeling. Tissue response to injury results in activation of inflammatory cells and second messengers, including growth factors and cytokines (eg, TNF-α,

Kulkarni Reconstructive Urology Center, Pune, India

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Corresponding Author: Pankaj M. Joshi
E-mail: drpankajmjoshi@gmail.com

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IL-1-β, and ICAM-1).[9,10] During urethroplasty, the fibrotic scar is excised and an anastamotic repair is performed. Tissue fibrosis following repair is thought to be the main pathological factor in subsequent urethral stricture recurrence and failure of repair.[11] Antifibrotic agents, such as docetaxel and mitomycin C, have been used in an attempt to reduce stricture formation, though research is limited with respect to safety and effectiveness.[12–16]

Tadalafil is used as treatment for erectile dysfunction (ED) in patients with PFUI.[17–19] However, the use of tadalafil to prevent stricture formation is relatively novel. Kurt et al.[11] showed promising results in rabbit models, with tadalafil shown to be protective against the development of strictures through a reduction in collagen deposition.[11] To date, tadalafil has not been used in human subjects with the aim of reducing stricture formation and failure post PFUI repair. We hypothesize that tadalafil's antifibrotic properties will result in improved wound healing post-urethroplasty, seen clinically as a subsequent reduction in repair failure. The objective is to determine if tadalafil may be a useful clinical adjunct in the repair of urethral injury.

Material and Methods

Ethics board approval was granted prior to the commencement of the study from Kulkarni Reconstructive Urology Center (KESI02012017). This is a longitudinal prospective non-randomized cohort study performed at our institute from 2017 to 2019. Most patients referred to our unit are usually complex. We evaluate them using conventional urethrogram and micturating cystourethrogram. For complex cases, we perform MRI using the Joshi protocol.[20,21] We have recently published our technique of 3D printing of PFUI as a learning and teach tool.[22] All male patients undergoing redo-urethroplasty for PFUI, who were willing to trial low dose tadalafil post-operatively and able to provide informed consent, met criteria for inclusion into the study. Men were administered 5 mg tadalafil daily, commencing 2 days post-op and continuing for 3 months duration. Patients younger than 18 years, females, complex cases such as recto-urethral fistula and primary cases were excluded from the study. The follow up period was >6 months with uroflow rate performed every 3 months. Uroflow results were compared to those men undergoing redo urethroplasty who did not take the medication.

Main Points

- The use of tadalafil can improve surgical outcomes in redo-PFUI urethroplasty cases.
- Success is likely due to anti-inflammatory properties of tadalafil.
- Further prospective studies are required to evaluate the role of tadalafil in all cases of PFUI repair and not just redo urethroplasty cases.

Success of the repair was defined as absence of symptoms and no need for additional surgical intervention at 3 months. Secondary success was defined as the need for a single subsequent endoscopic intervention. Failure was defined as the need for redo urethroplasty, or more than one endoscopic intervention, or the need for periodic dilatation.

A progressive perineal approach was used. The steps included adequate mobilization of proximal and distal urethral components, corporal separation, inferior pubectomy, corporal rerouting, superior pubectomy, and combined abdominoperineal approach.

Demographic data including age, previous attempts at surgical repair, type of repair, success rate, failures, and follow up were collected. Statistical analysis was performed using student T-test, chi square test, and Fisher exact tests (Microsoft Excel, USA). We considered a test to have statistical significance if P was less than .05.

Results

The study population included 60 redo urethroplasties performed at a tertiary center between 2017 and 2019. These patients had undergone a median of 1 (1-3) previous urethroplasty. The mean age of men was 31.0 years (18-60 years). Mean follow-up was 20.2 months (5-39 months). All men had suprapubic catheters in situ preoperatively.

Most men received a step 3 (inferior pubectomy) anastomotic urethroplasty (68.3%). Of the 60 patients, 29 received tadalafil and 31 patients did not. The demographics of the individual groups can be seen in Table 1. The men who received tadalafil were more likely to be older, diabetic, active smokers, have longer urethral gaps, and have undergone more previous urethroplasties than the men in the nontadalafil group.

The overall primary success rate was 83.3% (50 patients). The success rate in the tadalafil group was 96.6% (28/29 patients), compared with 71.0% (22/31) in the non-Tadalafil group ($P = .0008$). On subset comparison of men undergoing step 3 redo urethroplasty, men receiving tadalafil were also found to have better outcomes than those who did not ($P = .001$).

In our study population, there were 10 failures (Tables 2 and 3). The overwhelming majority of patients who failed did not

take tadalafil, with only one man on tadalafil having an unsuccessful redo urethroplasty. All 10 patients went on to have tadalafil with their redo surgeries. Eight of the 10 redo cases have had success, while two are on periodic dilatation. However, of the eight patients who had successful redo cases, two men required multiple operations as described below. Therefore, the secondary success was 93.3% (56 patients), with four patients requiring more than one endoscopic procedure following their initial redo-urethroplasty.

Patients Who Failed in the Nontadalafil Group

Three of the nine patients who failed redo urethroplasty required redo anastomotic surgery, of which one subsequently developed bulbar urethral necrosis and a pedicled preputial tube was required. Five required a laser VIU for a small anastomotic ring recurrence; there was no recurrence following this single intervention. Two patients remain on periodic dilatation.

Patients Who Failed in the Tadalafil Group

There was one patient who failed in the tadalafil group. This patient was a 22-year male who had undergone step 3 anastomotic urethroplasty which had failed. He subsequently underwent a redo perineal anastomotic urethroplasty which failed as well. A pedicled preputial tube repair was performed successfully with use of post-operative tadalafil. He has since been able to maintain urethral voiding.

Table 1. Demographics of the Tadalafil and Nontadalafil Groups

	Tadalafil	No tadalafil
Age (years)	31.9	30.3
Diabetes (n)	3	2
Active smoker (n)	10	2
Urethral gap	2.9 cm	2.8 cm
Previous urethroplasty	1.3	1.1
Type of redo urethroplasty		Step 1: 4
	Step 1: 4	Step 2: 4
	Step 2: 4	Step 3: 20
	Step 3: 21	Step 4: 2
		Step 6: 1

Table 2. Outcome of Cases as Per Type of Repair

Type of procedure	Number	Failure
Step 1	8 (13.3%)	0 (0%)
Step 2	8 (13.3%)	1 (12.5%)
Step 3	41 (68.3%)	8 (19.5%)
Step 4	2 (3.3%)	1 (50%)

Discussion

The mechanism of urethral injury during pelvic fracture is due to the distraction of the two severed ends of the urethra and replacement of the gap with fibrotic tissue.

After the initial injury, hemostasis and inflammatory responses are initiated, which result in wound healing and scar tissue formation. As mentioned before, several signal processes interact in order to achieve this response.[9,23] Cavalcanti[23] analyzed histological changes in patients with urethral stricture. There was a complete loss of the relationship between smooth muscle, extracellular matrix, and sinusoids in the peri-luminal area. The tissue was mainly composed of collagen. Patients with traumatic strictures showed poor vascularity in the scar tissue. There was increased collagen type III in the peri-luminal area and fewer elastic system fibers in the traumatic stricture.[23] Da Silva et al.[24] looked at the healthy ends of the urethra while performing anastomotic urethroplasty, which in fact showed structural changes with disarrangement and concentration of elastic fibers microscopically.[24] The urethral stricture is not simply due to collagen deposition but results from an imbalance of the extracellular matrix degradation, by decreased matrix metalloproteinase-1 (MMP1) levels, and tissue inhibitor of metalloproteinase-1 (MMP1:TIMP1) ratio and increased TIMP1 levels.[25]

ED after PFUI is difficult to estimate. The causative factors include vasculogenic, neurogenic, and psychogenic etiology. Tadalafil has been used for the treatment of ED with good response.[17,18] Phosphodiesterase-5 (PDE-5) inhibitors are the first treatment of choice, and the favorable response is more than 50%, except in venogenic ED. Tadalafil acts by inhibiting PDE-5 enzyme, which in turn increases cyclic guanosine monophosphate (cGMP) and generation of NO which causes relaxation of blood vessels and increased vascularity.[10,26] Nitric oxide has a defined role in wound healing. Inhibition of inducible NOS (iNOS) decreases collagen deposition induced by inflammation.[26]

In some studies, a protective effect of sildenafil due to the activation of antioxidant genes (NnF2, HO-1, and NQ0-1), apoptotic gene (Bcl-2, which has antiapoptotic effect), and attenuation of proinflammatory cytokines like TNF-α, IL-2-β, and ICAM-1 has been found.[10,27,28] Tadalafil has also been used as a protective drug in multiorgan failure syndrome.[29] Several studies have shown that PDE5 inhibitors improve

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Table 3. Outcomes of Patients Who Failed Initial Redo-Urethroplasty

Type of procedure following redo urethroplasty	Number	Failure	Outcome
Redo anastomotic urethroplasty	3	2 (66%) One patient had received tadalafil, one had not Both patients experienced bulbar urethral necrosis and required a pedicled preputial tube for repair	100%
VIU—laser	5	0% All five patients had not received tadalafil	100%
Periodic dilatation	2	100%Both patients had not received tadalafil	0%

oxygenation of corpus cavernosum. Tadalafil acts as a protective factor in preventing structural disorganization of the elastic fibers of the corpus cavernosum, reduces the inflammatory response, and assists in the remodeling process.[28,30] PDE-5I have also been used to improve flap survival by improving vascularity in an animal study.[31]

Kurt et al.[11] used rat models to show urethral strictures could after urethral thermal injury be prevented with the use of tadalafil after urethral thermal injury. The study showed that, in the tadalafil group, the collagen deposition in submucosal connective tissue was significantly less, proving the protective effect against formation of urethral stricture.[11]

At anastomotic urethroplasty, both bulbar arteries are transected during the process of circumferential dissection of the urethra and transection at the scar tissue. The blood supply of the urethra now depends on the backflow of the cavernosal arteries. If there is compromise of this precarious blood supply, the end of the urethra becomes ischemic resulting in failure of the surgery.[7] The rationale for the use of tadalafil in PFUI repair is to improve the flow in the cavernous artery hence increasing the backflow and improving the vascularity at the anastomotic site.[17,35]

Tadalafil is a competitive inhibitor of PDE-5, which inactivates cGMP. Inhibition of this PDE-5 increases intracellular cGMP, relaxing the smooth muscle resulting in dilatation of blood vessels in the corpus cavernosum leading to penile erection.[32–34] PDE-5 inhibitors induce upregulation of endothelial nitric oxide synthase and iNOS, which generate nitric oxide as well as increasing the activity of soluble guanylyl cyclase that downregulates the inflammatory process. Nitric oxide has anti-inflammatory, antioxidant and antifibrotic properties.[10,26] Tadalafil clearance is mostly hepatic via CYP3A enzyme. Its effect is lower on tadalafil compared to other PDE-5 inhibitors and hence tadalafil has a longer half-life.[29,34]

Most patients in our study required inferior pubectomy for adequate exposure and remaining scar tissue excision. During the repair, the urethra is circumferentially mobilized and transected at the level of the scar. The two healthy ends are anastomosed. The blood supply to the urethral ends is crucial for success of the repair. We hypothesize that tadalafil improves the blood supply between the severed ends of the urethra via multiple communications between the cavernosal and urethral arteries.

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PFUI is an ischemic injury, which disrupts the urethra at the level of the perineal membrane or the bulbomembranous junction. The dorsal penile artery gives circumflex branches, which are important for the blood supply of the bulbar urethra. When the urethra is mobilized during surgery, the dorsal circumflex arteries are also disrupted which can result in bulbo-urethral ischemia. Distal urethral blood flow is dependent on the cavernosal and dorsal penile arteries. Tadalafil improves blood flow in the cavernosal and dorsal penile arteries, which compensates for the disruption of the circumflex arteries during mobilization of the urethra. Tadalafil also has an antifibrotic role and a role in reducing tissue ischemia by promoting vascular growth factors. It is very difficult to quantify the improvement in microvascular blood flow so instead we have looked at outcome measures.

To our knowledge, there is no other study comparing the effect of tadalafil in redo urethroplasty for PFUI cases. In our study, the use of tadalafil improved the surgical outcomes for patients who underwent redo anastomotic urethroplasty for previously failed attempts. Even though this is a case control study, there

is a clinically and statistically significant difference in the two arms to promote the use of tadalafil. We acknowledge that a randomized controlled study would be the ideal way to study the use of tadalafil in this setting. This study also begs the question as to whether tadalafil may in fact be beneficial in all cases of PFUI, whether primary or redo cases. Clearly, more studies need to be done to answer these pertinent questions at hand.

There are a few important limitations associated with this study. This study focused on patients who underwent redo urethroplasty surgery, and no virgin cases were included. In future, tadalafil post initial urethroplasty should be considered as an area for further investigation. Second, our follow-up period is relatively short, with a mean follow-up of 20.2 months. We plan to continue to follow these patients into the future and will report on outcomes. Third, future studies should be randomized and involve a larger cohort of patients so that stronger and more accurate conclusions are able to be drawn.

The use of tadalafil in redo urethroplasty for PFUI cases improves surgical outcomes. We believe success is associated with the anti-inflammatory properties of tadalafil and the increased retrograde blood supply to the urethra. Further studies are required to evaluate its role in all cases of PFUI repair.

Ethics Committee Approval: Ethical committee approval was received from Kulkarni Reconstructive Urology Center (KESI02012017).

Informed Consent: Verbal informed consent was obtained from all participants who participated in this study.

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