Original Article

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Urology Section

Effect of Tadalafil on Prevention of Urethral Stricture after Direct Vision Internal Urethrotomy: A Prospective Cohort Study

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ABSTRACT

Introduction: Urethral stricture recurrence following Direct Vision Internal Urethrotomy (DVIU) remains a significant challenge. Phosphodiesterase type-5 inhibitors (PDE5-Is), such as tadalafil, have been proposed to reduce fibrosis and stricture recurrence by enhancing vascularity and inhibiting inflammation.

Aim: To evaluate the efficacy of tadalafil in preventing stricture recurrence after DVIU.

Materials and Methods: This prospective cohort study was conducted at the Department of Urology, IPGME&R, Kolkata, West Bengal, India, from March 2024 to February 2025. A total of 150 male patients with primary short anterior urethral strictures (<1 cm) were enrolled. Patients were divided into two groups: tadalafil group (n=81) and non tadalafil group (n=69). The exclusion criteria included recurrent or long strictures, congenital anomalies, cardiopulmonary compromise, and bleeding disorders. DVIU was performed under sedation and anaesthesia. Outcomes assessed were the need for further surgical intervention and peak urinary flow rate (Qmax) at three-month follow-up. Statistical analyses used was Chi-square test for categorical variables and Welch's t-test for continuous variables; p-value <0.05 was considered statistically significant.

Results: Baseline demographics were comparable. Further surgical intervention was significantly lower in the tadalafil group (18.5%) compared with the control group (33.3%; p-value=0.046). The mean Qmax was significantly higher in the tadalafil group (10.5±2.4 mL/s) than in the control group (9.1±2.8 mL/s; p-value=0.032). Kaplan-Meier analysis showed higher stricture-free survival in the tadalafil group (p-value=0.041).

Conclusion: Tadalafil significantly reduces stricture recurrence and improves urinary flow after DVIU. Larger, long-term multicentre studies are needed to validate these findings and to integrate tadalafil into routine DVIU protocols.

Keywords: Fibrosis, Follow-up studies, Phosphodiesterase 5 inhibitors, Treatment outcome, Urethrotomy

INTRODUCTION

Urethral stricture disease, defined as narrowing of the urethral lumen due to ischaemic spongiofibrosis, remains a challenging urological condition that impacts patient quality of life and bladder outlet function [1]. Aetiologies include trauma (iatrogenic and external), infection and inflammatory conditions such as lichen sclerosus [2]. Management options vary based on stricture characteristics. Short bulbar strictures (<1 cm) are often treated with Direct Vision Internal Urethrotomy (DVIU) or dilation, although success rates vary widely (22-100%), and long-term recurrence is common [3,4]. Urethroplasty, particularly excision and primary anastomosis, is the gold standard for durable outcomes [5]. Recent preclinical studies [6-8] have explored the role of phosphodiesterase type 5 (PDE5) inhibitors, such as tadalafil, in modulating fibrosis. Tadalafil functions as a selective inhibitor of PDE5, an enzyme prominently found in the smooth muscle cells of the corpus cavernosum in the penis, as well as in the pulmonary vasculature and the prostate. PDE5 breaks down cyclic guanosine monophosphate (cGMP), a crucial molecule in the vasodilatory process. By inhibiting PDE5, tadalafil prevents the degradation of cGMP, thereby enhancing and prolonging its effects [9]. Kurt O et al., demonstrated reduced collagen deposition and stricture formation in rabbit models treated with tadalafil after urethral injury [10]. In humans, Joshi DP et al., found tadalafil beneficial as adjunct therapy in redo pelvic fracture urethral injury repairs [11]. However, its role in preventing stricture recurrence post-DVIU remains underinvestigated. Given tadalafil's antifibrotic and vascular endothelial benefits, this study evaluated its efficacy in reducing recurrence rates and improving urinary flow following DVIU, addressing an important clinical gap.

MATERIALS AND METHODS

A prospective cohort study was conducted at the Department of Urology, IPGME&R and SSKM Hospital, Kolkata, West Bengal India, from March 2024 to February 2025, after Institutional Ethical Committee (IEC) approval (IPGME&R/IEC/2024/0447) and after obtaining informed consent from the participants.

Inclusion criteria: Male patients aged ≥18 years with primary short anterior urethral strictures (<1 cm) were included in the study.

Exclusion criteria: Recurrent or long strictures; congenital anomalies (e.g., hypospadias); cardiopulmonary compromise (NYHA III-IV and recent myocardial infarction); bleeding diatheses (INR >1.5, platelet count <50,000); and patient refusal were excluded form the study.

Sample size calculation: The sample size was calculated using G*Power 3.1, with effect size=0.5, alpha=0.05, and power=0.80. The calculated minimum sample was 65 per group. The effect size (Cohen's d=0.5) was chosen based on conventional standards for a moderate effect, as described by Cohen J, (1988), in the absence of prior data on the magnitude of treatment effect in similar populations [12].

Study Procedure: Patients chose tadalafil or non tadalafil treatment after proper counselling regarding available treatment options. As per institutional protocol, those consenting to adjunctive tadalafil received 5 mg orally once daily for 30 days, starting from postoperative day 1. Once tadalafil group enrollment was completed, subsequent patients formed the control group. The intervention was given per institutional protocol and not as part of this study. DVIU was performed under sedation and local anaesthesia using a cold knife urethrotome. Postoperative care included analgesia (paracetamol±tramadol), antibiotics (cefoperazone-

sulbactam±metronidazole) and per-urethral catheterisation for 2-4 weeks. Follow-up visits were scheduled at 1-2 weeks (catheter removal), 3-6 weeks and 3 months postoperatively. At 3 months, uroflowmetry and RGU-ASU imaging were performed if not already performed in the previous follow-up visits.

Outcome measures: The primary outcome measures included the need for further surgical intervention and the maximum urinary flow rate (Qmax), assessed at three months postoperatively. Qmax was measured using a Medtronic uroflowmeter in a private setting to ensure patient comfort and accuracy. A voided volume of ≥150 mL was considered necessary for a valid uroflowmetry reading. Additionally, retrograde and ascending urethrograms (RGU-ASU) were performed using contrast fluoroscopy to evaluate for stricture recurrence and to corroborate uroflowmetry findings.

STATISTICAL ANALYSIS

All data were analysed using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 26.0. Categorical variables were compared using the Chi-square test, while continuous variables were assessed with Welch's t-test to account for any unequal variances. Kaplan-Meier survival analysis was performed to evaluate stricture-free survival rates. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 150 patients were included in the study, with 81 in the tadalafil group and 69 in the non tadalafil group.

Patients in the tadalafil group had a mean age of 46.79±11.72 years, while those in the non tadalafil group had a mean age of 45.80±13.94 years (p-value=0.59). The mean duration of symptoms was 5.69±2.05 months in the tadalafil group and 6.46±2.48 months in the non-tadalafil group (p-value=0.08) [Table/Fig-1]. There were no statistically significant differences in these baseline parameters, confirming that both groups were demographically and clinically similar at the start of the study.

Variables	Tadalafil (n=81)	Non Tadalafil (n=69)	p-value
Mean age (years)	46.79±11.72	45.80±13.94	0.59
Symptom duration (months)	5.69±2.05	6.46±2.48	0.08
Operative time (minutes)	19.14±4.39	19.93±4.16	0.28
Blood loss (in mL)	3.99±1.97	4.83±2.61	0.06

[Table/Fig-1]: Baseline characteristics of study participants.

Further surgical intervention was required in 15 patients (18.5%) from the tadalafil group compared to 23 patients (33.3%) from the non-tadalafil group [Table/Fig-2]. This difference was statistically significant (p-value=0.046), suggesting that tadalafil significantly reduced the need for repeat interventions. The difference in recurrence requiring surgical intervention demonstrates the potential benefit of tadalafil in preventing stricture recurrence.

Surgery	Tadalafil (n=81)	Non Tadalafil (n=69)	p-value
Further surgery needed	15 (18.5%)	23 (33.3%)	0.046
Further surgery not needed	66 (81.5%)	46 (66.7%)	

[Table/Fig-2]: Comparison of need for further surgical intervention between groups.

The mean postoperative maximum urinary flow rate (Qmax) at three months was higher in the tadalafil group (10.5±2.4 mL/s) compared to the non tadalafil group (9.1±2.8 mL/s) [Table/Fig-3]. This difference was statistically significant (p-value=0.032). Patients receiving tadalafil achieved better urinary flow outcomes, indicating improved urethral patency. The higher Qmax values in the tadalafil group suggest enhanced functional recovery following DVIU.

	Tadalafil (n=81)	Non Tadalafil (n=69)	p-value
Mean Qmax (ml/s)	10.5	9.1	0.032
Standard Deviation	2.4	2.8	

[Table/Fig-3]: Comparison of postoperative maximum urinary flow rate (Qmax) between groups.

Kaplan-Meier survival analysis further demonstrated that the tadalafil group had higher stricture-free survival rates compared to the non tadalafil group, with a significant log-rank p-value (p-value =0.041). The mean stricture-free duration was 2.87±0.45 months for the tadalafil group and 2.62±0.51 months for the non tadalafil group. These findings indicate that tadalafil prolongs the stricture-free interval post-DVIU, potentially delaying recurrence and reducing the likelihood of early surgical re-intervention.

DISCUSSION

The findings of this study highlight the potential benefits of tadalafil as an adjunctive therapy following DVIU for anterior urethral strictures. Baseline characteristics, such as mean age, duration of symptoms, operative time and blood loss, were comparable between the tadalafil and non tadalafil groups, with no statistically significant differences. This similarity suggests that the treatment outcomes were not influenced by demographic or perioperative disparities, providing a reliable basis for interpreting the results.

The need for further surgical intervention was significantly lower in the tadalafil group (18.5%) compared to the non tadalafil group (33.3%, p-value=0.046). This finding implies that tadalafil can effectively reduce recurrence rates following DVIU. These results align with Kurt O et al., who demonstrated in animal models that tadalafil reduces collagen deposition and subsequent fibrosis in urethral tissues [10]. Similarly, Joshi DP et al., reported that adjunctive tadalafil therapy improved surgical outcomes in patients undergoing redo pelvic fracture urethral injury repair [11]. Such evidence supports the antifibrotic properties of tadalafil, which may be critical in minimising stricture recurrence.

Uroflowmetry results further demonstrated the efficacy of tadalafil. At three months, the mean maximum urinary flow rate (Qmax) was 10.5±2.4 mL/s in the tadalafil group compared with 9.1±2.8 mL/s in the non-tadalafil group (p=0.032). This significant improvement in Qmax indicates enhanced urethral patency and better functional recovery. Similar findings have been observed in studies [10,11] exploring pharmacological adjuncts in stricture management, suggesting that improved vascularity and reduced fibrosis directly translate into better urinary flow outcomes.

Stricture-free survival, as assessed by Kaplan-Meier analysis, was also higher in the tadalafil group, with a mean survival duration of 2.87±0.45 months compared to 2.62±0.51 months in the non tadalafil group (p-value=0.041). According to Kurt O et al., the use of tadalafil improved the surgical outcomes for patients who underwent redo anastomotic urethroplasty for previously failed attempts [10]. The prolonged stricture-free interval in the tadalafil group highlights its potential role in delaying recurrence and reducing the need for early repeat procedures. While long-term outcomes were not assessed in this study, these short-term findings provide an encouraging signal that tadalafil may enhance the durability of DVIU results.

The beneficial effects of tadalafil can be attributed to its pharmacological mechanism. Tadalafil is a selective phosphodiesterase type 5 (PDE5) inhibitor that prevents the breakdown of cGMP, a key mediator of smooth muscle relaxation and vasodilation. By increasing cGMP levels, tadalafil improves endothelial function and blood flow to urethral tissue, reducing ischaemia, which is a known factor in scar formation. Additionally, tadalafil has been shown to downregulate profibrotic pathways, particularly those mediated by Transforming Growth Factor-beta (TGF-β) and myofibroblast activation [9].

Studies by Noda M et al., [13], Mansour SM et al., and Mansour HM et al., have highlighted the antifibrotic and anti-inflammatory

effects of tadalafil, demonstrating reduced collagen synthesis and extracellular matrix deposition in both experimental and clinical settings [7,8].

Compared to the existing literature on DVIU outcomes, the results of this study suggest that adjunctive tadalafil may significantly enhance the success rate of this minimally invasive procedure. Initial studies of DVIU reported excellent outcomes, with success rates ranging from 50-85%; however, these studies predominantly reported short-term results. More recent studies with longer follow-up have shown lower long-term success rates, ranging from 6-28% [14,15]. By targeting the underlying pathophysiological mechanisms of scar formation, tadalafil offers a pharmacological means to prolong urethral patency and improve patient outcomes.

Limitation(s)

The present study had several limitations. First, the follow-up period was relatively short, with mean stricture-free survival of less than three months; therefore, late recurrences may have been missed. Second, the non randomised design, in which patients self-selected into the tadalafil or control group after counselling, introduces the possibility of selection bias. The single-centre nature of the study also limits the generalisability of the findings to other settings.

CONCLUSION(S)

Tadalafil appears to significantly reduce urethral stricture recurrence and improve urinary flow post-DVIU. These results support its potential role as an adjunct therapy. Daily tadalafil may enhance postoperative outcomes after DVIU for short-segment strictures. Large-scale multicentre RCTs with long-term follow-up and histological validation are needed to confirm these preliminary findings.

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