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EFFICACY OF INTRALESIONAL MITOMYCIN-C AFTER OPTICAL INTERNAL URETHROTOMY IN REDUCING RECURRENCE OF ANTERIOR URETHRAL STRICTURES

Original Research

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ABSTRACT

Background: Urethral stricture is a common urological condition characterized by fibrosis and narrowing of the anterior urethra, leading to lower urinary tract symptoms and a significant impact on quality of life. Optical internal urethrotomy (OIU) is a minimally invasive procedure frequently used for treatment; however, high recurrence rates remain a major challenge. Adjunctive therapies, such as intralesional mitomycin-C, have shown promise in reducing fibrosis and improving surgical outcomes. This study evaluates the efficacy of intralesional mitomycin-C in preventing recurrence after OIU.

Objective: To assess the effectiveness of intralesional mitomycin-C in reducing the recurrence of anterior urethral strictures following OIU.

Methods: A randomized controlled trial was conducted at the Urology Department of Bahawal Victoria Hospital, enrolling 100 patients aged 20–70 years with anterior urethral strictures. Patients with neurogenic bladder, fully obliterated strictures, untreated urinary tract infections, prior urethroplasty or OIU, or immunosuppressive medication use were excluded. Participants were randomly assigned into two equal groups. Group A underwent OIU followed by a submucosal injection of 0.1 mg mitomycin-C (diluted in 2 cc distilled water) at the urethrotomy site, while Group B underwent OIU alone. A 16 Fr Foley catheter was inserted in both groups for three days postoperatively. Follow-up visits occurred biweekly for three months, and efficacy was assessed based on recurrence-free status. Statistical analysis was performed using IBM SPSS version 25.0, with a p-value of <0.05 considered significant.

Results: The mean age of participants was 44.21 ± 7.88 years, with similar distributions in Group A (44.24 ± 7.92 years) and Group B (44.22 ± 7.44 years). The majority of patients (53.1%) were aged 20–45 years. The mean stricture length was 29.42 ± 2.93 mm, and the average duration was 4.32 ± 1.57 months in both groups. Efficacy was significantly higher in Group A (34 patients, 68.0%) compared to Group B (17 patients, 34.0%) ($p = 0.0007$). Stratified analysis showed a statistically significant reduction in recurrence among patients with non-traumatic strictures ($p = 0.005$), rural residence ($p = 0.042$), and penile strictures ($p = 0.021$).

Conclusion: Intralesional mitomycin-C significantly reduces the recurrence of anterior urethral strictures following OIU by inhibiting fibroblast proliferation and minimizing scar formation. Its routine use in clinical practice may improve long-term success rates and reduce the need for repeated interventions. Further studies with extended follow-up periods are recommended to establish its long-term efficacy.

Keywords: Anterior urethral stricture, fibroblast inhibition, intralesional mitomycin-C, minimally invasive urology, optical internal urethrotomy, recurrence prevention, urethral fibrosis.

INTRODUCTION

Urethral stricture is a longstanding urological condition that dates back to ancient Greek medical writings, characterized by a fibrotic narrowing of the anterior urethra due to scarring of the corpus spongiosum, a process known as spongiofibrosis (1). Among various anatomical locations, the membranous urethra accounts for the majority of strictures, particularly those secondary to instrumentation, while the penoscrotal junction represents a smaller yet significant proportion (2). Management strategies range from minimally invasive approaches, such as optical internal urethrotomy (OIU), to more complex reconstructive procedures, including tissue engineering and buccal mucosal graft urethroplasty (3). Despite variations in success rates, OIU remains the most commonly performed intervention due to its ease of application, minimal morbidity, and widespread preference among urologists (4). However, recurrence is a major challenge, often necessitating repeated interventions, which can exacerbate fibrosis and complicate future treatment options (5). Various prophylactic strategies have been explored to reduce stricture recurrence, including home self-catheterization, urethral calibration, and indwelling catheter placement, but these approaches have shown limited long-term success (5). More recently, the role of antifibrotic agents, particularly mitomycin-C and glucocorticoids, has gained attention for their potential in mitigating postoperative scarring (6). Mitomycin-C, an antineoplastic agent, exerts its effects by inhibiting mitosis, fibroblast proliferation, blood vessel formation, and collagen synthesis, thereby reducing excessive fibrotic tissue deposition (7). Prior research has demonstrated superior success rates in patients receiving intralesional mitomycin-C following OIU compared to those undergoing OIU alone, suggesting its potential benefit in stricture prevention (8).

Despite emerging evidence supporting the antifibrotic properties of mitomycin-C, its role in clinical practice remains incompletely understood, particularly within the local population where variations in disease etiology and treatment responses may influence outcomes. Given the persistent challenge of stricture recurrence and the need for more effective preventive strategies, this study aims to evaluate the efficacy of intralesional mitomycin-C in reducing recurrence rates following OIU. By addressing this gap, the findings may contribute to optimizing treatment protocols and improving long-term outcomes in patients with anterior urethral strictures.

METHODS

The study was designed as an experimental randomized controlled trial (RCT) and was conducted at the urology department of Bahawal Victoria Hospital (BVH), Bahawalpur, Pakistan, between June 5 and December 4, 2024. Ethical approval was obtained from the Institutional Review Board (Approval No: 2039/DME/QAMC Bahawalpur-16/01/2023). Patients diagnosed with anterior urethral stricture were recruited from the hospital's urology department and kidney center. Eligibility criteria included male patients with confirmed urethral strictures. Exclusion criteria encompassed patients with a history of prior internal optical urethrotomy or urethroplasty, completely obliterated urethral strictures, neurogenic bladder, untreated urinary tract infections, immunocompromised conditions, or corticosteroid use. Before enrollment, all participants were thoroughly informed about the study objectives, procedures, potential risks, and benefits, and written informed consent was obtained in accordance with ethical guidelines. Participants were randomly allocated into two equal groups, A and B, using a simple randomization technique. Each participant blindly selected a slip from a shuffled set, where half contained the letter "A" and the remaining half contained the letter "B." Baseline characteristics, including age, stricture duration, stricture length, and stricture site, were recorded for all patients. Group A underwent optical internal urethrotomy (OIU) followed by an intralesional injection of mitomycin-C at the 11 and 1 o'clock positions of the urethrotomy site. A total of 0.1 milligrams of mitomycin-C was administered submucosally using a 21-gauge cystoscopic needle after dilution in 2cc of distilled water. In contrast, Group B underwent OIU alone without adjunctive mitomycin-C injection. All procedures were performed under spinal anesthesia by a consultant urologist with a minimum of three years of post-fellowship experience. A standard perioperative antibiotic protocol was followed, with ciprofloxacin administered preoperatively and continued for seven days postoperatively to prevent infection. A 16 Fr Foley catheter was inserted postoperatively in all patients and retained for three days before removal.

Follow-up assessments were conducted biweekly for a total duration of three months to monitor stricture recurrence. Efficacy was determined based on the absence of symptomatic recurrence, as defined by operational criteria, and was recorded as either present or absent. Data collection was systematically documented on a structured proforma, which included variables such as age, stricture

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duration, site, length, type (traumatic or non-traumatic), residence (rural or urban), and efficacy outcome. Statistical analyses were performed using IBM SPSS version 25.0. Continuous variables, including age, stricture length, and stricture duration, were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on normality, which was assessed using the Shapiro-Wilk test. Categorical variables, such as efficacy (yes/no), stricture type, stricture site (penile, bulbar, membranous, prostatic), and residence, were expressed as frequencies and percentages. The Chi-square test was applied to compare efficacy between the two groups, with a p-value of <0.05 considered statistically significant. To assess the impact of confounding variables on treatment efficacy, stratification was performed based on age, stricture duration, stricture site, stricture length, stricture type, and residence. Post-stratification analysis was conducted using the Chi-square test or Fisher's exact test, as appropriate, to determine statistical significance, with a threshold of $p<0.05$. The study was approved by the Institutional Review Board of the National Institute of Child Health, Karachi (IERB-04/2022).

RESULTS

A total of 100 patients were included in this randomized controlled trial, equally divided into Group A and Group B. The age of the participants ranged from 25 to 65 years, with a mean age of 44.21 ± 7.88 years. The mean ages for Group A and Group B were 44.24 ± 7.92 and 44.22 ± 7.44 years, respectively. The majority of participants (53.1%) belonged to the 20–45-year age group. The mean duration of stricture was 4.32 ± 1.57 months in both groups. The mean stricture length was 29.42 ± 2.93 mm, with comparable values between Group A (29.40 ± 2.92 mm) and Group B (29.40 ± 2.95 mm). The efficacy of intralesional mitomycin-C following optical internal urethrotomy (OIU) was observed in 34 patients (68.0%) in Group A, while only 17 patients (34.0%) in Group B, who underwent OIU alone, exhibited efficacy. The difference between the two groups was statistically significant ($p = 0.0007$). Stratification of efficacy based on age, stricture duration, stricture length, stricture site, stricture type, and residence was performed. Among patients aged 20–45 years, efficacy was noted in 65.38% of Group A and 62.96% of Group B ($p = 0.854$). In the 46–70 age group, 70.83% of patients in Group A and 69.57% in Group B showed efficacy ($p = 0.924$). Patients with a stricture duration of ≤4 months exhibited efficacy in 76.67% of Group A and 70.0% of Group B ($p = 0.559$), whereas those with stricture duration >4 months had efficacy rates of 55.0% in Group A and 60.0% in Group B ($p = 0.749$).

For strictures ≤3 cm in length, efficacy was observed in 65.38% of Group A and 55.17% of Group B ($p = 0.440$), while for strictures >3 cm, efficacy was noted in 70.83% of Group A and 80.95% of Group B ($p = 0.430$). A significant difference was found in efficacy between non-traumatic and traumatic strictures. In non-traumatic cases, efficacy was achieved in 75.86% of patients in Group A compared to 39.29% in Group B ($p = 0.005$), whereas in traumatic strictures, 57.14% of patients in Group A and only 27.27% in Group B demonstrated efficacy ($p = 0.047$). Stratification by residence showed that in rural areas, efficacy was observed in 66.67% of Group A and 39.29% of Group B ($p = 0.042$), while in urban areas, efficacy was achieved in 69.57% of Group A and only 27.27% of Group B ($p = 0.005$). Based on stricture site, penile strictures had an efficacy rate of 83.33% in Group A compared to 16.67% in Group B ($p = 0.021$), while bulbar strictures showed efficacy in 70.83% of Group A and 42.31% of Group B ($p = 0.042$). Membranous strictures had lower efficacy, with 33.33% in Group A and 25.0% in Group B ($p = 0.706$). Prostatic strictures exhibited the highest efficacy difference, with 81.82% in Group A compared to 30.0% in Group B ($p = 0.017$).

Table 1: Stratification of efficacy with respect to age, duration of stricture, site of stricture, length of stricture, type of stricture and residence.

		Group A (n=50)		Group B (n=50)		
		Efficacy		Efficacy		P-value
		Yes	No	Yes	No	
Age (years)	20-45	17 (65.38%)	09 (34.62%)	17 (62.96%)	10 (37.04%)	0.854
	46-70	17 (70.83%)	07 (29.17%)	16 (69.57%)	07 (30.43%)	0.924
Duration (months)	≤4	23 (76.67%)	07 (23.33%)	21 (70.0%)	09 (30.0%)	0.559

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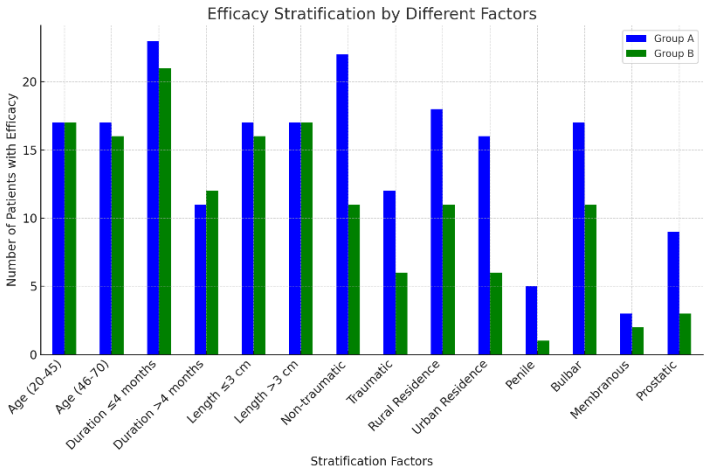
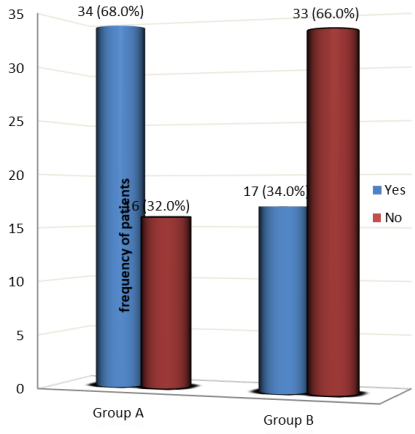
		Group A (n=50)		Group B (n=50)		
		Efficacy		Efficacy		P-value
		Yes	No	Yes	No	
	>4	11 (55.0%)	09 (45.0%)	12 (60.0%)	08 (40.0%)	0.749
Length (cm)	≤3	17 (65.38%)	09 (34.62%)	16 (55.17%)	13 (44.83%)	0.440
	>3	17 (70.83%)	07 (29.17%)	17 (80.95%)	04 (19.05%)	0.430
Type	Non-traumatic	22 (75.86%)	07 (24.14%)	11 (39.29%)	17 (60.71%)	0.005
	Traumatic	12 (57.14%)	09 (42.86%)	06 (27.27%)	16 (72.73%)	0.047
Residence	Rural	18 (66.67%)	09 (33.33%)	11 (39.29%)	17 (60.71%)	0.042
	Urban	16 (69.57%)	07 (30.43%)	06 (27.27%)	16 (72.73%)	0.005
Site	Penile	05 (83.33%)	01 (16.67%)	01 (16.67%)	05 (83.33%)	0.021
	Bulbar	17 (70.83%)	07 (29.17%)	11 (42.31%)	15 (57.69%)	0.042
	Membranous	03 (33.33%)	06 (66.67%)	02 (25.0%)	06 (75.0%)	0.706
	Prostatic	09 (81.82%)	02 (18.18%)	03 (30.0%)	07 (70.0%)	0.017





Efficacy of intralesional mitomycin-C after optical internal urethrotomy (OIU)

DISCUSSION

Urethral stricture is a well-recognized condition characterized by fibrosis and scarring of the urethral mucosa and spongiosal tissue, leading to a narrowing of the urethral lumen. It predominantly affects the anterior urethra, with an incidence of approximately 229–627 cases per 100,000 individuals (9). Multiple etiological factors, including sexually transmitted infections, inflammation, external trauma, iatrogenic injury, catheterization, and prior urethral instrumentation, contribute to its development (10). The resulting obstructive lower

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urinary tract symptoms significantly impact the physical, psychological, and financial well-being of affected individuals (11). Management strategies for urethral stricture disease range from reconstructive techniques to minimally invasive interventions. Urethroplasty remains the gold standard due to its high success rates and lower recurrence rates; however, it is technically demanding and not always feasible (12). Direct Vision Internal Urethrotomy (DVIU) is frequently employed for its simplicity and minimally invasive nature, though it is primarily indicated for non-obliterative strictures of the bulbar urethra, single defects measuring less than 2 cm, and primary urethral strictures (13). Despite its widespread use, DVIU has a recurrence rate ranging from 9% to 60%, with an overall success rate of approximately 50% (14). Repeated DVIU procedures are generally discouraged due to their progressively declining efficacy and increased fibrosis formation (15).

Optimizing DVIU outcomes has been an area of ongoing research, with recent findings suggesting that neoadjuvant mitomycin-C may significantly reduce recurrence rates (16). In this study, 68.0% of patients in the mitomycin-C group demonstrated efficacy compared to only 34.0% in the OIU-only group, with a statistically significant difference ($p = 0.0007$). This aligns with previous studies, where the mitomycin-C group exhibited a 100% success rate at three months, whereas the control group had only 50% efficacy (17). Another study conducted in a local population found that patients receiving mitomycin-C had a 60% higher success rate in preventing recurrence than those undergoing OIU alone. In a cohort of 40 patients with anterior urethral strictures, the recurrence rate was 10% in the mitomycin-C group compared to 50% in the control group, with a significant p-value of 0.006. Similar research has demonstrated that the use of intralesional Tri-inject (triamcinolone, mitomycin-C, and hyaluronidase) results in a 94.2% success rate in preventing recurrence after urethrotomy (18). Further investigations have highlighted the role of mitomycin-C in suppressing fibrosis-related pathways. Studies have demonstrated that submucosal injection of mitomycin-C significantly reduces early recurrence rates, with the recurrence rate in the OIU-only group reported at 47%, while it remained as low as 13% in the mitomycin-C group. Additionally, uroflowmetry findings indicated an average flow rate of 13 mL/sec in the mitomycin-C group compared to 11.75 mL/sec in the OIU-only group, reinforcing the functional benefits of the antifibrotic intervention (8). Mechanistically, mitomycin-C has been shown to inhibit fibroblast proliferation by modulating the mRNA miR-21 pathway, which regulates fibroblast apoptosis through PDCD4 protein induction. Research has demonstrated that fibroblast viability is significantly reduced when miR-21 is inhibited, leading to increased apoptosis via the Bax/BCL-2 protein ratio. Additionally, PDCD4 protein modulates the Rapamycin pathway, which influences extracellular cytokine expression, including IL-6 and IL-8, both of which are implicated in fibrosis formation (19). The ability of mitomycin-C to downregulate PDCD4 and miR-21 expression further supports its role in preventing urethral fibrosis and recurrence following urethrotomy (20).

The findings of this study reinforce the potential benefits of mitomycin-C in reducing recurrence rates in anterior urethral strictures; however, certain limitations must be acknowledged. The follow-up duration of three months, though adequate for assessing short-term recurrence, does not provide insight into long-term outcomes. Additionally, while randomization minimized selection bias, factors such as patient comorbidities and variations in stricture etiology may have influenced results. Future research should focus on larger, multicenter trials with extended follow-up periods to establish long-term efficacy and optimize treatment protocols. Further molecular studies may also elucidate additional antifibrotic mechanisms of mitomycin-C, potentially leading to novel therapeutic strategies. The findings of this study suggest that intralesional mitomycin-C is a promising adjunct to OIU in reducing recurrence rates in anterior urethral strictures. Its ability to modulate fibroblast proliferation and prevent excessive scar formation underlines its clinical significance. While the current evidence supports its efficacy, ongoing research is warranted to refine its application and establish standardized treatment protocols for broader clinical implementation.

CONCLUSION

This study highlights the efficacy of intralesional mitomycin-C in reducing the recurrence of urethral strictures following optical internal urethrotomy, reinforcing its potential as an effective adjunct therapy. By inhibiting fibroblast proliferation and minimizing scar formation, mitomycin-C offers a promising strategy to improve patient outcomes and reduce the need for repeated interventions. Given its significant impact on recurrence prevention, its routine use in clinical practice may enhance the long-term success of urethrotomy and lower patient morbidity. These findings contribute to the growing body of evidence supporting antifibrotic therapies in urological procedures and underscore the need for further research to refine treatment protocols and establish long-term efficacy.

Author Contribution

Author	Contribution
Umair Khan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Jawad Ahmad	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Owais Mureed	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Bilal	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Farzana Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Hafiz Muhammad Usman Abid	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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