

Role of Mitomycin C in Anterior Urethral Stricture Recurrence after Internal Urethrotomy

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ABSTRACT

Background: Urethral stricture, an ancient urologic disease, remains a common in men with high morbidity. IOU refers to procedure that opens the stricture by incising it transurethrally. The most common complication is recurrence. Mitomycin-C with its anti-fibroblast and anti-collagen properties has decreased the recurrence rate of trabeculectomy and myringotomy.

Aim: To compare the efficacy of Mitomycin-C with internal urethrotomy versus internal urethrotomy alone in the prevention of stricture recurrence in anterior urethra.

Study design: Randomized controlled trial.

Setting and duration of study: Urology department of Jinnah teaching hospital, Lahore, 1.5 years

Methodology: 80 men were included in the study after approval of study and informed consent from all patients. Patients were divided into A and B groups by lottery method: Group A underwent internal optical urethrotomy followed by sub-mucosal injection of 0.1mg mitomycin C in urethrotomy site (11 & 1 O' clock) and Group B patients were only treated with internal optical urethrotomy. A 16 Fr indwelling catheter was placed for 3 days in both groups. Patients were called after 3 months or earlier for follow up if patient becomes symptomatic and retrograde urethrogram was done. All the information was entered in a designed Performa.

Results: In this study, out of 80 cases, patient's age was 49.43±8.10 years in Group-A and 48.98±7.20 years in Group-B; mean length of stricture was 9.7±0.26 cm in Group-A and 9.75±0.29 cm in Group-B. Comparison of efficacy of Mitomycin-C with internal urethrotomy versus internal urethrotomy alone in the prevention of anterior urethral stricture recurrence shows that 24(60%) in Group-A and 14(35%) in Group-B had efficacy whereas 16(40%) in Group-A and 26(65%) did not show the efficacy (as per operational definition), P value 0.02.

Conclusion: The efficacy of Mitomycin-C with IOU is significantly higher when compared with internal urethrotomy alone in the prevention of anterior urethral stricture recurrence rate.

Keywords: Stricture, Recurrence, Internal optic urethrotomy, Mitomycin-C, Efficacy, Recurrence

INTRODUCTION

Stricture urethra is basically lumen narrowing of urethra by injury or disease. It is a common problem of men with high morbidity⁸. It is a relatively common disease with prevalence of 0.6% of the at risk population². Trauma to the urethral epithelium or underlying corpus spongiosum leave a scar causing a urethral stricture. Stricture can develop in whole part of the urethra from the proximal urethra to the distal after trauma; either accidental or iatrogenic, infection, ischemia, inflammation or unknown causes⁸.

Different procedures have been adopted for the management of urethral strictures depending on the length, location and depth of the stricture³. IOU is a safe and first line treatment for urethral strictures based of etiology and location¹ The success rate of this technique is controversial in literature as high recurrence rates, ranging from 20% to 60%^{3,4,5,9}. Various techniques have been used to oppose the wound contraction and prevention of recurrence, such as repeated clean intermittent self catheterisation (CISC), indwelling Foley's catheter and urethral stents.[10] Several therapies like brachytherapy, injection of captopril, steroids and mitomycin C have been said to minimize the recurrence rate after DVIU as adjuvant^{3,6,7,8}.

MitomycinC acts as inhibiting DNA synthesis derived from *Streptomyces Caespitosus*. It is useful by preventing replication of fibroblasts and epithelial cells which cause delay in wound healing, and also inhibiting collagen synthesis, thus delaying wound contraction. The drug has been also used to prevent fibrosis after myringotomy and trabeculectomy and has better outcome in these procedures^{3, 8}.

Mazdak et al. reported the stricture recurrence in 10% of patients in the mitomycin C-treated group and in 50% patients in control group (p=0.006)⁸. Recent studies have shown an overall success of 94.2% after IOU with Tri-inject injection (triamcinolone, mitomycin C, and hyaluronidase) in anterior urethral strictures [1]. In another study Mitomycin C injection submucosally after internal urethrotomy reduced the early recurrence with a stricture recurrence rate of 47% in the IOU only group while 13% in Mitomycin-C group³.

As mitomycin-C use has shown reduction in rate of early recurrence of strictures in various international studies and no such study has yet been conducted in our clinical setup, we designed this project to find the efficacy of mitomycin C in preventing recurrence rate after IOU. MitomycinC C application can replace the use of stents or long term catheters following internal urethrotomy is the main aim of our study in view of its efficacy, affordability, and safety.

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MATERIAL AND METHODS

This randomized control trial study was completed in the Urology ward of Jinnah hospital, Lahore in six months after approval from the hospital ethical review committee. Male patients with age range between 25-65 and patients with anterior urethral stricture <1.5cm in length, diagnosed on retrograde urethrogram and patients diagnosed during last 1 year were included. Efficacy was determined by absence of recurrence i.e., stricture of same or more caliber and length on urethrogram than at baseline determined on a retrograde urethrogram assessed after 3 months of intervention. Anterior urethral stricture in patients was defined as all patients with urethral stricture <1.5cm in length and showing narrow in caliber of the urethral lumen in any part of the urethra from the distal urethra to the proximal on retrograde urethrogram. Patients with previous history of urethroplasty or internal optical urethrotomy, benign prostatic hypertrophy (on history/medical record) patients with completely obliterated urethral stricture and having neurogenic bladder with patients with untreated urinary tract infection including patients with history of immunocompromised and corticosteroids users were excluded from the study.

Eighty patients who were fulfilling the inclusion criteria included in our study, after ethical committee approval, informed consent was taken from all patients. Patient was randomly divided into A & B groups by lottery method. Group A patients underwent internal optical urethrotomy followed by submucosal injection of 0.1 milligram MitomycinC (diluted with 2cc distilled water) at the urethromoy place (11 & 1 O' clock) using 21-gauge cystoscopic needle. In group B, patients were only treated with internal optical urethrotomy. Procedure was performed in GA or SA.

All operated Patients were given antibiotic (Ciprofloxacin) preoperatively that will continue for 7 days postoperatively. After the procedure, a 16 Fr Foley catheter was placed for 3 days in both groups. Follow up was done at interval of 3 months and earlier if patient becomes symptomatic (i.e. poor stream, straining or urinary retention). On follow up patients were evaluated by history, examination and retrograde urethrogram. Confounding variables like age, site, length, caliber and density of the stricture was addressed by stratification of subjects in both groups. All the information was entered in a designed Performa (attached).

Results were evaluated on the basis of follow-up urethrogram. If patient has normal urethrogram, it was considered as no recurrence. Stricture of lesser caliber and length than previous one was concluded as partial recurrence whereas, stricture of same or more caliber and length than previous stricture was concluded as recurrence. Efficacy was labeled as per operational definition.

Data was analyzed by using SPSS version seventeen. Quantitative variables like age and length and caliber of stricture were calculated. Frequency and percentage were calculated for nominal variables i.e., efficacy at 3 months. Data was stratified for age and length of stricture and cause of stricture and post stratification for efficacy between the two group estimated by Chi-square test. p< .05 was taken as statistical significance.

RESULTS

A total of eighty cases (forty in each group) fulfilling the inclusion criteria were enrolled to compare the efficacy of mitomycin C with internal urethrotomy versus internal urethrotomy alone in the prevention of stricture recurrence in anterior urethra. distribution age the patients was done, it shows that 12(30%) in Group-A and 13(32.5%) in Group-B were between twenty five to forty five years of age whereas 28(70%) in Group-A and 27(67.5%) in Group-B were between 46 to 65 years of age, mean±standard deviation was calculated as 49.43±8.10 years in Group-A and 48.98±7.20 years fall in Group-B (Table.1). Average length of stricture was calculated as 9.7±0.26 cm in Group-A and 9.75±0.29 cm in Group-B (Table 2).

Comparison of Efficacy of Mitomycin C with IOU versus internal optic urethrotomy alone in the prevention of stricture in anterior urethral recurrence shows that 24(60%) in Group A and 14(35%) in Group had efficacy whereas 16(40%) in Group-A and 26(65%) did not show the effect, p value was 0.02 (Table 4). The data was stratified for age and length of stricture and cause of stricture and post stratification Chi-square test was used for efficacy between the two groups. P < .05 was taken as statistical significance (Table 5,6,7).

Table: 1 Age distribution of patients in our study (n=80)

Age in years	Group A	Group B
25-45	12(30%)	13(32.5%)
46-65	28(70%)	27(67.5%)
Total	40(100%)	40(100%)
Mean±SD	49.43±8.10	48.98±7.20

Table 2: Mean length of stricture in total no of patient. (n=80)

Length of stricture	Group A	Group B
Mean	9.7	9.75
SD	0.26	0.29

Table 4: comparing the efficacy of MitomycinC with IOU versus internal optic urethrotomy alone in the prevention of urethral stricture recurrence in anterior urethra (n=80)

Efficacy	Group A	Group B
Yes	24(60%)	14(35%)
No	16(40%)	26(65%)

Table: 5: Stratification for efficacy with regards to age (n=80) [age 25-45 years]

Group	Efficacy	
	Yes	No
A	7	5
B	4	9

P value 0.16

Table 6: Stratification for efficacy with regards to age (n=80) [age 46-65 years]

Group	Efficacy	
	Yes	No
A	17	11
B	10	17

P value 0.16

Table 7: Stratification for efficacy with regards to length of stricture

Group	Efficacy	
	Yes	No
A	14	10
B	7	13

P value 0.12

Table 8: Stratification for efficacy with regards to length of stricture (n=80) [Upto>1.0cm]

Group	Efficacy	
	Yes	No
A	10	6
B	7	13

P value 0.10

Table 9: Stratification for causes of stricture

Group	Efficacy	
	Yes	No
A	6	2
B	2	4
Idiopathic/ unknown (P value 0.27)		
A	8	7
B	7	13
Lichen sclerosus (P value 0.49)		
A	5	4
B	4	6
Urethritis (P value 0.22)		
A	5	3
B	1	3

P value 0.11

DISCUSSION

Urethral stricture is ancient urologic diseases with high morbidity. Internal optic urethrotomy refers to endoscopic procedure that opens the stricture by incising transurethral approach. The most common complication occurs after IOU is recurrence of stricture. Success rate of internal urethrotomy is approximately 20%. Mitomycin C has properties of antifibroblast and anticollagen and in study reports of clinical trial it has increased the success rate of trabeculectomy and myringotomy⁸.

Aim of this study was to evaluate the efficacy of Mitomycin C in reducing the rate of early recurrence of strictures as there was no such study has been conducted in our clinical setup. We designed this project to estimate the efficacy of Mitomycin C in prevention of recurrence in urethral stricture after IOU. As known of its efficacy, affordability, ease of application and safety; Mitomycin C application can replace the use of old concept of stents or long term catheters following internal optic urethrotomy that may not only help urologist to delineate guidelines for treatment of urethral strictures but also beneficial for patients in terms of long term relief and better prognosis of urethral strictures.

In this study, out of eighty cases, (forty in each group), 12(30%) in Group A and 13(32.5%) in Group B were between 25 to 45 years of age whereas 28(70%) in Group-A and 27(67.5%) in Group B were between 46 to 65 years of age, mean±SD was calculated as 49.43+8.10 years in Group A and 48.98+7.20 years in Group-B, mean length of stricture was calculated as 9.7+0.26 cm in Group-A and 9.75+0.29 cm in Group-B. Comparison of efficacy of Mitomycin C with internal urethrotomy versus internal urethrotomy alone in the prevention of anterior urethral stricture recurrence shows that 24(60%) in Group-A and 14(35%) in Group-B had efficacy whereas 16(40%) in Group-A and 26(65%) did not show the efficacy, P value was 0.02.

In consistent with our study, Mazdak et al. reported a trial on forty male patients with anterior urethral strictures. In Mitomycin C -treated group recurrence rate is 10% and

in 50% of subjects in the other group. This difference in recurrence rate between these two groups were statistically significant ($p=0.006$)⁸.

Recent studies have shown an overall success rate of 94.2% after IOU with intralesional Tri-inject injection (triamcinolone, mitomycin C, and hyaluronidase) for urethral strictures in anterior urethra¹.

Another study showed that injection of Mitomycin C submucosally after internal optic urethrotomy is effective in reducing the early recurrence rate. Analysis of the results revealed recurrence rate of 47% in the IOU only group while the recurrence rate in the Mitomycin C group was only 13%. These differences were statistically significant. Average uroflowmetry of the recurrences in Mitomycin C group was 13ml/sec, while IOU group was 11.75 ml/sec³. These findings of our study are supported with the hypothesis of study i.e., "difference in efficacy of mitomycin C with IOU versus alone IOU in the prevention of recurrence in anterior urethra" is justified.

So Mitomycin C application can replace the use of stents or long term catheters following IOU that is not only help end-urologist to delineate guidelines for treatment of urethral strictures but also beneficial for patients in terms of long term relief and better prognosis of urethral strictures.

CONCLUSION

There is significant role of Mitomycin C with IOU in the prevention of stricture recurrence in anterior urethra.

Conflict of interest: No conflict of interest

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