

ORIGINAL ARTICLE

To Compare the Recurrence Rate of Strictures after Internal Optical Urethrotomy with Intralesional Injection of Mitomycin C versus without Mitomycin C Injection in Patients Presenting with Anterior Urethral Stricture

ISMAT ULLAH¹, MUHAMMAD WAQAR SHAHID², MUHAMMAD AZEEM MUGHAL³, RAHAT USMAN⁴¹Consultant Urologist, DHQ Hospital Narowal Pakistan²Consultant Urologists³Senior Registrar, Pakistan Kidney & Liver Institute Research Centre Lahore Pakistan⁴Specialist Urology, Abeer Medical Centre Jeddah Saudi ArabiaCorrespondence author: Ismat Ullah, E-mail: asmat_online@yahoo.com, Cell: 00966534118005

ABSTRACT

Background: The urethral strictures occurred due to narrowing of urethra. These may occur after an injury or ureteral or excretory system diseases, due to the injury to urothelium or corpus spongiosum that lead to the development of scar tissues. Mitomycin C can be used as chemotherapeutic agent because of its quality of being anti-tumour actions.

Aim: To compare the recurrence rate of strictures after internal optical urethrotomy with intralesional injection of Mitomycin C versus without Mitomycin C injection in patients presenting with anterior urethral stricture.

Study Design: Randomized controlled trial.

Place and Duration of Study: Department of Urology, Lahore General Hospital, Lahore from 5th September 2016 to 5th March 2017.

Methodology: Sixty male patients age 18-70 years, diagnosed with anterior (penile and bulbar) urethral stricture up to 2.0cm were included. Patients were randomly divided into two groups; Group A patients were treated with internal optical urethrotomy alone and Group B patients treated with internal optical urethrotomy with intralesional injection of Mitomycin C. After the procedure, an 18F or 20F indwelling catheter left for 7 days. After 6 months, surgical site evaluated and if stricture again developed, then recurrence labeled.

Results: The mean age was 39.32±11.38 years, mean duration of stricture was 6.85±3.32 months and the mean stricture size was 1.21±0.45 cm. The recurrence occurred in 18 (30%) patients. Significant difference was noted for recurrence in both groups (p-value<0.05).

Conclusion: The recurrence rate with anterior urethral stricture is significantly lower in with Mitomycin C as compared to without Mitomycin C.

Keywords: Recurrence, Urethral stricture, Mitomycin C

INTRODUCTION

The urethral strictures are defined as contraction of the urethral lumen because of development of fibrosis, which change the urethral epithelium and primary corpus spongiosum which can develop in any urethral part. This disease negatively effects the quality of life of patients and causes the significant urological pathologies like urinary tract infections and its recurrence, and possibly more severe outcomes like renal failure, detrusor dysfunction, Fournier's gangrene or urethral carcinoma.¹

Palminteri et al² conducted a study in Italy and observed the urethral strictures characteristics by using data of 1439 males. The mean age of the patients with urethral strictures was 45.1 years (range from 2-84 years). The mean size of stricture was 4.2 cm with huge majority of strictures develop in anterior urethra (92.2%), especially in bulbar urethra (46.9%). Notable, the patients with bulbar strictures were younger in age than patients having strictures in other urethral parts. About 73.6% patients received the surgical interventions for such stricture. About 32.1% of such patients already underwent more than one surgical procedure, while 23.2% had urethrotomy only, out of which 97.4% had urethroplasty and 2.6% had urethrotomy.

Urethral strictures develop due to several causes and can have several manifestations, from asymptomatic at presentation to severe discomfort after urinary retention. Developing the effective drainage of urinary bladder can be problematic, and detailed understanding of anatomy of the urethra and urological technology is important.³

Posterior urethral injury is the most common concern of pelvic region and may occur in around 10% cases.⁴ Around 80% strictures that may occur due to instrumentation used during trans-urethral resection of prostate for benign diseases in males. The remaining 20% occur normally at penoscrotal end. During trans-urethral resection of prostate, resectoscope can be moved from side to side over urethra at penoscrotal junction 800 times in single procedure.⁵

Few researchers suggested that the endoscopic treatment of urethral strictures by using the dilation or urethrotomy worsens the scar formation, thus may lengthen the stricture and its severity, complicating the succeeding open repair.⁶ Internal optical urethrotomy manage the stricture directly by giving the incision. Patients with superficial spongio-fibrosis may advantage it when the incision is done through all the depths of scar. Predictors of success are length of stricture and severity of the spongio-fibrosis.⁷ Internal optical urethrotomy along with Mitomycin C subsequently short-term fresh intermittent catheterization

is a minimally invasive method and extensively available method to manage the complex recurrent strictures of size less than 3cm and bladder neck contractures without any complication and 76% cases do not require additional surgeries.⁸

The rationale of this study is to compare the recurrence of stricture after internal optical urethrotomy with and without intralesional injection of Mitomycin C in patients presenting with anterior urethral stricture. In routine urethral strictures are treated with internal optical urethrotomy. Mitomycin C is chemotherapeutic agent used to cure many diseases including cancer by virtue of its anti-tumour activity. Literature has showed that Mitomycin C can be useful in preventing recurrence of stricture after surgery. But there is no local evidence present in literature which can help in implementation of Mitomycin C for patients presenting with anterior urethral stricture. So we want to conduct this study to find whether Mitomycin C is as effective in preventing recurrence of anterior urethral stricture as reported in literature above.

METHODOLOGY

This randomized controlled trial was conducted at Department of Urology, Lahore General Hospital, Lahore from 5th September 2016 to 5th March 2017 and comprised 60 patients. Patients were randomly divided into two groups; Group A patients were treated with internal optical urethrotomy alone and Group B patients treated with internal optical urethrotomy with intralesional injection of Mitomycin C. Male patients of age >18 years and <70 years with anterior (penile & bulbar) urethral stricture up to 2.0cm were included. Patients with benign prostatic hyperplasia, recurrent urethral strictures, or chronic disease like malignancy, HIV and chronic renal failure (creatinine >1.2mg/dl) were excluded. In both groups the procedure was done under spinal anesthesia and by a single surgeon to avoid the surgical bias. In lithotomy position, urethrotome passed and stricture identified. With the help of cold knife, internal optical urethrotomy done only in group A while in group B, additional to internal optical urethrotomy, submucosal injection of mitomycin C (0.1 mg in 2ml distilled water) was injected at marked urethrotomy site in 4 quadrants (at positions of 1, 5, 7, & 11 o'clock) by using the 22 Gauge cystoscopic needle. After procedure, the 18F or 20F indwelling catheter was placed for 7 days. After discharge patients followed-up in OPD for 6 months. After 6 months, surgical site evaluated and if stricture again developed, then recurrence labeled. Urethral stricture is an abnormal narrowing of the urethra, due to scarring process involving corpus spongiosum covered by urothelium detected on ultrasonography and history of urinary peak flow rate is <10/ml/sec and patients complaints of difficulty in voiding so that patient is unable to pass urine in a stream void. **Uroflowmetry:** Grade 1 (good) peak flow rate >15 ml/sec, Grade 2 (fair) peak flow rate between 10-15 ml/sec and Grade 3 (poor) peak flow rate <10 ml/sec. **Subjective Evaluation:** Grade 1 (excellent) patient voids as before injury, Grade 2 (moderate) patient void with some difficulty, stream is thin and intermittent and Grade 3 (no improvement) voiding is so affected that patient is unable to pass urine in stream. Data was analyzed in SPSS-21. Comparison of both groups for recurrence was done by

using Chi-square test. P-value≤0.05 was considered significant.

RESULTS

The mean age of patients was 36.83±10.62 in Mitomycin C group and 41.80±11.76 years in without Mitomycin C group patients. The mean value of duration of stricture in with Mitomycin C group was 6.70±3.26 months and its mean value in without Mitomycin C group patients was 7.00±3.42 months. Similarly the mean value of size of stricture in with Mitomycin C group was 1.15±0.42 and its mean value in without Mitomycin C group patients was 1.27±0.48 (Table 1). The recurrence was noted in 18 cases, out of which 5 cases had Mitomycin C and 13 did not have Mitomycin C group, similarly the recurrence not happened in 42 cases in which 25 were from with Mitomycin C group and 17 were from without Mitomycin C group. Significant difference was calculated for recurrence in both groups (p=0.024) [Table 2].

Table 1: Baseline evaluation of patients (n=60)

Variable	With Mytomycin C	Without Mytomycin C
Age (years)	36.83±10.2	41.80±11.76
Stricture duration	6.70±3.26	7.00±3.42
Stricture Size	1.15±0.42	1.27±0.48

Table 2: Comparison of recurrence in both study groups

Recurrence	With Mitomycin C	Without Mitomycin C	Total
Yes	5 (16.7%)	13 (43.3%)	18 (30.0%)
No	25 (83.3%)	17 (56.7%)	42 (70.0%)
Total	30 (100%)	30 (100%)	60 (100%)

Chi value=5.07, p-value=0.024

Table 3: Comparison of recurrence of age, stricture duration and stricture size in both groups

size in both groups				
Variable	Recurrence	With Mitomycin C	Without Mitomycin C	P value
Age (years)				
≤30	Yes	5	6	0.308*
	No	4	1	
>30	Yes	-	7	0.009*
	No	21	16	
Stricture duration				
≤6	Yes	1	6	0.080*
	No	14	9	
>6	Yes	4	7	0.450*
	No	11	8	
Stricture size				
≤1	Yes	5	13	0.024**
	No	25	17	
>1	Yes	5	13	0.024**
	No	25	17	

*Not Significant

**Significant

When the data was stratified for age of patients, patients aged ≤30 years, recurrence occurred in 5 cases with Mitomycin C and in 6 cases without Mitomycin C. The difference was insignificant for this age strata (p>0.05). In patients aged >30 years, the recurrence occurred in 7 cases who did not received Mitomycin C. The significant difference was noted in both groups for this age strata (p=0.009). In patients with stricture for ≤6 months old, recurrence occurred in 1 case with Mitomycin C while in 6 cases without Mitomycin C. In patients with stricture for ≤6 months old, recurrence occurred in 4 cases with Mitomycin C and in 7 cases without Mitomycin C. The insignificant difference was noted (p>0.05) in both strata. The patients

with stricture size ≤ 1 , the recurrence occurred in 5 cases with Mitomycin C group and in 13 cases without Mitomycin C. Similarly in patients with stricture size >1 , the recurrence occurred in 5 cases with Mitomycin C group and in 13 without Mitomycin C. The significant difference was noted ($p < 0.05$) in both groups (Table 3).

DISCUSSION

Urethral strictures are the disease of ancient times. Several methods have been approved to decrease the rate of recurrence of these strictures after the internal optical urethrotomy, like placement of catheter for a long time and self-clean intermittent catheterization with changing success. Mitomycin C has properties of anti-fibroblast and anti-collagen and is used during trabeculectomy, in myringotomy, and after excision of keloids scars in the current surgical practices.⁹⁻¹²

In our study the recurrence happened in 18 (30%) patients, 5 were from with Mitomycin C group and 13 were from without Mitomycin C group. The significant difference was noted (p -value < 0.05). Ali et al¹³ demonstrated that the frequency of recurrence of urethral strictures was 14.1% in patients given Mitomycin C during procedure while in 36.9% patients without Mitomycin C ($p=0.002$). The Mitomycin C also displayed the increased duration for the recurrence of strictures than without using mitomycin C ($p=0.002$). Mitomycin C was observed to be highly successful in averting the recurrence of urethral strictures after the internal optical urethrotomy. Vanni¹⁴ also found that there is a significant decrease in the frequency of recurrence after treatment of urethral stricture by using intralesional Mitomycin C. Thus the combination of anti-fibroblast agents comprising of Mitomycin C is being used in cases with successful effects. In another study, the recurrence of strictures was 47% without Mitomycin C while frequency of recurrence of strictures with Mitomycin C was 13% only. This difference between both groups was statistically significant ($p < 0.05$).¹⁵

Another trial has also showed that in 40 patients underwent surgery with Mitomycin C, recurrence was 10% while in patients underwent surgery without Mitomycin C, recurrence was 50% and difference was significant ($p < 0.05$).¹⁶ Kumar et al¹⁷ observed the rate of recurrence of urethral strictures in 20% cases only after using the intralesional injections. They concluded that optical internal urethrotomy in combination of intralesional injection of Vatsala-Santosh PGI tri-inject is the safe and effective therapeutic procedure that is minimally invasive for anterior urethral strictures.

Hradec et al¹⁸ reported that the urethrotomy was done in 149 males patients with strictures and the findings were evaluated post-operatively for 1-3 years. In this series of males patients underwent the urethrotomy without corticoid injections had recurrence of strictures in around 19.4% cases. Tabassi et al¹⁹ conducted another study on seventy cases of urethral strictures who underwent internal urethrotomy and intraurethral inaction of Mitomycin C. Recurrence occurred in 35.3% patients ($n=34$) with Mitomycin C and in 41.7% patients ($n=36$) without Mitomycin C. Statistically insignificant difference was observed for recurrence in both groups but the duration of recurrence reduced significantly with Mitomycin C. Out of

one hundred and twenty patients, recurrence of urethral strictures was noted in 9.4% cases with Mitomycin C while in 22.9% cases without Mitomycin C ($p=0.029$).²⁰

CONCLUSION

The recurrence rate in patients with anterior urethral stricture is significantly lower in with Mitomycin C group as compared to the patients without Mitomycin C group. The overall frequency of recurrence in this study was 18 (30%) which is high and cannot be ignored.

REFERENCES

1. Zaid UB, Lavien G, Peterson AC. Management of the Recurrent Male Urethral Stricture. *Current Urol Reports* 2016;17(4):1-8.
2. Palminteri E, Berdondini E, Verze P, De Nunzio C, Vitarelli A, Carmignani L. Contemporary urethral stricture characteristics in the developed world. *Urology* 2013;81(1):191-7.
3. Broghammer JA. Urethral strictures in males. 2013 [cited 2014]; Available from: <http://emedicine.medscape.com/article/450903-overview>.
4. Singh SK, Pawar DS, Khandelwal AK. Transperineal bulboprosthetic anastomotic repair of pelvic fracture urethral distraction defect and role of ancillary maneuver: a retrospective study in 172 patients. *Urol Ann* 2010;2(2):53.
5. Mundy A, Andrich D. Urethral Stricture Review Article Institute of Urology, London, UK. *Br J Urol* 2012.
6. Barbagli G, Sansalone S, Djinojic R, Romano G, Lazzeri M. Current controversies in reconstructive surgery of the anterior urethra: a clinical overview. *Int Braz J Urol* 2012;38(3):307-16.
7. Dubey D. The current role of direct vision internal urethrotomy and self-catheterization for anterior urethral strictures. *Indian J Urol* 2011;27(3):392.
8. Farrell MR, Sherer BA, Levine LA. Visual internal urethrotomy with intralesional mitomycin C and short-term clean intermittent catheterization for the management of recurrent urethral strictures and bladder neck contractures. *Urology* 2015;85(6):1494-500.
9. Santucci RA, Joyce GF, Wise M. Male urethral stricture disease. *J Urol* 2007;177(5):1667-74.
10. Jampel HD. Effect of brief exposure to mitomycin C on viability and proliferation of cultured human Tenon's capsule fibroblasts. *Ophthalmology* 1992;99(9):1471-6.
11. Yamamoto T, Varani J, Soong HK, Lighter PR. Effects of 5-fluorouracil and mitomycin C on cultured rabbit subconjunctival fibroblasts. *Ophthalmology* 1990;97(9):1204-10.
12. Ayyildiz A, Nuhoglu B, GüLERKAYA B, Caydere M, Üstün H, Germyanoglu C, et al. Effect of intraurethral Mitomycin-C on healing and fibrosis in rats with experimentally induced urethral stricture. *Int J Urol* 2004;11(12):1122-6.
13. Ali L, Shahzad M, Orakzai N, Khan I, Ahmad M. Efficacy of mitomycin C in reducing recurrence of anterior urethral stricture after internal optical urethrotomy. *Korean J Urol* 2015;56(9):650-5.
14. Vanni AJ. New frontiers in urethral reconstruction: injectables and alternative grafts. *Translational Androl Urol* 2015;4(1):84.
15. Ravi Shankar THS, Ramesh KR, Shivashankarappa M, Imdad AN. A prospective, comparative study on the effect of mitomycin c on anterior urethral stricture recurrence after internal urethrotomy. *JEMDS* 2014;3(68):14628-32.
16. Mazdak H, Meshki I, Ghassami F. Effect of mitomycin C on anterior urethral stricture recurrence after internal urethrotomy. *Eur Urol* 2007;51(4):1089-92.
17. Kumar S, Garg N, Singh SK, Mandal AK. Efficacy of optical internal urethrotomy and intralesional injection of Vatsala-Santosh PGI tri-inject (triamcinolone, mitomycin C, and hyaluronidase) in the treatment of anterior urethral stricture. *Advances Urol* 2014;2014.
18. Hradec E, Jarolim L, Petrik R. Optical internal urethrotomy for strictures of the male urethra. Effect of local steroid injection. *Eur Urol* 1980;7(3):165-8.
19. Tabassi KT, Yarmohamadi A, Mohammadi S. Triamcinolone injection following internal urethrotomy for treatment of urethral stricture. *Urol J* 2011;8(2):132.
20. Bitencourt CS, Pereira PA, Ramos SG, Sampaio SV, Arantes EC, Aronoff DM, et al. Hyaluronidase recruits mesenchymal-like cells to the lung and ameliorates fibrosis. *Fibrogenesis Tissue Repair* 2011;4(1):3.