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Original Article

Study the outcomes of intralesional injection of triamcinolone and mitomycin-C mixture versus triamcinolone alone injection following direct vision internal urethrotomy for treatment of anterior urethral stricture

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ABSTRACT

Purpose: To study the effect of dual agent (mixture of triamcinolone and mitomycin-C) after direct vision internal urethrotomy and compare the results with triamcinolone intralesional injection only.
Materials and methods: A total of 70 male patients with symptomatic anterior urethral stricture of size <2-2.5cm. Strictures >2.5 cm in size were excluded from the study. All Patients were randomized into two groups. In group A, dual agent (mixture of triamcinolone and mitomycin-C) is injected following DVIU. In group B, single agent (triamcinolone) is injected following DVIU. An indwelling 18 Fr Foley catheter of same make was left in place for 7-14 days. All patients were followed up for 6 weeks, 12 weeks and then every 3 monthly following trial of void (TOV) for 2 years.
Results: The overall recurrence rate group 1 was 42.85% (15 out of 35 patients) i.e. a success rate of 57.15% whereas recurrence rate group 2 was 20% (7 out of 35 patients) i.e. a success rate of 80%(p-value<0.05). Complication rates were comparable in both the groups (p-value >0.05).
Conclusion: In this study, we found mixture of triamcinolone and mitomycin-C is superior to triamcinolone alone in terms of recurrence rate and that the difference is significant (p-value<0.05). There are few studies using dual agents for paraurethral injection after DVIU.

Keywords: triamcinolone, mitomycin-C, paraurethral

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INTRODUCTION

Urethral stricture disease has always been a challenge for urologists. Different treatment modalities that are used for treatment of urethral stricture disease are dilatation, urethrotomy, stent placement, and urethroplasty. Steenkamp et al. have found no significant difference in efficacy between dilation and internal urethrotomy as initial treatment of strictures [1]. Internal urethrotomy is a safe first line treatment for urethral strictures independent of etiology and location, with an overall primary success rate of 60–70% [2]. Endoscopic treatment is recommended before various forms of urethroplasty are contemplated [2]. Pansadoro and Emiliozzi [3] have shown that the curative success rate of direct visual internal urethrotomy (DVIU) is approximately 30 to 35%. The low success rate and the recurrence of stricture despite treatment have prompted the search for new treatment methods. Application of steroid at time of urethrotomy produces better result than urethrotomy alone [5, 6]. Mitomycin C is useful in delaying the healing process by preventing replication of fibroblasts and epithelial cells and inhibiting collagen synthesis. It is also proposed that it can delay wound contraction [7]. Thus this study was conducted to see the benefit of combining the two agents for preventing recurrence of stricture after urethrotomy over use of a single agent.

MATERIAL AND METHODS

A total of 70 patients with symptomatic anterior urethral stricture (primary or secondary) were treated by optical internal urethrotomy followed by intralesional injection of either triamcinolone alone or triamcinolone and mitomycin-C mixture during a period from January 2015 to December 2017 in LLRM Medical College and SVBP Hospital, Meerut, U.P.. The study was approved by the institute ethical committee and informed consent was taken from the patients before enrolment in the study.

Inclusion criteria: Males >16 years. Patients with urethral stricture less than 2 cm.

Exclusion criteria: Patients with multiple strictures or completely obliterated urethral stricture. Patients who were unwilling or unfit for surgery. Patients with hypospadias, chordee, any other congenital anomaly or patients with neurogenic bladder, systemic or immune disease or who are already on steroids or immunosuppressant for some other illness.

Patients presenting for the first time for treatment were referred to as primary, whereas those who had undergone some procedure for the treatment of stricture prior to reporting to us were referred to as secondary. Diagnosis of urethral stricture was made on the basis of clinical history, uroflowmetry, and retrograde urethrography. Patients were randomized into two groups according to random number table. In group 1, dual agent(mixture of triamcinolone and mitomycin-C) is injected following DVIU whereas in group 2, single agent (triamcinolone) is injected following DVIU. The procedure was done under monitoting anaesthesia care(mac) or spinal anesthesia. All patients received antibiotic prophylaxis preoperatively. Optical internal urethrotomy was done in usual manner using cold knife. The mixture was prepared by diluting triamcinolone 40 mg and mitomycin-C 2 mg, in 10 mL of saline and was injected intralesionally at the site of urethrotomy using William's endoscopic needle. At every site 1-2 mL was injected with a total of 5 – 10 ml according to length of stricture.

After confirming free passage of cystoscope into the bladder, an 18 Fr silicone catheter was left in place for 14 days. Culture specific broad spectrum antibiotics were administered perioperatively and continued till catheter removal. Postprocedure evaluation was done on the basis of history and uroflowmetry. Retrograde urethrography and micturating cystourethrography were done only if patient developed obstructive voiding problems or flow rate below 10 mL/second. Follow up was done at regular interval of 6 weeks, 12 weeks and then 3 monthly for next 2 years. Any symptoms pertaining to recurrence were noted as reduced stream of urine, retention of urine, and burning micturition. If the symptoms recurred within 6 months, it was not considered recurrence. Procedure was considered successful if patient did not report any voiding difficulty and maximum flow rate >10 mL/second for a voided volume of at least 100 mL after 6 months of procedure.

RESULTS

Median followup was 24.6+- 4.6m in group 1 and 24.5+-5.6m in group 2. Median age at presentation in group 1 was 47±14.44 years and in group two was 47±16.07. Out of these patients, 40 patients were primary (i.e. they had not undergone any procedure for stricture earlier) and 30 patients were secondary (i.e. they had undergone some procedure for stricture other than urethral dilatation earlier). Patients of both group were divided according to their length of stricture in groups of <1cm, >1-1.5cm and >1.5-2cm. . Patients were further categorized depending urethral calibration (<6 Fr and ≥6 Fr). Of these 70 patients, 48 (68.57%) had bulbar urethral stricture, 16 (22.85%) had pendular urethral stricture, and 6 (8.57%) patients had

junctional urethral stricture. Patients were also divided on the basis of degree of spongiofibrosis in the mild, moderate and severe category as assessed subjectively by the operating urologist. Etiology of stricture was classified as inflammatory, iatrogenic, traumatic and unknown. Maximum patients(34.28%) had inflammatory cause (UTI/STD) as their etiology. Maximum patients had urethral calibration >6Fr. Preoperative symptoms of stricture in both groups like thinning of urinary stream, frequency of micturition, straining at micturition, retention of urine, feeling of incomplete evacuation, burning micturition and terminal dribbling are as shown in Table 2. Preoperatively culture of urine was obtained. 49(70%) of total patients had sterile culture.

S. no.	Characteristics		Group A	Group B	P value
1.	Age (in years)		47±14.44	47±16.07	0.755
2.	Type	Primary	19	21	0.629
		Secondary	16	14	
3.	Site	Pendular	6	10	0.41
		Junctional	4	2	
		Bulbar	25	23	
4.	Length	0-0.5	0	0	0.755#
		0.5-1	10	8	
		1-1.5	14	7	
		1.5-2	11	10	
5.	Etiology	Inflammatory	14	10	-
		Iatrogenic	7	9	
		Traumatic	6	7	
		Unknown	8	9	
6.	Degree of Spongiofibrosis	Mild	14	18	0.47
		Moderate	17	12	
		Severe	4	5	
7.	Pre operative urethral calibration	<6 Fr	10	13	0.44
		>6 Fr	25	22	
8.	Mean pre operative peak flow volume		4.87±1.12 ml/s	5.02±1.33 ml/s	0.71
9.	Pre operative urine culture	Sterile	26	23	0.433
		Infective	9	12	
10.	Complications	Haematuria	4	4	-
		Pyuria	0	1	
		Fever	0	1	
		Spongiofibrosis	1	0	
		Erectile Dysfunction	1	0	
11.	Post operative hospital stay		1.76±0.66 days	1.89±1.02 days	0.67
12.	Mean Post operative peak flow volume		13.40±2.30ml/s	14.63±3.24 ml/s	0.31
13.	Recurrence rate		42.85%	20%	0.039
14.	Mean time to recurrence (in months)		11.73±3.23	15.14±3.13	0.02
15.	Median time to follow up		24.6+-4.6m	24.5+-5.6m	0.02

#after merging cells of 0-0.5cm and >0.5-1cm cells.

Table 1: Etiology of stricture in the two groups

Etiology	Group A	Group B
Inflammatory	14	10
Iatrogenic	7	9
Traumatic	6	7
Unknown	8	9

Table 2: Preoperative symptoms in two groups

Preoperative symptom	Group A	Group B
Thinning of urinary stream	31	27
Frequency of micturition	22	25
Straining at micturition	16	20
Retention of urine	11	13
Feeling of incomplete evacuation	11	8
Burning micturition	7	7
Terminal dribbling of urine	4	6

The baseline characteristics of the patients like age of the patients, type, site, length and etiology of stricture, degree of spongiofibrosis, preoperative urethral calibration and urine culture, mean preoperative peak flow volume were compared and the difference between the two groups were found to be insignificant as shown in Table no. 1. Post operatively hospital stay, complications, rate of recurrence, time of recurrence, need for secondary intervention were analysed between the two groups. Site of stricture, with bulbar urethral stricture regarding length, type, diameter, and etiology have been shown in Table 1. The difference was not significant between these characteristics. Hospital stay between the two groups was not found to be statistically significant (p value <0.05). Complications following intervention were as follows : haematuria, pyuria, fever, spongiofibrosis, erectile dysfunction and are given in table no. 3. Fifteen (42.85%) patients of group 1 developed recurrence after OIU and injection of triamcinolone. Seven (20%) patients of group 2 developed recurrence after OIU and injection of triamcinolone and mitomycin C. The difference between the two groups was statistically significant(p-value<0.05). Mean time to recurrence in group 1 was 11.73±3.23 months and in group 2 was 15.14±3.13 months. Mean time to recurrence was also found to be significant (p-value<0.05).

Table 3 : Rate of complications in group A and group B

Complication	Group A	Group B
Haematuria	5	4
Pyuria	1	2
Fever	1	2
Erectile dysfunction	2	1
Spongiofibrosis	2	3

All patients tolerated the therapy and none had local or systemic side effects of the injection.

DISCUSSION

Mitomycin C is an antitumor antibiotic isolated from Streptomyces caespitosus. It has been found to inhibit fibroblast proliferation and prevent scar formation [10, 11]. Ayyildiz et al. have shown antifibrotic effect of MMC on experimentally induced urethral stricture in rats [12]. Mazdak et al. in 2007 reported study on 40 patients who were treated with urethrotomy with and without mitomycin C. Recurrence was seen in 2 out of 20 patients (10%) in mitomycin C group and 10 out of 20 patients (50%) in the other group [7]. Vanni et al. reported study on 17 patients of bladder neck contracture who were treated with bladder neck incision and intralesional MMC [13]. At a median followup of 12 months (range 4 to 26), 13 patients (72%) had a patent bladder neck after 1 procedure, as did 3 (17%) after 2 procedures and 1 after 4 procedures. All of the patients presenting with a prior indwelling urethral catheter or requiring a dilation schedule had a stable, patent bladder neck.

Mazdak et al. in 2010 reported study on 25 patients treated by internal urethrotomy and intraurethral submucosal triamcinolone injection [14]. Recurrence was seen in 5 out of 24 patients (21.7%) and among 21 patients treated only by internal urethrotomy recurrence was seen in 11 patients (50%). The success rate in patients with strictures less than 1 cm in length was 95.8%, whereas that in patients with strictures of 1 to 3 cm in length was 57.7% () [6]. Tabassi et al. studied 70 patients of urethral stricture who were treated with internal urethrotomy and intraurethral triamcinolone injection. Recurrence was noted in 12 patients out of 34 and in 15 patients out of 36 in control group. No statistically significant difference was noted in recurrence rate but time to recurrence decreased significantly in experimental group [15].

In our study we found that injection of two agents was found to be superior compared to use of single agent following OIU. The recurrence rate following injection of both triamcinolone and mitomycin C was 20% compared to 42.85% following injection of triamcinolone alone. The use of two agents also increased the mean time to recurrence 15.14±3.13 months from 11.73±3.23 months due to the use of single agent. Thus there was a significant difference in both the recurrence rate(p-value=0.039) as well as the mean time to recurrence(p-value=0.02). Complication rates were comparable between the two groups. There was no significant difference between the post operative hospital stay between the two groups (p-value>0.05) but the need for secondary intervention in the follow-up period decreased due to the use of two agents.

Therefore combining two agents for use of paraurethral injection after OIU has encouraging results over the use of single agent.

CONCLUSION

Recurrence rates in group 1 was 42.85% while recurrence rates in group 2 was 20% i.e. success rate in group 1 was 57.15% while success rate in group 2 reached 80%. Recurrence rates were found to be statistically significant between these two groups (p-value<0.05).Thus optical internal urethrotomy with intralesional injection of triamcinolone and mitomycin C mixture is a safe and effective minimally invasive therapeutic modality for short segment anterior urethral strictures which is found to be more effective than optical internal urethrotomy with intralesional injection of triamcinolone alone. Complication rates were comparable in both the groups(p-value >0.05).

Overall mixture of triamcinolone and mitomycin-C is found to be superior than triamcinolone alone in terms of recurrence rate. The limitation of the study is its limited number of patients. Although definitive conclusion can be drawn after meta-analysis of data from different studies involving larger cohort.

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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