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Efficacy of holmium laser urethrotomy and intralesional injection of Santosh PGI tetra-inject (Triamcinolone, Mitomycin C, Hyaluronidase and N-acetyl cysteine) on the outcome of urethral strictures

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Introduction To study the efficacy of holmium laser urethrotomy with intralesional injection of Santosh PGI tetra-inject (Triamcinolone, Mitomycin C, Hyaluronidase and N-acetyl cysteine) in the treatment of urethral strictures.

Material and methods A total of 50 patients with symptomatic urethral stricture were evaluated by clinical history, physical examination, uroflowmetry and retrograde urethrogram preoperatively. All patients were treated with holmium laser urethrotomy, followed by injection of tetra-inject at the urethrotomy site. Tetra-inject was prepared by diluting acombination of 40 mg Triamcinolone, 2 mg Mitomycin, 3000 UHyaluronidase and 600 mg N-acetyl cysteine in 5–10 ml of saline, according to the stricture length. An indwelling 18 Fr silicone catheter was left in place for 7–10 days.All patients were followed-up for 6-18 months postoperatively by history, uroflowmetry, and if required, retrograde urethrogram and micturating urethrogram every 3 months.

Results 41 (82%) patients had asuccessful outcome,whereas 9 (18%) had recurrences during a follow-up ranging from 6–18 months. In <1 cm length strictures, the success rate was 100%, while in 1–3 cm and >3 cm lengthsthe success rates were 81.2% and 66.7% respectively. This modality, thus, has an encouraging success rate, especially in those with short segment urethral strictures (<3 cm).

Conclusions Holmium laser urethrotomy with intralesional injection ofSantosh PGI tetra-inject (Triamcinolone, Mitomycin C, Hyaluronidase, N-acetyl cysteine) is a safe and effective minimally-invasive therapeutic modality for short segment urethral strictures.

Key Words: Hyaluronidase ‹› Mitomycin C ‹› N-acetyl cysteine ‹› tetra-inject ‹› Triamcinolone

INTRODUCTION

Urethral stricture disease has always been a challenge for urologists. Treatment of urethral stricture disease includes 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]. Ho:YAG laser urethrotomyis a safe and effective minimally-invasive therapeutic modality for urethral stricturewith results comparable to those of conventional urethrotomy [3].

Internal urethrotomy does not provide an epithelial approximation, but rather aims to separate the scarred epithelium so that healing occurs secondarily. If epithelialisation progresses completely before wound contraction significantly narrows the lumen,

the internal urethrotomy may be successful. However, if wound contraction significantly narrows the lumen before completion of epithelialization, the stricture recurs. Injection of steroid at the site of incision ostensibly prevents scar formation by decreasing the amount of collagen fibers and fibroblasts in wound tissue [4].The application of steroid at the time of holmium laser urethrotomy produces a better result than urethrotomy alone [5]. Mitomycin C is useful in delaying the healing process by preventing replication of fibroblasts and epithelial cells and inhibiting collagen synthesis. It hasalso been proposed that it can delay wound contraction [6, 7]. Hyaluronidase instillation during optical internal urethrotomy (OIU) may decrease the incidence of urethral stricture recurrence [8].The exact mechanism by which this is achieved in urethral stricturesis not known, but it is used as antifibrotic agent in hypertrophic scars, keloids and pulmonary fibrosis. Intralesional injectiondecreases fibroblast proliferation, collagen and glycosaminoglycan synthesis and suppresses pro-inflammatory mediators in the wound healing process [9].There is no previous study on the use of N-acetyl cysteine in urethral strictures. A study by Rhalebet al.indicated that N-acetyl cysteine is useful in idiopathic pulmonary fibrosis *in vitro* [10]. Earlier it has been used as an antifibrotic agent in the treatment of idiopathic pulmonary fibrosis, as it inhibits collagen synthesis in rat cardiac and hepatic fibroblasts. Thus, this study was conducted to investigate the benefit of combining all four agents in preventing recurrence of stricture after urethrotomy.

MATERIAL AND METHODS

A total of 50 patients with symptomaticurethral stricture were treated with holmium laser urethrotomy and intralesional injection of Tetra-inject during the period 1st July 2012 to 31st December 2013 at a tertiary level centre in north India.The study was approved by the institute's ethical committeeand informed,written consent was obtainedfrom the patients. Those with completely obliterated urethral strictures were excluded from the study. Patients presenting for the first time for treatment were referred to as primary, whereas those who had undergone some prior procedure for the treatment of stricture were referred to as secondary. Diagnosis of urethral stricture was made on the basis of clinical history, uroflowmetry and retrograde urethrography. The stricture location was divided on the basis of three segments- penile, bulbar and posterior, which in itself included both membranous and prostatic. The strictures were categorized by length as <1 cm, 1–3 cm >3 cm. The procedure was performed under general or regional anesthesia.The holmium laser was set foran energy of 2 J and frequency of 10–15 Hz. The chosen settings seem to offer a satisfactory compromise between low depth of tissue penetration and low coagulation effect Furthermore,the vaporization of tissue presents an additional advantage overconventional cold knife urethrotomy. A combination of 40 mg Triamcinolone, 2 mg Mitomycin, 3000 U Hyaluronidase and 600 mg N-acetyl cysteine was diluted in 5–10 ml of saline according to the stricture length.The solution was then injectedby William's endoscopic needleat multiple sites throughout the strictured segment at the site of urethrotomy. After confirming the free passage ofa cystoscope into the bladder, an 18 Fr silicone catheter was left in place for 7–10 days. Culture-specific broad spectrum antibiotics were administered perioperatively and continued until catheter removal. Post-procedure evaluation was done by history and uroflowmetry. Retrograde urethrography and micturating cystourethrography wereperformed only if the patient developed obstructive voiding problems or presented with a flow rate below 15 ml/second. Follow-up was done at regular intervals for 6–18months. Any symptoms pertaining to recurrence,including reduced stream of urine, retention of urine, burning micturation, were noted. The procedure was considered successful if the patient did not report any voiding difficulty and where maximum flow rate >15 ml /second for a voided volume of at least 150 ml.

RESULTS

Mean age of patients at presentation was 43.8 years with a range of 9–years. The mean duration of symptoms was 9.65 months. The baseline characteristics of the patients regarding etiology, type, location and length are shown in Table 1. We foundthat decreased urine flow and increased frequency, followed by dysuria, nocturia and acute retention,were the most common symptoms in case of anterior urethral stricture.

The overall success rate in our study using Ho-laser urethrotomy and intralesional tetra-inject was 82%.The table shows 9 recurrences from a total of 50 patients (18%). Of these, 8 were seen in 1–3 cm length strictures, while 1 was seen in >3 cm. No recurrence was observed where the stricture length was <1 cm.

The recurrence rate in 1–3 cm and >3 cm stricture categories was 18.2% (8 recurrences in 44 patients) and 33.3% (1 reccurence in 3 patients) respectively; the difference being non-significant (pvalue 0.450). On applying the Chi square test the difference in recurrence in terms of etiology, location and

Table 1. *Distribution of recurrence with respect to various stricture characteristics*

S. no.	Characteristic	Subtype	Total (50)	Recurrence (09)
01.	Etiology			
		Traumatic	22 (44%)	07 (31.2%)
		Inflammatory	05 (10%)	00
		Iatrogenic	05 (10%)	01 (20%)
		Idiopathic	18 (36%)	01 (5.5%)
02.	Type			
		Primary	34 (68%)	04 (11.8%)
		Secondary	16 (32%)	05 (31.3%)
03.	Location			
		Penile	02 (04%)	00
		Bulbomembranous	46 (92%)	08 (17.4%)
		Posterior	02 (04%)	01 (50%)
04.	Length			
		<1 cm	03 (06%)	00
		1-3 cm	44 (88%)	08 (18.2%)
		>3 cm	03 (06%)	01 (33.3%)

Table 2. *Mean peak flow rates (ml/second)*

	Preoperative	Postoperative
In cases with recurrence	5.7	7.8
In non-recurrent cases	4.6	15.3

length was not found to be statistically significant (pvalues 0.076, 0.390, and 0.450 respectively). Applying Fisher's Exact test yielded no statistically significant difference in recurrence between the primary and secondary cases (p value 0.124). Mean peak flow rates in both groups are depicted in Table 2.

DISCUSSION

Internal urethrotomy has found an important place in the management of urethral stricture disease since the 1980s.Unfortunately, this modality have been associated with a significant incidence of stricture recurrence. Pansadoro and Emiliozzi (1996) reported curative success rates of internal urethrotomy to be approximately 30–35% [11]. This variable experience has prompted urologists to explore alternative methods to improve outcomes.The addition of laser to the field of urethral strictures did not significantly improveresults. As reported by Nissel et al., the success rate of Nd: YAG laser was 50% and that of KTP 59–61% [12]. The introduction of Holmium laser as a treatment modality for urethral stricture disease produced good results. Kural et al. [13], in their study of 13 patients, reported a success rate of 69%,while Matsuoka et al. [14], in a study on 31 patients reported a success rate of 74%.

In an attempt to improve the results of OIU, various intralesional agents have been investigated. In our study, we injected tetra-inject (Triamcinolone, Mitomycin, Hyaluronidase, N-acetyl cysteine) intralesionally after holmium laser urethrotomy, yielding a beneficial outcome in a <3 cm urethral stricture.
Mazdak et al. in 2009 reported a study of 25 patients treated by internal urethrotomy and intraurethral submucosal Triamcinolone injection [15]. Recurrence was observed in 5 out of 24 patients (21.7%), whereas 11 among 21 patients (50%)treated by internal urethrotomy alone reported recurrence. Kumar et al. [5] in 2012 studied 50 patients (stricture length <3 cm) treated byholmium laser with Triamcinolone (80 mg) under spinal anaesthesia. The overall recurrence rate was 24%. The success rate in patients with strictures less than 1 cm in length was 95.8%, whereas that in strictures of between 1 and 3 cm in length was 57.7% (p = 0.002) [5].
Mazdak et al. in 2007 investigated 40 patients treated with urethrotomy with and without Mitomycin C [6]. 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. Mitomycin acts by inhibiting DNA synthesis by cross-linking DNA between adenine and guanine. It is useful in delaying the healing process by preventing replication of fibroblast and epithelial cells and inhibiting collagen synthesis.
Chung et al. studied 120 patients who underwent OIU for urethral stricture [8]. Recruited patients were randomly divided into two groups: group A and B. Patients in group A (60 patients) received HA/CMC (hyaluronidase and carboxymethylcellulose) instillation and patients in group B (60 patients) received lubricant instillation after internal urethrotomy [8]. Among 120 initial participants, 53 patients in group A and 48 patients in group B had completed the experiment. The recurrence of urethral stricture was observed in 5 cases (9.4%) in group A and 11 (22.9%) in group B (p = 0.029). This mechanism intreatment of urethral stricture is not entirely elucidated, but Hyaluronidase ameliorates pulmonary fibrosis and is also used in treatment of hypertrophic scar and keloid. The mechanism is supposed to be recruitment of autologous MSC-like cells to the lungs and the decrease of TGF-b production and collagen deposition [16]. In treatment of hypertrophic scar and keloid, intralesional injection decreases fibroblast proliferation, collagen and glycosaminoglycan synthesis and suppresses pro-inflammatory mediators in the wound healing process [17].
There has been no previous study of the use of N-acetyl cysteine in urethral strictures. Earlier it has been used as an anti-fibrotic agent in the

treatment of idiopathic pulmonary fibrosis, with proven inhibition of collagen synthesis in rat cardiac and hepatic fibroblasts [10].

The overall success rate in our study was 82%. In <1 cm length strictures the success rate is 100%, in 1–3 cm 82% and >3 cm is 67%. Thus, the combination of these four agents – Triamcinolone, Hyaluronidase, Mitomycin C and N-acetyl cysteine Tetra-inject is an effective treatment for short segment (upto 3 cm) urethral strictures.

CONCLUSIONS

Holmium laser urethrotomy with intralesional injection of tetra-inject (Triamcinolone, Mitomycin C, Hyaluronidase, N-acetyl cysteine) is a safe and effective minimally-invasive therapeutic modality for short segment urethral strictures. The overall success rate in our study using Ho-laser urethrotomy and tetra-inject was 82%, compared to a historical control rate of 60 to 70% [2, 3].

Thelimitation of the study is its non-comparative nature. However, compared to the results of Ho-laser urethrotomy obtained from previous studies [13, 14] adding Tetra-inject has produced encouraging results.The modest number of patients with a relatively short follow-up period is another limitation. Our results requirefurther verificationby a randomised study ofa larger cohort.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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