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Effect of Mitomycin C on Anterior Urethral Stricture Recurrence after Internal Urethrotomy

Hamid Mazdak [a,*], *Iraj Meshki* [a], *Fatemeh Ghassami* [b]

[a] *Department of Urology, Azahra Hospital, Isfahan Medical University, Isfahan, Iran*
[b] *East Sage Investigative Company and Isfahan Medical University, Isfahan, Iran*

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Abstract

Objectives: Urethral stricture is one of the oldest known urologic diseases and remains a common problem with high morbidity. Internal urethrotomy refers to any procedure that opens the stricture by incising or ablating it transurethrally. The most common complication of internal urethrotomy is stricture recurrence. The curative success rate of internal urethrotomy is approximately 20%. Mitomycin C has antifibroblast and anticollagen properties and in sporadic reports of animal and clinical studies it has increased the success rate of trabeculectomy and myringotomy. This study evaluated the efficacy of mitomycin C in the prevention of anterior urethral stricture recurrence after internal urethrotomy.

Patients and methods: Forty male patients with anterior urethral strictures were randomized to undergo internal urethrotomy with or without urethral submucosal mitomycin C injection. Using general anaesthesia, the urethrotomy was performed under direct vision. Mitomycin C (0.1 mg) was injected submucosally at the urethrotomy site in 20 patients. The patients were re-evaluated after 6 mo and the stricture recurrence rate was compared between the two groups (χ^2 analysis).

Results: Urethral stricture recurred in 2 patients (10%) in the mitomycin C-treated group and in 10 patients (50%) in the other group. This difference in stricture recurrence between the two groups was statistically significant ($p = 0.006$).

Conclusions: To our knowledge, this is the first prospective, randomized, clinical trial to evaluate the efficacy of mitomycin C application in internal urethrotomy. Submucosal injection of mitomycin C significantly reduced stricture recurrence after internal urethrotomy. Further investigations are warranted to confirm its efficacy and safety.

* Corresponding author. No. 93, Boostan Alley, First Apadana Street, Isfahan, Iran.
Tel. +98 31 16618333; Fax: +98 31 16700298.
E-mail address: mazdak@med.mui.ac.ir (H. Mazdak).

1. Introduction

Urethral stricture is one of the oldest known urologic diseases and remains a common problem with high morbidity [1]. Injuries to the urethral epithelium or the underlying corpus spongiosum may result in a scar that can cause an anterior urethral stricture [1]. Some anterior urethral strictures are the result of trauma (usually straddle trauma) [1,2]. The incidence of iatrogenic strictures and those secondary to balanitis xerotica obliterans seems to be on the rise. Gonorrheal strictures, on the other hand, are vanishing. However, in many cases of anterior urethral stricture disease, the aetiology remains unknown [1].

Internal urethrotomy refers to any procedure that opens the stricture by incising or ablating it transurethrally to allow the scar to expand. The goal is for the resultant larger calibre to be maintained after healing [1].

There is confusion in the literature regarding the curative success rate of internal urethrotomy. A recent report by Santucci and McAninch [3], using actuarial techniques, showed the curative success rate of internal urethrotomy to be approximately 20%. Because of this dismal success rate, several techniques have been used to oppose the process of wound contraction and to prevent stricture recurrence. They include indwelling Foley catheter, home self-catheterisation, and urethral stents. Unfortunately, these methods have complications and often the stricture inevitably recurs unless the procedure is continued indefinitely [1].

Mitomycin C has antifibroblast and anticollagen properties [4] and in sporadic reports of animal and clinical studies it has increased the success rate of trabeculectomy for glaucoma [5–7] and myringotomy for otitis media [8–11].

This study evaluated the efficacy of mitomycin C in preventing anterior urethral stricture recurrence after internal urethrotomy.

2. Patients and methods

Forty male patients with bulbar urethral strictures were randomized to undergo internal urethrotomy with or without urethral submucosal mitomycin C injection. Preoperative evaluation included a complete history and physical examination, urine culture, and retrograde urethrography. All patients had a history of straddle injury or other blunt perineal trauma. The exclusion criteria were a stricture length of >1.5 cm on urethrography, benign prostate hypertrophy, posterior urethral stricture, and a history of any previous therapeutic procedure. All preoperative infections were treated with antibiotics.

Under general anaesthesia and using a 20F Wolf urethrotome, urethrotomy was performed under direct vision with a cold-knife incision of the stricture at the 12 o'clock position by a single surgeon (H.M.). Before incising the mucosa, 0.1 mg mitomycin C (in 2 ml distilled water) was injected submucosally at the planned urethrotomy site in four quadrants (1, 5, 7, and 11 o'clock positions) using a 22-gauge cystoscopic needle in 20 patients. The other 20 patients did not undergo submucosal injections. After the procedure, an 18F or 20F indwelling catheter was left for 5 d.

Retrograde urethrography was performed every 6 mo after the internal urethrotomy or as soon as patients complained of obstructive voiding symptoms.

Relative frequency of stricture recurrence was compared between the two groups by χ^2 analysis using SPSS software. The Student *t* test was used to compare age and preoperative stricture length between the two groups.

3. Results

Follow-up data were available for all patients. Mean follow-up period was 15 mo (range: 6–24 mo). Mean patient age was 29.8 yr (range: 15–70 yr) and 29.2 yr (range: 11–66 yr) in the mitomycin C-treated and the untreated groups, respectively. Mean stricture length as measured on retrograde urethrography was 0.76 mm (range: 0.5–1 mm) and 0.74 mm (range: 0.5–1 mm) in the mitomycin C-treated and the untreated groups, respectively. Mean calibre of the stricture as measured on retrograde urethrography was 1.2 mm (range: 1–1.5 mm) and 1.3 mm (range: 1–1.7 mm) in the mitomycin C-treated and the untreated groups, respectively. There were no statistically significant differences with regard to patient age and stricture length and calibre and follow-up period between the twp groups (Table 1).

Urethral stricture recurred in 2 patients (10%) in the mitomycin C-treated group and in 10 patients (50%) in the untreated group. The χ^2 analysis showed that this difference in stricture recurrence between the two groups was statistically significant ($p = 0.006$; Table 2). Mean length and calibre of

Table 1 – Mean ± standard deviation of age and stricture length and calibre before surgery

Groups	Age, yr	Stricture length, cm	Stricture calibre, mm
With mitomycin C	29.8 ± 14.8	0.76 ± 0.15	1.2 ± 0.1
Without mitomycin C	29.2 ± 13.9	0.74 ± 0.17	1.3 ± 0.2
p	0.896	0.621	0.751

Table 2 – Number and percent of recurrences in mitomycin C-treated and untreated groups

Outcome	Treatment			
	With mitomycin C		Without mitomycin C	
	No.	%	No.	%
Recurrence	2	10	10	50
Without recurrence	18	90	10	50
Sum	20	100	20	100

recurrent strictures at the end of the study were 0.71 mm (range: 0.69–0.73 mm) and 1.3 mm (range: 1.2–1.4 mm) in the two mitomycin C-treated patients and 0.84 mm (range: 0.5–1.1 mm) and 1.2 mm (range: 0.9–1.5) in the untreated patients.

Only one patient in the mitomycin C group with stricture recurrence developed obstructive symptoms before 6 mo.

4. Discussion

The urethrotomy procedure involves incising strictured and healthy tissues to allow the scar to expand (release of scar contracture) and the lumen to heal enlarged [1].

With epithelial apposition, wound healing occurs with primary intention. Internal urethrotomy does not provide an epithelial approximation but rather aims to separate the scarred epithelium so that the healing occurs by secondary intention. Although the exact pathophysiology of the healing process following internal urethrotomy remains poorly understood, it is assumed that if epithelialisation progresses completely before wound contraction, the internal urethrotomy may be a success but if wound contraction significantly narrows the lumen before completion of epithelialisation, the stricture recurs [1]. Any drug or procedure that can delay wound contraction may thus decrease the likelihood of stricture recurrence.

Mitomycin C is an alkylating antineoplastic antibiotic derived from *Streptomyces caespitosus*. It acts by cross-linking DNA between adenine and guanine, thereby inhibiting DNA synthesis. It also suppresses cellular RNA and protein synthesis and is not cell cycle specific. Therefore, it is useful in delaying the healing process by preventing replication of fibroblasts and epithelial cells and inhibiting collagen synthesis [12]. It is proposed that it can delay wound contraction.

Other studies on mitomycin C have shown its efficacy in preventing fibroblast proliferation and development of fibrosis after myringotomy and trabeculectomy, thus improving the success rate of these procedures [8,13].

To our knowledge, this is the first prospective, randomized, clinical trial to evaluate the efficacy of mitomycin C application in internal urethrotomy. Submucosal injection of mitomycin C significantly reduced the stricture recurrence rate after internal urethrotomy. Admittedly, our follow-up period is too short to draw firm conclusions regarding the long-term success rate and many strictures may recur within 2 yr following internal urethrotomy. However, it would be quite unlikely for the difference in the recurrence rates in the two groups to completely disappear at longer term follow-up.

Although flexible endoscopy has proved superior to retrograde urethrography in the follow-up, we opted for the latter because of its less invasive nature and the unavailability of outpatient flexible endoscopy in our department (and hence the need to admit the patient to the hospital for urethroscopy in the operating theatre).

In view of its efficacy, ease of application, and safety, mitomycin C application can replace the use of stents or long-term catheters following internal urethrotomy. Further investigations are warranted to confirm its efficacy and safety in this context.

5. Conclusions

To our knowledge, this is the first prospective, randomized, clinical trial to evaluate the efficacy of mitomycin C application in internal urethrotomy. Submucosal injection of mitomycin C significantly reduced the stricture recurrence rate after internal urethrotomy. In view of its efficacy, ease of application, and safety, it can replace use of stents or long-term catheters following internal urethrotomy. Further studies involving larger numbers of patients will hopefully better elucidate the safety and efficacy of this approach.

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Editorial Comment

Enzo Palminteri,
Centre of Urethral and Genitalia Surgery, Arezzo, Italy
enzo.palminteri@inwind.it

This article develops the old subject about the results of internal urethrotomy in the patient with urethral strictures [1].

All patients had a history of straddle injury, but in our hands traumatic strictures have proven unsuitable to be resolved endoscopically because of the hard scar. In the preoperative and postoperative evaluation the authors do not use the standardised investigations for urethral strictures, such as uroflowmetry and voiding urethrography. The follow-up period is too short and patients were not followed with urethroscopy to check the treated urethral tracts; therefore, we are missing the most interesting direct information on the urethral lumen.

They have described an internal incision at the 12 o'clock position although mitomycin has been injected in the rest of the untouched scarred area at the 1, 5, 7, and 11 o'clock positions but not in the incised place. Considering that we do not have a postoperative urethroscopic check, many doubts remain about the destiny of the untouched scarred area.

The antifibrotic effects of mitomycin on urethral tissues should be verified by histologic tests although we know that urethral biopsies could cause a stricture.

We highlight the complications of intravesical chemotherapy in the form of drug cystitis that occurred in oncologic patients treated with mitomycin and due to bladder wall calcification [2]. With regards to the supposed safety of the mitomycin, the authors do not mention the effect of the drug on urethritis with urethral wall calcification.

As the authors indicate, today the exact pathophysiology of urethral stricture disease and of the healing process following urethral treatments remains poorly understood. To better understand the histologic processes, we need more detailed studies. This article points out the necessity of studying drugs that stop the evolution of the urethral fibrotic mechanisms and support the surgical treatments in urethral repairs [3,4].

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