

Prospective comparative study of visual internal urethrotomy and visual internal urethrotomy with intralesional triamcinolone and mitomycin c in treatment of stricture urethra

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Abstract

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. 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%. Visual internal urethrotomy was done in usual manner using cold knife. Injection is prepared by diluting triamcinolone 40mg, mitomycin 2mg in 5-10mL of saline according to length of stricture and was injected intralesional at the site of urethrotomy using William's endoscopic needle. At every site 1-2mL was injected. After confirming free passage of cystoscope into the bladder, an 16 or 18 Fr foley's catheter was left in place for 2-3 days. In our study total of 7 patients lost follow up and among remaining 37 patients total of 10 patients had recurrence, 8 patients in group A had recurrence at end of 6 months, 1 patients at 3 months after procedure and 7 patients at 6 months after procedure whereas in group B only 2 patients had recurrence 1 at 3 months and 1 at 6 months post procedure, both groups were statistically comparable with respect to age stricture length, site and etiology. From our study we can conclude that, Injection of both triamcinolone, mitomycin C at stricture site after VIU can be considered as safe and effective adjuvant modality compared to VIU alone for short term management of stricture urethra.

Keywords: Visual internal urethrotomy, intralesional triamcinolone, stricture urethra

Introduction

Urethral strictures have plagued men since antiquity, with descriptions in Indian literature dating as far back as 1000 BC. Stricture disease of urethra is always a challenge for almost all practicing urologists. Strategies to care for men with anterior urethral strictures depend less on pathophysiologic mechanism and more on accurate determination of the anatomic characteristics of the stricture including its location, length, luminal diameter and previous treatment. Urethral stricture disease is scarring process involving epithelium and the spongy erectile tissue of the corpus spongiosum, Patients who have urethral strictures most commonly present with symptoms such as obstructive voiding symptoms or with UTI (urinary tract infections) such as prostatitis and epididymitis. For appropriate treatment plan to be devised, the important factors to be determined are the length, location, density of

spongiofibrosis and depth. Treatment options available are dilatation, DVIU, placement of stent, single or various stages of urethroplasty and lasers.

Management by endoscopy is routinely done first for short bulbar urethral strictures before other modality of treatment. The success rate of single DVIU is reported to be 20 to 60%^[1]. The urethrotomy procedure involves incision through the scar to healthy tissue to allow the scar to expand (release of scar contracture) and the lumen to heal enlarged. The goal is to have the resultant larger luminal caliber which has to be maintained after healing. Urethrotomy separates the scarred epithelium and healing occurs by secondary intention. If wound contraction takes place before full epithelialisation, it significantly narrows lumen and result in recurrence. Evaluations by Pansadoro and Emiliozzi (1996) and others showed the curative success rate of direct visual internal urethrotomy to be approximately 30% to 35%^[2]. Mitomycin C with its anti-fibroblast and anti-collagen activity when injected submucosally has shown to decrease risk of recurrence after an urethrotomy^[3]. Injection of steroid triamcinolone intralesional following internal urethrotomy, gives better result than internal urethrotomy alone^[4]. It enhances endogenous production of collagenase and decreases formation of scar and obviates scar formation. In this study we analyzed the outcome of VIU with injection of steroid (triamcinolone) & mitomycin c in terms of urethral stricture recurrence when compared to VIU alone for a follow up period of 6months.

Methodology

After receiving ethical committee approval from our institution, around 44 patients with stricture of urethra who are symptomatic and presenting at our hospital who fulfil inclusion criteria were selected. Data was collected in pretested proforma.

Here patients are divided into two groups A and B in first group only VIU is done and in second group VIU along with INTRALESIONAL INJECTION OF TRIAMCENOLONE AND MITOMYCIN C is done. Postoperative results were compared between 2 groups.

Complete history, Physical examination, Examination of genitalia and perineum, USG KUB, Retrograde urethrography, routine investigations for surgery such as complete blood count, HIV, HbsAg, blood urea, serum. Creatinine, serum. Electrolytes.

Optical internal urethrotomy was done in usual manner using cold knife. All patients were given prophylactic antibiotic inj. Gramocel (ceftriaxone).

1gm iv stat 30 minutes before procedure, under all aseptic precautions spinal anaesthesia given patient placed in lithotomy position parts painted and draped, Cystoscopy using 20 fr sheath and ureteric catheter of 5 fr passed through stricture portion into the bladder. Using Sachse urethrotome and cold knife internal urethrotomy done at 12 o, clock position, bladder entered and thorough cystoscopy done, Injection is prepared by diluting triamcinolone 40mg, mitomycin 2mg in 5-10mL of saline according to length of stricture and was injected intralesional at the site of urethrotomy using William's endoscopic needle. At every site 1-2mL was injected. After confirming free passage of cystoscope into the bladder, an 16 or 18 Fr silicone catheter was left in place for 3-5 days.

Post procedure evaluation

It 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 1 month, 3 months and 6 months post procedure. Any symptoms pertaining to recurrence were noted as reduced stream of urine, retention of urine, and burning micturition. 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.

Inclusion criteria

All patients with symptomatic short segment (less than 2 cm) anterior urethral stricture.

Exclusion criteria

1. Patients with completely obliterated urethral stricture.
2. Patients with BXO.
3. Patient who has not given consent for procedure.
4. Patients with recurrent urethra stricture.
5. Strictures more than 2 cm in length.

After the procedure patients were catheterized for 2 days, Foley's was removed on post op day 3 in both groups patient were followed up for 1,3 and 6 months after procedure and evaluated based on history and uroflowmetry, uroflowmetry was done in all patients at 6 months post-surgery irrespective of recurrence of symptoms where as in patients with recurrence of symptoms uroflowmetry was done at time of recurrence and AUG was done in follow up period if the patient suffer by difficulty in voiding symptoms.

When patients presented with symptoms suspicious for recurrence, such as thin stream of urine, straining to void and burning micturition, uroflowmetry was done. The treatment was reported successful if they don't complain any voiding symptoms and had a PFR >10ml/sec. Repeat ASU was done in patients with recurrence i.e., those with voiding complaints and PFR <10ml/sec.

Results

Table 1: Comparison of Group A and Group B by site

Site	Group A	%	Group B	%	Total	%
Bulbar	21	95.45	19	86.36	40	90.91
Penile	1	4.55	3	13.64	4	9.09
Total	22	100.00	22	100.00	44	100.00

Chi-square with Yates's correction = 0.2750 P = 0.6000

- In group A 21 patients and in group B 19 patients had stricture in bulbar urethra.
- I.e., 95.45% patients in group a and 86.36% in group b has stricture in bulbar urethra and P value is 0.6000, hence it can be concluded that there is no statistical difference between proportions of study groups in relation to location of stricture.

Table 2: Comparison of Group A and Group B with mean Uroflowmetry (Post OP) by independent t test

Groups	n	Mean	SD	SE	t-value	P-value
Group A	17	20.22	13.02	3.27	-1.22794	0.113832
Group B	20	25.36	12.38	2.77		

- In our study mean PFR in group A is 20.22 and in group B is 25.36.
- P valve is 0.113832 which is more than 0.005 which is statistically insignificant hence it can be concluded that there is no improvement in peak flow rate by performing VIU with intralesional triamcinolone and mitomycin C when compared to VIU alone.

Table 3: Comparison of Group A and Group B by recurrence of after 3 months

Recurrence of after 3 months	Group A	%	Group B	%	Total	%
No	17	94.44	19	95.00	36	94.74
Yes	1	5.56	1	5.00	2	5.26
Total	18	100.00	20	100.00	38	100.00
Chi-square with Yates's correction = 0.0000 P = 1.0000						

Table 4: Comparison of Group A and Group B by recurrence of after 6 months

Recurrence of after 6 months	Group A	%	Group B	%	Total	%
No	10	58.82	19	95.00	29	78.38
Yes	7	41.18	1	5.00	8	21.62
Total	17	100.00	20	100.00	37	100.00
Chi-square with Yates's correction = 5.1220 P = 0.0240*						

*p<0.05

- In our study at end of 3 months 4 patients in group A and 2 Patients in group B had lost follow up and 1 among 18 patients in group A had recurrence and 1 among 20 patients in group B had recurrence, P value at end of 3 months is 0.469 it is not statistically significant.
- At the end of 6 months a total of 5 patients in group A had lost follow up and 2 patients in group B had lost follow up i.e., total of 7 patients in our study had lost follow up at end of 6 months and at 6 months 7 more patients had recurrence in group A and 1 more patient in group B had recurrence.
- Since the p-value is 0.024, i.e. lesser than 0.05 (or 5 percent), it can be concluded that there is difference between the means and proportions of study groups in relation to time taken for recurrence of stricture after intervention at 6 months after procedure
- By conventional criteria the association between the study groups and recurrence of stricture after intervention is considered to be statistically significant at 6 months after procedure.

Table 5: Comparison of Group A and Group B by overall recurrence of stricture

Overall recurrence of stricture	Group A	%	Group B	%	Total	%
No	9	52.94	18	90.00	27	72.97
Yes	8	47.06	2	10.00	10	27.03
Total	17	100.00	20	100.00	37	100.00
Chi-square with Yates's correction = 4.6582 P = 0.0310*						

*p<0.05

- In our study total of 10 patients had recurrence 8 in group A and 2 patients in group B had recurrence at 6 months after intervention i.e., 47.06% patients in group A and 10% patients in group B had recurrence at 6 months with P value of 0.0310 which is statistically significant.
- Since P value is 0.0310 which is less than 0.05, it can be concluded that there is difference between the proportions of study groups in relation to recurrence as per stricture causes.
- By conventional criteria the association between the study groups and recurrence of stricture is considered to be statistically significant.
- In contrast, we can conclude that VIU with intralesional triamcinolone and mitomycin C injection Technique is superior to the visual internal urethrotomy Technique in terms of preventing recurrence of stricture with an Overall success rate of 52.94% in Group A and 90% in Group B at 6 months after intervention.

Discussion

Prevalence of stricture urethra in male is estimated to be 0.9%. Urethral stricture disease is a scarring disease leading to narrowing of the urethra due to scar tissue, leading to obstructive voiding symptoms. It is a common condition resulting in narrowing or obliteration of the urethral lumen and may involve any segment of the urethra from the urethral meatus to the bladder neck.

Approximately 50% of urethral strictures occur in the bulbar urethra, 30% in the penile urethra, and the remainder in a combination of the two.

The most common causes of urethral stricture are idiopathic causes, iatrogenic causes (catheterization and transurethral surgery), inflammatory causes and trauma (pelvic fracture). VIU has low success rates for the treatment for urethral stricture whereas Open surgery excision and primary anastomosis has long-term cure rates of 90-95%, Urethroplasty has higher success rate but is less popular because it is costly, technically more demanding, and more time-consuming procedure with more morbidity than VIU, but internal urethrotomy is a simple procedure in treatment of stricture disease and is followed as first treatment modality, though the success rate is 33% by 10 years which was lower to urethroplasty on long follow up.

Many studies composed of reviews series evaluating short-term outcomes of VIU shown success rates ranging from 22% to 100%.

Strictures of length less than 1 cm, located in the bulbar urethra and have a larger urethral lumen at the time of treatment are shown to produce better results when treated with VIU. Patients with long strictures (>2 cm), those with strictures in penile urethra or membranous stenosis, or multiple strictures usually show poor response to VIU and has high recurrence rates. Internal urethrotomy involves incision of stricture setting apart fibrosed epithelium so that healing occurs by secondary intention, for VIU to be successful epithelialization should occur completely before wound contraction, if wound contraction occurs before completion of epithelialisation it results in recurrence.

Thus, any procedure or drug which delays contraction of wound would help in decreasing the recurrence of stricture.

Many studies have evaluated the effect of antifibrotic agents on urethral strictures, such as hyaluronidase, botulinum toxin A, mitomycin C, somatostatin, glucocorticoids and somatostatin analogs, halofuginone.

Steroids are hypothesized to reduce scar formation by reducing the rate of collagen synthesis in fibroblasts during the wound healing process, steroids have anti-inflammatory action and at level of wound tissue they also reduce collagen production and also decrease fibroblast proliferation and mitomycin c which is antitumor antibiotic is also found to inhibit fibroblast proliferation and scar formation, hence both drugs are found to delay wound contraction and also decrease scar formation.

In our study we used these two drugs given intralesional using Williams cystoscopic needle following VIU to know efficacy of these drugs in reducing stricture urethra recurrence.

Mitomycin C is derived from bacteria *Streptomyces caespitosus*. It inhibits DNA synthesis by cross-linking DNA between adenine and guanine. It also suppresses cellular RNA and protein synthesis. By this way, it inhibits collagen synthesis and also prevents replication of epithelial cells and fibroblasts resulting in delaying in healing.

Estrem et al and Fontana et al showed that mitomycin c has better success rates after myringotomy and trabeculectomy by preventing fibroblast proliferation and fibrosis^[5, 6].

Mazdak et al. showed that injection MMC injected into urethra submucosally had low rates of recurrence of stricture.

Vanni et al in his study reported significant reduction in recurrence of urethral stricture with intralesional mitomycin C, Kumar et al. also recorded only 20% of cases had recurrence after intralesional injection of mitomycin.

LiquatAli et al showed there is decrease in recurrence by using mitomycin C^[7].

Nabi and Dogra et al study revealed, use of intralesional steroid and Nd:YAG laser in treatment of traumatic prostatic and supra prostatic strictures. In this study mean follow-up period was 23 months, all 3 patients were voiding well, were asymptomatic and at 3 months had normal results on cystoscopy, urethroscopy and uroflowmetry^[8].

Hosseini et al. in his study of VIU with clean intermittent catheterization with or without triamcinolone ointment showed that at follow-up of 12 months, recurrence rate was 30% in the triamcinolone group and was 44% in the other^[9].

A randomized control trial of 50 patients by Mazdak et al showed decreased recurrence rates in triamcinolone (dose-40mg) group (21.7%) compared to control group (50%) after mean follow-up time of 13.7±5.5 months^[10].

Tabassi et al in his double-blinded, placebo-controlled, randomized study including 70 patients showed that the triamcinolone group had significantly decreased time to recurrence, months 8.08±5.05 compared to control group 3.6±1.59 months without evidence of complications from steroid injection^[11].

Zhang et al in his systematic review of 8 studies showed that, in 203 patients, VIU with corticosteroids have statistically significant decreased time to recurrence compared to VIU alone^[12].

In our study follow up period was 6 months from last intervention i.e., VIU or VIU with intralesional triamcinolone and mitomycin c, to assess recurrence rate between two groups at end of 6 months,

For assessing the recurrence after VIU we have to follow up for long term. As it is found that every year success rate decreases by of 10 to 20 % per year after VIU, which may continue till up to five years. Following VIU recurrence rate of 35% to 60% have been reported.

Holm -Nielsen and colleagues reported 50% to 75% recurrence during a two year follow up^[13].

In our study overall recurrence was 47.06% in VIU group and 10% in VIU with intralesional triamcinolone and mitomycin C group.

According to Naude et al, most of the recurrence occurs during 3-12 months after visual internal urethrotomy^[14].

A study conducted in PGI Chandigarh using VIU with intralesional triamcinolone, mitomycin C and hyaluronidase showed overall recurrence rate after first OIU is 19.4% (20 out of 103 patients), that is, a success rate of 80.6%. Overall recurrence rate after second procedure was 5.8% (6 out of 103 patients), that is, a success rate of 94.2%.

In our study recurrence in the control group(A) was 47.06% compared to 10% in triamcinolone and mitomycin C group group(B). There was significantly decrease in recurrence rate in group B (mitomycin C and Triamcinolone group) compared to group.

A. Recurrence rate between the groups in our study reached statistically significant value (p=0.0310).

In our study 10 patients had recurrence repeat VIU with advice of clean intermittent self-catheterisation was done for 2 patients, urethroplasty with end to end anastomosis is planned for 2 patients, urethroplasty with buccal mucosal graft is advised for 1 patient, rest 4 patients were not willing for further management in our hospital.

Conclusion

So, from our study we can conclude that, Injection of both triamcinolone, mitomycin C at stricture site after VIU can be considered as safe and effective adjuvant modality compared to VIU alone for short term management (6 months) of stricture urethra.

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