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ENDOLUMINAL AND ENDOSCOPIC MANAGEMENT OF URETHRAL STRICTURE

Martin SY Mak[1], James HL Tsu[2], Wayne Lam[1]

[1]Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[2]Division of Urology, Department of Surgery, Queen Mary Hospital, Hong Kong SAR, China

Corresponding Author: lamwayne@hku.hk

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ABSTRACT

Background and Objective

Urethral stricture in the male population is one the oldest described urological condition. Significant variability in clinical practice means that standardized management of urethral stricture remains controversial. Since the first description of modern-day direct visual internal urethrotomy (DVIU) by Sachse in 1974, this, alongside with various endoscopic treatment techniques, continues to be by far the most commonly performed procedures for the management of urethral strictures. This article aims to summarise and review the latest literature on endoscopic management of urethral strictures.

Material and Methods

We conducted a Pubmed and Medline search to identify publications related to endoscopic management of male urethral strictures between 1980 and 2019. Preference was given to recent and larger studies. Original research articles, review articles, abstracts, and opinion articles were included. Keywords used for the search were “male urethral stricture,” “urethrotomy,” “DVIU,” “urethral dilation,” “urethral stent”, “intermittent self-catheterisation”, “mitomycin C”, “steroids”, and “urethroplasty.”

Recent Findings

The long-term efficacy of endoscopic management of urethral stricture is poor. Recent novel advances with adjunct treatment have yet to demonstrate improvement in long-term treatment success. Repeated endoluminal or endoscopic treatments, especially for long and recurrent urethral strictures, are ineffective. They appear to delay patients from receiving definitive treatments, and potentially increase complexity and decrease the success rate of any future urethral reconstructive treatment.

Summary

There is overwhelming evidence to suggest limited long-term efficacy of endoluminal or endoscopic treatments for urethral stricture. Novel adjunctive therapies showed promising initial results, but none have yet to demonstrate durable efficacy. Endoscopic treatment of urethral stricture disease should only be reserved for patients who are not willing to undergo reconstructive surgery, or not fit for anesthetics.

Key Words: *Urethral stricture; urethral dilatation; optical urethrotomy; direct internal visual urethrotomy; endoscopy*

Urethral stricture is the scarring of subepithelial tissue of the corpus spongiosum that results in the narrowing of the urethral lumen.[1] As constriction progresses over time, it results in the development of predominantly voiding lower urinary tract symptoms (LUTS).[2] This is associated with other potentially significant consequences that may require urgent urological input, including acute urinary retention, periurethral abscess, hydronephrosis, and renal failure.[3] Previous studies have demonstrated that urethral stricture not only has a profound impact on the patient's quality of life,[4–6] but also poses significant economic burden to society.[7]

Stricture may develop at any site along the entire urethra. The location of stricture highly relates to its etiology. According to a retrospective study of all strictures that had been reconstructed at a single high-volume centre, vast majority of strictures were anterior (92.2%), with most occurring in the bulbar urethra (46.9%), followed by penile (30.5%), penile and bulbar (9.9%), and panurethral (4.9%) strictures. Causes of strictures were iatrogenic in 38.6%, idiopathic in 35.8%, lichen sclerosus in 13.4%, and trauma-related in 10.8%. The main iatrogenic strictures were from catheterization (16.3%), previous hypospadias repair (12.2%), and in patients following transurethral surgery (9.1%).[8]

The management of urethral strictures has been challenging for centuries. Urethral dilatation was first described by Shusruta in 600 BC, [9] and it remains a common practice in modern-day urology. 'Blind' internal urethrotomy has been first described 1855, [10] and Sachse further advanced the technique into the modern-day DVIU with endoscopic control in 1974.[11] Further refinements of endoscopic surgery for urethral stricture have developed since. In general, they usually involve either using a different energy source (such as holmium laser) to perform internal urethrotomy, or application of adjunct agents at the time of DVIU or dilatation to reduce the risk of reformation of scarring. However, data regarding the long-term efficacy using these techniques remains very limited.

Despite the growing consensus of its poor long-term efficacy especially for patients with long-segment or recurrent urethral stricture diseases, endoscopic management of urethral stricture continues to be the most commonly performed technique for urethral strictures today.[12–14] This article aims to summarize and provide a narrative review of the latest literature on the endoscopic management of urethral strictures.

METHODS

We conducted a Pubmed and Medline search to identify publications related to endoscopic management of male urethral structures between 1980 and 2019. Preference and priority were given to recent and larger studies. Original research articles, review articles, abstracts, and opinion articles were included. Keywords used for the search were "male urethral stricture," "urethrotomy," "DVIU," "urethral dilation," "urethral stent", "intermittent self-catheterisation", "mitomycin C", "steroids", "paclitaxel", "quality of life," "cost-effective," and "urethroplasty."

DIRECT VISUAL INTERNAL URETHROTOMY (DVIU)

DVIU is a procedure that involves endoscopic incision of scarred urethral tissue, thereby releases contracted scar tissue and expand the urethral lumen. The surgery usually involves the use of an endoscopic cold knife or a laser, under general or spinal anesthesia. For this treatment technique to be effective and durable, re-epithelialization across the incised portion of the urethra must proceed faster than wound contracture, otherwise, recurrence is inevitable.[15] DVIU provides a minimally invasive approach to achieve a patent urethra that would allow unobstructed voiding with minimal side effects. The procedure could be conveniently done as a day case with a very short learning curve. As such, DVIU is one of the most commonly performed procedures for urethral strictures amongst urologists.[12–14] However, the success rate of DVIU reported in the literature varies widely, ranging from 8 to 80%.[11,16–26] Such wide variation is likely due to discrepancy in study patient selection, duration of follow-up assessment, and methods to define success following treatment and recurrence of stricture.

The risk of stricture recurrence following DVIU has been reported to be greatest at 3–6 months,[17,27] with a very modest stricture-free rate of only 50–60% for up to 4 years of follow-up from one study.[17] However, stricture-free rates further reduce dramatically following repeated DVIU for urethral stricture recurrence.[16,20,22] After the second treatment, the stricture-free rate at

3 months was 30–50% at 24 months and 0–40% at 48 months. After the third treatment, the stricture free rates at 3, 6 and 24 months were astonishingly reported to be zero.[17] In another study conducted by Santucci et al., the stricture-free rates were also shown to be very poor when urethral stricture recurrences were treated with DVIU, with stricture-free rates after the first, second, third, fourth and fifth urethrotomy of 8%, 6%, 9%, 0%, and 0% respectively.[22] In contrast, urethroplasty has a stricture-free recurrence of 90–95%.[28,29] A recent randomized controlled trial compared open urethroplasty and endoscopic urethrotomy for recurrent bulbar urethral stricture found the need for re-intervention was lower in urethroplasty (16%) compared to urethrotomy (28%) at two years follow-up.[30] These studies suggest that the long-term stricture-free rate following DVIU is only very modest even after a single procedure. DVIU has been carried out inappropriately and excessively, most likely due to its convenience and familiarity. Early referral for urethral reconstructive surgery for many of these patients perhaps should be considered, which could have provided a more definitive cure with lesser long-term consequences.[31] However, DVIU still has an important role for patients who are not fit to undergo reconstructive surgery, in patients perhaps with a treatment-naive short segment stricture disease, or patients with short-segment recurrence following urethral reconstructive surgery.

Post-DVIU Catheterization

Urethral catheterization is routinely carried out by many urologists following DVIU. This is done assuming that the urethral catheter would act as a scaffold and allows the urethra to mould around it as the urethra heals, thereby minimizing the stricture recurrence. Perhaps the more reasonable indication of leaving urethral catheter in-situ following DIVU is to reduce the risk of early postoperative extravasation and infective complications.[33] However, both the practice of and optimal duration of urethral catheterization following DVIU have been controversial, ranging from no urethral catheterization at all to 6 weeks according to literature.[11,18,19,21,34,35]

Some reports found that leaving the urethral catheter in-situ for longer than 3–5 days was associated with increased recurrence.[36,37] Studies on the effects of the size of the urethral catheter on stricture recurrence rate is limited. Yuruk, E et al reported decreasing the catheter diameter from 22Fr to 18Fr significantly decreases stricture recurrence rates.[37] It is postulated that larger bore urethral catheters potentially exert greater pressure on the urethral wall, reducing blood flow and hindering the re-epithelialization process. This subsequently leads to the healing of the incised urethra with fibrosis, causing stricture recurrence.[38,39] Silicone catheters are generally preferred due to its comparatively more favorable biocompatibility, whereas latex catheters have been implicated in the etiology of urethral strictures due to its associated antigenicity property.[40]

Complications of DVIU

A recent meta-analysis of complications of cold-knife urethrotomy reported an overall complication rate was 6.5%, with the most common complications include impact on erectile function (5%), urinary incontinence (4%), extravasation (3%), urinary tract infection (2%), hematuria (2%), epididymitis (0.5%), urinary retention (0.4%), and the development of scrotal abscess post-operatively (0.3%).[41] The risk of erectile dysfunction is particularly common in patients with long and dense strictures requiring extensive incisions.[42,43] It is difficult to explain the exact mechanism for this, but deep urethral incisions, especially at 10 o'clock and 2 o'clock positions, carry risks of entering the corpus cavernosum, which has been postulated to induce erectile dysfunction.[5] Injury of the corpus spongiosum during DVIU can also result in the development of perineal hematoma and urethral hemorrhage.[44] Peri-operative infection has been reported to significantly increase stricture recurrence.[25] Thus, DVIU should be covered by prophylactic antibiotics. Risk factors of developing complications following DVIU include positive urine culture, history of urethral trauma, multiple strictures segments and long (>2 cm) strictures.[45]

URETHERAL DILATION

Urethral dilatation involves the use of sequentially sized instruments to radially dilate the urethra and gently stretch the scar tissue. This leads to the expansion of urethral lumen to restoring patency, without requiring traumatic shearing forces.[5,15] A major advantage of

using urethral dilatation to treat urethral stricture is that it can be done as a daycare procedure without the need of general or spinal anesthesia. It also requires a lesser degree of surgical expertise and equipment. A wide range of different types of urethral dilators available.

Graduated metal urethral dilating devices are commonly used, such as Van Buren, Beniquet, and Clutton's dilators. However, as they are inserted 'blindly' into the urethra, such procedures are associated with potential complications including bleeding, urethral perforation with extravasation, creation of a false urethral passage, fossa navicularis stricture, or rarely, rectal injury.[46,47]

To minimize these risks, endoscopically-guided or guidewire-assisted urethral dilatation has been developed. These include the use of urethral balloon dilators, S-shaped coaxial dilators, and Amplatz renal dilators.[48,49] Currently, there is no randomized controlled trial comparing the efficacy of urethral dilation and internal urethrotomy. No studies have demonstrated a significant difference between dilation and urethrotomy in terms of success rate and complication rate.[27,32]

To improve the efficacy of urethral dilatation, novel drug-coated balloon dilators (DCB) have been developed recently. A recent study investigated the use of a novel drug-coated balloon for urethral dilation to mechanically dilate a stricture while delivering paclitaxel (Optilume DCB). Paclitaxel is an anti-proliferative drug, which in theory reduces the production of collagen by the scarred collagen-rich connective tissue synthesized by smooth muscle cells.[50] Initial reports have been promising, with an anatomic success rate of 75% at 12 months without significant complications.[51] However, long-term and comparative data are lacking. An ongoing multi-centre, single-blind randomized controlled clinical trial comparing the use of Optilume DCB with DVIU or urethral dilatation may hopefully be able to further investigate the safety and effectiveness with this device.[52]

PREDICTORS OF STRICTURE RECURRENCE FOLLOWING ENDOLUMINAL OR ENDOSCOPIC URETHRAL STRICTURE TREATMENT

Various risk factors have been identified to be associated with high stricture recurrence rates following DVIU or urethral dilatations. For patients with urethral stricture length of over 1cm, the risk of stricture recurrence following urethral dilatation of DVIU has been demonstrated to be significantly higher.[36,53,55] Other factors associated with increased stricture recurrence risk include penile and membranous urethral strictures,[20,21,54] patients with strictures at multiple locations across the urethral length, [20, 55] those who have undergone previous urethral dilatations of DIVU,[22] or in patients with extensive periurethral spongiofibrosis.[1,56] Patients who are elderly, obese,[57] or had untreated pre-operative urinary tract infection[25] also have been reported to have a higher risk of urethral stricture recurrence following DVIU or urethral dilatations.

URETHRAL STENT

The use of permanent urethral stent following internal urethrotomy and dilatation was first introduced by Milroy et al in 1988.[58] Initial reports showed promising results, with 86–100% success rate for treating urethral stricture in the short term (<18 months) and a 42–90% success rate in the medium term (24–36 months).[59–63] However, long-term results (>10 years) were not as promising, with only a 13–45% success rate.[59,63,64] De Vocht et al also reported patient satisfaction 10 years after placement of the Urolume wall stent and found that only 2 of 15 patients were satisfied with the results after stenting.[64] It is associated with an unacceptably high stent-related complication in up to 86%.[20] These include perineal pain, dysuria, incontinence, post-void dribbling, recurrent urinary tract infections, stent migration and stent obstruction by stone encrustation & tissue ingrowth.[20,59,64,65] A study on urethral Urolume wall stent (AMS, Minnetonka, MI, USA) for recurrent bulbar urethral strictures in 60 patients over 12 years found that the reoperation rate was high at 45%. Of these patients, the commonest surgical interventions required were transurethral resection of obstructing stent hyperplasia (32%), urethral dilatation or urethrotomy for stent obstruction or stricture (25%) and endoscopic litholapaxy for stent encrustation or stone (17%).[59]

To reduce the aforementioned complications associated with permanent urethral stents, the use of temporary stents has been investigated. Such concept is based on the theory that insertion of a urethral stent

immediately following urethral dilatation or urethrotomy prevents contraction of the urethra during the healing process, and provides a scaffold for re-epithelization of urethral caliber.[66] Wong et al. demonstrated the efficacy of 3 month Memokath stent deployment in the management of recurrent urethral strictures with 78% (17/22) of patients remaining strictures free at a median follow-up of 23 month.[67] Jordan et al further investigated the durability of Memokath™ 044TW stent in a 1 year randomized trial. Their study found that urethral patency in stented patients was maintained significantly longer than patients in the control arm (median 292 vs. 84 days, $p < 0.001$) with lesser associated side effects.[68] However, such a technique should be used with caution. Horiguchi, et al. reported that a single application of temporary urethral stenting carries a high risk of complicating the stricture and requiring complex urethroplasty.[69]

Treatment of urethral stricture using permanent urethral stents should be discouraged, especially for patients who are considered to be candidates for formal urethral reconstructive surgery.

A Summary of Endoscopic or Endoluminal Treatments is outlined in Table 1 below.

ADJUNCTIVE THERAPY TO REDUCE RECURRENCE RATE

Intermittent Self-Catheterization

Intermittent self-catheterization was first reported by Lapides et al.,[70] in particular for patients with neurogenic bladder. This practice was later adopted for the management of urethral stricture by Lawrence et al.[71] Intermittent self-dilatation (ISD) allows raw, cut edges of urethral strictures to be splinted open regularly, thereby delaying the onset of symptoms and reducing the risk of recurrence after endoscopic treatments. Two systematic reviews concluded that ISD may decrease the risk of recurrence after endoscopic treatment. However, both studies could not conclude the durability of ISD due to the very low quality of the evidence in the present literature.[72,73] Despite studies demonstrating the potential benefits of prolonging the duration of ISD following endoscopic treatments in delaying the onset of recurrence, there is no evidence

TABLE 1 Summary of Endoscopic or Endoluminal Treatments

	Success rate	Advantages & Disadvantages	Complications
DVIU	50–60% on 4 years of follow-up for treatment-naive cases	Require general or spinal anesthesia Most require post-internal urethrotomy urinary catheterization Surgical expertise and equipment required May result in progression of scarring to adjacent healthy urethral mucosa leading to disease progression if stricture recurs	Urinary extravasation Urinary retention Hematuria Urinary tract infection Epididymitis Scrotal abscess Urinary incontinence Erectile dysfunction
Urethral Dilatation	50–60% on 4 years of follow-up for treatment-naive cases	Daycare procedure Can be done under local anesthesia Less surgical expertise and equipment required Preservation of adjacent healthy urethra	Hematuria Urethral perforation with extravasation Creation of false urethral passage Rarely rectal injury
Urethral Stents	13–45% on 10 years of follow-up	High stent-related morbidities in up to 86%, many challenging to manage High reoperation rate of up to 45%	Perineal pain Dysuria Urinary incontinence Post-void dribbling Recurrent urinary tract infections Stent migration Stent obstruction by stone encrustation & tissue ingrowth

on the sustainability of these benefits.[74,75] Lubahn et al. reported that in patients with urethral strictures, the practice of ISD, was significantly associated with a poor overall quality of life, especially in younger patients. Regardless, long-term ISD is a palliative option for patients with urethral strictures who cannot undergo or do not elect urethral reconstructive surgery. However, implementing long term ISD in young patients with strictures amenable to reconstruction should not be encouraged.[76]

Mitomycin C Intralesional Injection

The anti-fibroblastic properties of Mitomycin C (MMC) in mitigating scar formation was demonstrated in in-vitro studies and rat models with induced urethral injury.[77] Mazdak et al. found DVIU with MMC for bulbar urethral strictures had significantly fewer stricture recurrences (10% vs. 50%, P = 0.006), although outcomes were measured at a relatively short follow-up period of 6 months. MMC was injected into 4 quadrants of the strictured urethral segment with a total dose of 0.4 mg, followed by a cold-knife incision at 12-o'clock.[78] Another study by Ali *et al.* with a larger sample size and longer follow-up showed significantly fewer patients in the DVIU with MMC cohort experienced stricture recurrence over an 18 month follow-up period (14.1% vs. 36.9%, P = 0.002). MMC was injected after DVIU at a concentration of 0.1% at the 1-, 11-, and 12-o'clock positions.[79] A recent study by Farrell MR et al. evaluated DVIU with intralesional MMC injection, followed by 1 month of postoperative daily ISD in 44 patients who have failed prior endoscopic management or urethroplasty. Over a median follow-up of 25.8 months, 75.0% of patients (33/44) required no additional surgical intervention. Cold-knife incisions were made at 12-, 3-, and 9-o'clock positions followed by intralesional injection of 10 mL MMC (0.4 mg/mL) in 0.2-0.4 mL aliquots.[80]

Steroid Therapy

Corticosteroids have been a well-established treatment for skin scars and mucosal strictures by decreasing collagen production. It is, therefore, not surprising that steroid has been used to decrease urethral stricture recurrence rate. Administration of steroids to the urethra can be applied either by direct urethral submucosal injections, or ointment to the urethral mucosa by coating catheters with steroids before performing ISD.

Few small cohort investigations have shown that the use of urethral submucosal injection of triamcinolone decreased recurrence rate, although follow-up periods in these studies were short.[81,82] Tavakkoli-Tabassi et al reported that the use of urethral injection of triamcinolone significantly delays the time to recurrence in the experimental group (8.08 ± 5.55 versus 3.6 ± 1.59 months, $p < 0.05$) without causing significant complications.[83] However, its long-term efficacy remains uncertain. The use of triamcinolone or contractubex ointments of the clean intermittent catheterization does not appear to provide any additional benefit.[84] However, there have been suggestions that this technique may be more helpful for patients with distal penile urethral stricture disease due to lichen sclerosus et atrophicus.

EFFECTS OF REPEATED ENDOSCOPIC TREATMENTS ON FUTURE URETHRAL RECONSTRUCTION

It has been suggested that repeat endoscopic treatments result in increased stricture complexity in nearly 50% of cases, and subsequent urethroplasty appeared to be more complex than anticipated when compared with urethrography findings at initial diagnosis in 16% of patients.[69] It has also been reported that these patients are associated with a higher failure rate after undergoing subsequent curative urethroplasty.[85–87] Horiguchi et al. noted that a single application of temporary urethral stenting carries a high risk of complicating the stricture and requiring complex urethroplasty.[69] This is likely due to cumulative tissue injury manifests as amplified spongiofibrosis.[85] As success rate diminishes drastically with repeated endoluminal treatments, such practice appears to delay patients from receiving definitive treatment, with an impact on patients' quality of life. Hudak et al. reported that repeated endoluminal treatments caused an eightfold increase in the time from stricture diagnosis to curative urethroplasty.[85] Such practice is likely due to the lack of training in urethral reconstruction amongst urologists, resulting in a hesitancy to perform primary urethroplasty in correctly-selected

patients for whom primary reconstruction would have been the treatment of choice.[14]

CONCLUSIONS

Endoluminal and endoscopic treatments are commonly used for the treatment of urethral stricture. However, they are all associated with very high stricture recurrence rates. Many appear to be used inappropriately and excessively for its convenience and familiarity in the past few decades. Such treatments should only be offered to urethral strictures with favourable characteristics following appropriate patient counselling. Repeated treatments should be avoided due to its low efficacy and its potential impact on future urethral reconstruction outcomes.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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