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Early Experience with Hyaluronic Acid Instillation to Assist with Visual Internal Urethrotomy for Urethral Stricture

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Purpose: The clinical usefulness of hyaluronic acid (HA) instillation during visual internal urethrotomy (VIU) for decreasing the incidence of recurrent urethral stricture was assessed.

Materials and Methods: Twenty-eight patients were treated by VIU with HA instillation between May 2007 and June 2009. After insertion of a Foley catheter following urethrotomy, HA was instilled via an 18-gauge tube catheter between the urethral lumen and Foley catheter. Seventeen cases were analyzed retrospectively 12 months postoperatively. We evaluated the success rate of this procedure by comparing retrograde urethrography (RGU) results, maximum flow rates, and postvoid residual urine volumes preoperatively and 3 and 12 months postoperatively. Success was defined as either a maximum flow rate of at least 15 ml/s or no visible urethral stricture on RGU at 12 months postoperatively.

Results: Total success rates were 76.5% (13/17) and 52.9% (9/17) at 3 and 12 months postoperatively, respectively. By etiology, success rates at 3 and 12 months postoperatively, respectively, were 66.7% and 33.3% for inflammation, 66.7% and 50.0% for trauma, and 83.3% and 66.7% for unknown causes. Success rates were 63.6% for strictures less than 10 mm in length and 33.3% for strictures of 10 mm or more in length at 12 months postoperatively. Success rates were 61.5% for single strictures and 25% for multiple strictures at 12 months postoperatively.

Conclusions: The success rate of VIU with HA instillation was not better than that observed in the literature for conventional VIU.

Key Words: *Hyaluronic acid; Surgery; Urethral stricture*

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INTRODUCTION

Urethral stricture is a common cause of lower urinary tract symptoms in patients. There are various causes of urethral stricture, for example, trauma, urethral catheterization, urologic instrumentation, and sexually transmitted diseases [1].

Treatment depends on the localization, length, and type of the stricture [2]. The most common technique for the management of urethral strictures is visual internal urethrotomy (VIU), because it is an easy, minimally invasive technique. VIU was first performed by Hans Sachse in 1971. Dilatation, laser urethrotomy, and permanent urethral stent applications have also been used [3].

VIU is the appropriate choice of treatment for urethral strictures; however, one shortcoming of this technique is the frequent recurrence of stricture. The short-term success rate of VIU varies from 39% to 73% for strictures shorter than 1.5 cm, whereas the long-term recurrence rate is 26.9% to 56% [4-6]. Self-catheterization, intralesional injection of steroids, and mitomycin-C have been used to reduce and prevent recurrences [7-9]. Submucosal injection of mitomycin-C reduces the stricture recurrence rate after internal urethrotomy, because mitomycin-C has anti-fibroblast and anti-collagen properties [7,8]. Steroids are known to decrease the accumulation of collagen fibers and

fibroblasts, which results in the inhibition of fibroblast proliferation in wound tissue [9-11].

Lim et al reported that the efficacy of a hyaluronic acid (HA) and carboxymethylcellulose (CMC) bioresorbable membrane that reduced postoperative adhesions improved with the intraoperative coadministration of a neurokinin 1 receptor antagonist in a rat model [12]. Da-Silva et al reported that human urethral stricture tissue has a low level of HA and a high level of dermatan sulfate, which suggests that administration of HA into stricture sites might decrease the possibility of recurrence [13]. Through a similar mechanism, the authors hypothesized that HA/CMC would decrease fibrotic inflammation or the adhesion of incised tissue in VIU. Currently, bioresorbable membranes composed of HA/CMC effectively prevent intertissue adhesion. The physical barriers Seprafilmtm™ Adhesion Barrier (Genzyme Biosurgery, Cambridge, MA, USA), Interceed® Absorbable Adhesion Barrier (Ethicon, Somerville, NJ, USA), and ADEPT® Adhesion Reduction Solution (Baxter Healthcare Corporation, Deerfield, IL, USA) are the only approved methods for preventing abdominal and pelvic adhesions in the United States. Because the solution type, as opposed to the membrane type, is much preferred for spreading on incised tissues, we chose to use a mixed solution of HA/CMC (Guardix®; Biorane, Seoul, Korea), which has been shown to significantly reduce postsurgical adhesion [14]. The aim of this study was to assess the clinical usefulness of urethral instillation of a mixed solution of HA/CMC during VIU for decreasing the incidence of recurrent urethral strictures.

MATERIALS AND METHODS

Between May 2007 and June 2009, 28 patients with a diagnosis of urethral strictures and treated with VIU were enrolled in the study. Patients with a history of urethral surgery were excluded.

In a total of 17 patients, the etiology was identified as inflammation in 3 (17.6%), trauma in 6 (35.3%), unknown in 6 (35.3%), and post-transurethral resection (TUR) in 2 (11.8%). Regarding stricture length, 11 patients (64.7%) had a 10 mm or shorter stricture, and 6 patients (35.3%) had a 10 mm or longer stricture. Regarding number of sites, 4 patients had multiple strictures (23.5%), and 13 patients had a single stricture (76.5%). Regarding stricture location, 4 patients (23.5%) had a stricture at the penile urethra, 12 (70.6%) at the bulbous urethra, and 1 (5.9%) at the membranous urethra (Table 1).

VIU at the 12 or 6 o'clock position was performed under spinal anesthesia using a 21 F Storz urethrotome with a straight cold knife. After urethrotomy, an 18 F Foley catheter was inserted into the bladder through the urethra. Guardix® (1.5 ml) was then instilled via an 18-gauge tube catheter between the urethral lumen and the Foley catheter after about 5 minutes of subcoronal compression to spread the Guardix® solution evenly in the incised urethra.

The Foley catheter was removed 2 weeks after the VIU was performed. The patients returned 3 and 12 months after surgery to undergo uroflowmetry and an examination of postvoid residual urine. We compared preoperative and postoperative values, including retrograde urethrography (RGU) results, maximum flow rates, and postvoid residual urine volumes. Success was defined as a maximal velocity of at least 15 ml/s by uroflowmetry or no visible urethral stricture by RGU. Before 12 months postoperatively, VIU was considered to have failed if a patient required another operation or additional procedures, such as urethral dilatation.

This study retrospectively analyzed 17 patients who had undergone one VIU procedure; 11 cases were excluded because of the lack of follow-up 12 months postoperatively.

TABLE 1. Success rates according to the etiology, length, number, and site of urethral stricture in patients

	No. of cases	Success rate at 3 mo	Success rate at 12 mo
Total	17	13/17 (76.5)	9/17 (52.9)
Etiology			
Inflammation (%)	3 (17.6)	2/3 (66.7)	1/3 (33.3)
Trauma (%)	6 (35.3)	4/6 (66.7)	3/6 (50)
Post-TUR (%)	2 (11.8)	2/2 (100)	1/2 (50)
Unknown (%)	6 (35.3)	5/6 (83.3)	4/6 (66.7)
Length of site			
<10 mm (%)	11 (64.7)	9/11 (81.8)	7/11 (63.6)
≥ 10 mm (%)	6 (35.3)	4/6 (66.7)	2/6 (33.3)
Stricture number			
Single (%)	13 (76.5)	10/13 (76.9)	8/13 (61.5)
Multiple (%)	4 (23.5)	3/4 (75.0)	1/4 (25.0)
Site of stricture			
Penile (%)	4 (23.5)	3/4 (75.0)	1/4 (25.0)
Bulbous (%)	12 (70.6)	10/12 (83.3)	8/12 (66.7)
Membranous (%)	1 (5.9)	0/1 (0)	0/1 (0)

TUR: transurethral resection

RESULTS

The mean age of the patients was 53.1±16.5 years (range, 18-83 years). Only 2 patients had benign prostatic hyperplasia. The total success rates at 3 and 12 months postoperatively were 76.5% (13/17) and 52.9% (9/17), respectively (Table 1). The maximal flow rate, average flow rate, and postvoid residual urine volume at 3 and 12 months postoperatively were 17.9 and 16.7 ml/s, 11.6 and 9.8 ml/s, and 23.1 and 18.2 ml/s, respectively (Table 2). By etiology, success rates were 33.3% (1/3) for inflammation, 50% (3/6) for trauma, 66.7% (4/6) for unknown causes, and 50% (1/2) for post-TUR at 12 months postoperatively. By stricture length, success rates were 63.6% for strictures less than 10 mm and 33.3% for strictures of 10 mm or more at 12 months postoperatively. By number of sites, the success rates were 61.5% for single strictures and 25% for multiple strictures at 12 months postoperatively. By site of stricture, the success rates were 25% for the penile urethra,

TABLE 2. Changes (Mean±SD) in Qmax, Qave, and postvoid residual urine volume at 3 and 12 months postoperatively

	Preoperative	Postoperative, 3 mo	Postoperative, 12 mo
Qmax (ml/s)	7.7±4.8	17.9±6.2 ($p<0.001$)[a]	16.7±4.9 ($p<0.001$)[a]
Qave (ml/s)	3.8±2.0	11.6±4.5 ($p<0.001$)[a]	9.8±4.6 ($p<0.001$)[a]
RU (ml)	80±83	23.1±40.5 ($p<0.05$)[a]	18.2±22.8 ($p<0.05$)[a]

SD: standard deviation, RU: residual urine, Qmax: maximal flow rate, Qave: average flow rate. [a]: compared with preoperative data

66.7% for the bulbous urethra, and 0% for the membranous urethra at 12 months postoperatively (Table 1).

Of the 8 failed cases, the maximum uroflow rate was greater than 15 ml/s in 4 cases (average maximal flow rate, 19.8 ml/s) at 3 months postoperatively; however, these patients did not meet the criteria for success at 12 months postoperatively. These 4 patients, who had an average maximal flow rate of 11 ml/s (range, 8-13 ml/s) and an average postvoid residual urine volume of 31.3 ml 12 months postoperatively, refused another operation because their daily activities were not adversely affected. One patient who had difficulty voiding also refused another reoperation for urethral stricture because of old age (83 years). Two patients underwent a repeat VIU and perineal urethroplasty. One patient was lost to follow-up after the 12-month postoperative visit. Postoperative complications from VIU consisted of hematuria in 2 patients, which did not require additional procedures. No HA/CMC-related complications were observed after urethral instillation of Guardix®.

DISCUSSION

VIU is the primary treatment option for patent urethral stricture because it is a simple and effective treatment. However, the frequent stricture recurrence rate and the need for additional surgery are shortcomings of this procedure. Byun and Song reported a VIU success rate of 94%; 46% of all patients needed only one surgery, 54% needed a second surgery, and 21% needed a third surgery [1]. The average number of times a patient underwent VIU was 2.13. Chung et al reported a success rate of 64.5% for patients who underwent surgery only once, 42.4% for patients who underwent surgery twice, and 23.5% for patients who underwent surgery 3 times [15]. In this study, the success rates at 3 and 12 months postoperatively were 76.5% and 52.9%, respectively. The short-term results were the same as or better than those observed in the literature for conventional VIU. However, the long-term results were clearly not better than those observed in the literature for conventional VIU.

Factors that influence the success rate of VIU include the length and location of the strictured urethra. Byun and Song reported that all surgeries failed when the length of the stricture was greater than 2.5 cm, that 41% of all patients with a stricture length of 0.5 to 1.5 cm underwent a second VIU, and that 71% of all patients with a stricture length of 1.5-2.5 cm underwent a second VIU [1]. The average number of VIUs per patient was 1.49 cm for stricture lengths of 0.5-1.5 cm and 2.46 cm for stricture lengths of 1.5-2.5 cm. These data indicate that the longer the stricture, the greater the recurrence rate and the greater the number of VIU procedures required. Huh et al reported that the success rate of the first VIU was 81.8% for stricture lengths of 0.5 to 1.0 cm and 33.3% for stricture lengths of 1.6 to 2.0 cm [2]. In our study, the success rate was 63.6% for stricture lengths of less than 10 mm and 33.3% for stricture lengths of 10 mm or more. In our study, as in the literature, the success rate of VIU was better for short strictures than for longer strictures. However, 2 of the 4 failed cases who had long strictures (range, 15-70 mm) refused to undergo another operation. Although these 2 cases did not meet the criteria for success at 12 months postoperatively, their daily lives were not adversely affected by their refusal of another operation. The clinical success rate associated with long strictures in the current study was thought to be better than the results observed in the literature; however, the findings should be confirmed in a large-scale, randomized controlled study.

Regarding stricture location, Huh et al reported a first-VIU success rate of 66.7% for penile urethra strictures, 65.2% for bulbous urethra strictures, and 50% for membranous urethra strictures [2]. Chung et al reported higher success rates for bulbous urethra strictures than for penile urethra strictures and for short strictures than for long strictures [15]. In our study, success rates were 25% for penile urethra strictures, 66.7% for bulbous urethra strictures, and 0% for membranous urethra strictures; these rates are similar to those observed in the literature. Regarding the number of strictures, success rates were 61.5% for single strictures and 25% for multiple strictures, in agreement with data in the literature.

Much effort has been undertaken to improve the success rate of urethra stricture surgery and to decrease the recurrence rate of stricture. Over the past 20 years, improvements in endoscopic surgery have contributed to the success rate of urethral stricture surgery [10,11,16-18]. Triamcinolone, mitomycin-C, transforming growth factor beta oligodeoxynucleotide, and gene therapy-such as recombinant adenovirus and retrovirus gene transfer-have also been used as adjuvant treatment [17,18].

Mazdak et al reported the effects of mitomycin-C on anterior urethral strictures, and Shin et al reported the effects of mitomycin-C on urethral strictures in the rat [7,8]. Mitomycin-C was reported to have anti-replication properties in animal and clinical studies. These studies suggest that mitomycin-C might inhibit the renewal of the epithelium and synthesis of collagen secreted by fibroblasts in the affected urethra, which prevents scar formation and subsequently causes restricture.

Gücük et al used a steroid-coated (triamcinolone acetonide 1%) 18 F hydrophilic dilatation catheter in post-VIU patients [10]. The steroids, which induce a fibroblast reaction, suppressed (experimentally and clinically) a decrease in the accumulation of collagen fibers and fibroblasts and inhibited the proliferation of fibroblasts in wound tissue. These effects suggest that the local administration of steroids may prevent wound contraction, and thus recurrence, in patients treated for urethral strictures. The beneficial effects of steroids might also positively affect outcomes after hypospadias repair and urethroplasty. Furthermore, Jeon and Shim performed VIU with an Nd:YAG laser and triamcinolone injection, which resulted in a high success rate of 82.1% [11]. No specific complications or adverse effects were observed.

Regardless of its etiology, urethral stricture can cause the formation of scar tissue, which can decrease the caliber of the urethral lumen and result in stricture. Regulation of the extracellular matrix plays an important role in tissue development, remodeling, and wound healing. Da-Silva et al, who proposed the theoretical possibility that undesirable scar tissue could be prevented pharmacologically, reported that the HA concentration was about 50% lower in strictured human bulbous urethra than in normal urethra [13]. It was suggested that the low concentration of HA and total glycosaminoglycans in urethral strictures may account for the undesirable biomechanical properties of urethral scar tissue. Therefore, the authors hypothesized that application of HA/CMC to the incised tissue of urethral strictures might decrease the amount of scar tissue and result in less adhesion between incised scar tissue.

HA is thought to create a liquid-type barrier. The viscous solution, known as Sepracoat (Genzyme Corporation, Cambridge, MA, USA), was developed for use as a coating during surgery to protect tissues against operative trauma. However, this agent is absorbed rapidly and must be used within a crucial time period of 36 h to prevent adhesion formation [19]. As a result, it was shown to have only moderate efficacy against the formation of *de novo* adhesion, which limits its widespread use [20]. To overcome these limitations, HA was modified by combining it with CMC, and new HA derivatives have been obtained in the form of a resorbable solution. The HA/CMC solution is a highly viscous, hydrated suspension because of the cross-linked reaction between the functional groups of the HA molecules; therefore, its residence time at the injured surface is longer than that of the original form of HA.

Guardix® is a mixed solution of HA and CMC that serves as a membrane barrier. The modified liquid barrier is formed *in situ* by spraying the solution onto injured sites that are prone to adhesion formation. This highly viscous solution adheres to tissue and is hydrolyzed, is absorbed, and undergoes renal excretion several days after application. For these reasons, Guardix® was chosen for its anti-adhesion effects to supply HA to the incised stricture tissue in the current study. Park et al reported that the HA/CMC solution decreased the overall incidence of postoperative adhesions and that it appears to be superior to oxidized regenerated cellulose membranes because this sprayable solution is easy to use and is suitable for site-specific adhesion prevention after multifocal injuries [21]. Kim et al reported that using an HA/CMC solution with continuous ambulatory peritoneal dialysis (CAPD) catheter insertion is an effective method for reducing the incidence of greater omental adhesions and the rate of reoperation for catheter reposition [22].

In our study, VIU was unsuccessful in one case that was caused by a penetrating injury with a sharp object that resulted in membranous urethral transaction and intraperitoneal bladder rupture. Therefore, VIU is not expected to achieve satisfactory results in cases of extensive injury and membranous urethral injury.

The aim of this retrospective, cross-sectional study was to determine the usefulness of the injection of HA/CMC for preventing the recurrence of urethral stricture after VIU. Some shortcomings of this study included the absence of a control group and the small number of patient groups. The short-term results were the same as or better than those observed in the literature for conventional VIU. However, the long-term results were clearly not better than those observed in the literature for conventional VIU. The authors believe that some positive outcomes resulted from this procedure. For example, failed cases with longer strictures did not require additional clinical procedures for voiding problems. Thus, we suggest that a large-scale, controlled trial be conducted with long-term follow-up to determine the efficacy and usefulness of HA/CMC urethral instillation during VIU compared with that of VIU without HA/CMC instillation. We recommend that a large-scale, multicenter, randomized controlled trial be conducted in patients who have undergone a first VIU for anterior urethral stricture.

CONCLUSIONS

This study was designed to evaluate whether the urethral instillation of HA/CMC during VIU would decrease the recurrence rate of urethral stricture. Unfortunately, the procedure did not demonstrate a favorable success rate 12 months postoperatively compared with outcomes of conventional VIU reported in the literature. However, because of the limitations of this retrospective study and the possibility that the success rate would be better in a select patient population, we suggest that a large-scale, randomized controlled trial be conducted in a larger number of patients with long-term follow-up to examine the efficacy and usefulness of HA/CMC urethral instillation with VIU.

Conflicts of Interest

The authors have nothing to disclose.

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