The effects of Guardix-sol® in preventing recurrence of urethral stricture after endoscopic internal urethrotomy

: A prospective, multicentre, randomized controlled study

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Abstract

Purpose: To evaluate the effects of Guardix-sol® on the recurrence of urethral stricture after treatment with endoscopic internal urethrotomy (EIU).

Materials and Methods: A total of 120 patients who underwent EIU for urethral stricture between June 2010 and May 2011 were invited for the present study. Of recruited patients, 120 met our inclusion criteria and were randomized into 2 groups: The experimental group (60 patients, group A) received a Guardix-sol® instillation and the control group (60 patients, group B) received a lubricant instillation after internal urethrotomy. Patients were evaluated at 4 weeks (V1), 12 weeks (V2) and 24 weeks (V3) after surgery. The effectiveness of Guardix-sol® instillation was evaluated based on the overactive bladder symptom score (OABSS), International Prostate Symptom Score (IPSS)/ Quality of Life (QoL) and measurements of peak urine flow rate (Qmax), voided volume and post-voiding residual urine volume (PVR). The visual analogue scale (VAS) pain score and degree of satisfaction were also determined for each participant.

Results: The mean ages in group A and group B were 58.63±15.97 and 54.57±18.69 ($p=0.337$), respectively. 53 patients in group A and 48 patients in group B completed this study. VAS pain scores were 0.67±0.76 and 3.60±1.52 ($p<0.001$), and degrees of satisfaction were 0.67±0.60 and 1.47±1.07 in group A and group B at V1 ($p<0.001$). 6 out of 53 subjects in Group A and 7 out of 48 subjects in group B showed no improvement in symptoms, equivalent to surgical failure ($p=0.473$). 5 patients in group A and 11 in group B experienced recurrence ($p=0.029$).

Conclusion: Guardix-sol® instillation during EIU may decrease the incidence of urethral stricture recurrence. In addition, the use of Guardix-sol® was effective in reducing pain after surgery without adverse effects.

Introduction

Urethral stricture is describes a decrease in urethral lumen diameter through fibrosis or scarring of the urethral epithelium that may develop at any site in the urethra.[1] Major causes of urethral stricture include blunt trauma in the perineal region, history of intraurethral instrumentation such as urethral Foley catheterization and transurethral operation, ischemia and urethritis. Many cases occur through no known cause, but presumably through past perineal trauma the patient does not remember.[2] Urethral strictures require active treatment because complications such as lower urinary tract symptoms, reduced in renal function, and urinary tract infection may occur. Since Saches introduced visual internal urethrotomy in 1971,[3] endoscopic internal urethrotomy (EIU) has been used widely for treating urethral stricture. However, the success rate remains low, at about 30%-50%, due to frequent recurrences of stricture post-operatively.[4] In an attempt to reduce recurrence, Laser surgery, self-catheterization after EIU, converting enzyme inhibitor gels, and steroid injections have been used (Table 4).[5-8]

Materials recently developed to prevent post-operative adhesion include hyaluronic acid (HA) and carboxymethylcellulose (CMC), which is marketed as Guardix- sol® , Hanmi Medicare, Seoul, Korea.

As a major constituent of extracellular matrix, the anionic polysaccharide HA is found in connective tissues, skin, cartilage and synovial fluid. As a hydrophilic and non-immunogenic macromolecule, HA easily coats and lubricates mucus membrane. The physical properties of HA, suggest the use of this compound to reduce or prevent trauma at the site of surgery. CMC, derived from cellulose by carboxymethylation of the glucosidic hydroxyl groups, represents another series of anionic polysaccharides. Significantly more hydrophilic than cellulose, HA is used as a filler, viscosity agent, lubricant and stabilizer of pharmaceutical products, cosmetics

and foods.[9] Accordingly, Guardix-sol®, which contains HA and CMC, is used to prevent adhesion after surgery. Despite this use, no prospective study has tested Guardix-sol® for effectiveness in surgery for urethral stricture. In the present study, we tested the effectiveness of Guardix-sol® in preventing re-stricture of the urethra after EIU treatment.

Patients and methods

Subjects and study design

A total of 120 patients who were treated for urethral stricture by EIU between June 2010 and May 2011 were invited to participate in present study. This study is a randomized, open label, multicenter prospective controlled study involving 7 medical institutions. The study proceeded upon obtaining approval from the institutional review board.

Inclusion criteria for the study included (1) urethral stricture due to traumatic, inflammatory, iatrogenic and unknown causes and observed by retrograde urethrography and (2) willingness and ability to participate in this clinical study. Excluded from the study were patients who (1) underwent endoscopic internal urethrotomy in the past to treat urethral stricture, (2) underwent any other transurethral surgeries (3) underwent radical prostatectomy for prostate cancer, (4) were observed to have 1.5 cm or more of urethral stricture, (5) had neurogenic bladder, or (5) had a urinary tract infection.

All of the 120 patients met our inclusion criteria and were randomly assigned to either (1) an experimental group (60 patients, group A), who received Guardix-sol® instillation or (2) a control group (60 patients, group B), who received an instillation of lubricant at urethra after internal urethrotomy.

At enrollment in the study (V0), information regarding the duration of illness and a medical history were collected. V0 also included a physical examination including blood pressure and heart rate measurements, routine hematological tests, urinalysis, and retrograde urethrography. Patients were evaluated at 4 weeks (V1), 12 weeks (V2) and 24 weeks (V3) after surgery. Failure was defined as the need to repeat surgical intervention

during the follow-up period. The peri- and post-operative complications were recorded such as wound infections, bleeding, and extravasation.

Surgical technique

EIU was performed at the 12 o'clock position with the patient under general or spinal anesthesia using a 21 Fr. Storz urethrotome with a straight cold knife. After urethrotomy, an 18 Fr. Foley catheter was inserted. Upon pulling the Foley to block the bladder neck, Guardix-sol® (5 ml) was instilled using an 18-gauge tube catheter between the urethral lumen and the Foley catheter. After instillation, the Foley catheter was pulled out as far as it covers the bladder neck, wrapped up with gauze, and bound for 1 week. The Foley catheter was removed 2 weeks after the EIU was performed.

Assessment of efficacy and safety

To evaluate the efficacy of Guardix-sol® in preventing urethral stricture recurrences, subjects were assessed at every visit by determining the overactive bladder symptom score (OABSS), International Prostate Symptom Score (IPSS) and by measuring the peak urine flow rate (Qmax), voided volume and the post-voiding residual urine volume (PVR). The degree of patient satisfaction was recorded on a scale ranging from 0 (extremely satisfied) to 3 (extremely dissatisfied). The visual analogue scale (VAS) pain score was assessed on a 10-point Liskert scale and the Quality of Life (QoL) score was also determined. Retrograde urethrography (RGU) was performed at V2. The safety of the Guardix-sol® treatment was assessed at V1, V2, and V3 based on the patient's history, a physical examination and the presence or absence of adverse effects.

Statistical analysis

The OABSS, IPSS, Qmax, voided volume and PVR before and after endoscopic internal urethrotomy were compared using Student's paired *t*-test. The chi-square test was used to analyze the recurrence rate and causes and locations of recurrences. Statistical analyses were performed using Open Office.org Calc (Open Office.org® version 3.2.0, Oracle Corp, Redwood Shores, CA, USA) and MedCalc (MedCalc® version 11.2.1.0, MedCalc Software, Mariakerke, Belgium). A p-value < 0.05 was considered statistically significant.

Result

From the entire group of 120 subjects, 7 and 12 subjects in group A and group B, respectively, were lost to follow-up and therefore excluded. Data collected from the records of 53 and 48 patients, respectively, in the experimental and control groups who completed the follow-up period were analyzed (Fig 1).

The mean ages of subjects in group A and group B were 58.63±15.97 and 54.57±18.69 years (p=0.337), respectively, and the corresponding BMI values were 25.42±2.28 and 25.93±2.87 kg/m^2 (p=0.423). Stricture locations based on RGU in group A were the bulbar area (62.26%), penile area (33.96%) and both (3.78%), and in group B were the bulbar area (64.58%), penile area (31.25%) and both (4.17%) (p=0.957). Causes of stricture in group A were trauma (33.96%), infection (11.32%), iatrogenic (16.98%) and unknown (37.74%), and in group B were trauma (31.25%), infection (12.50%), iatrogenic (20.83%) and unknown (35.42%) (p=0.956). Irritative subscores based on IPSS were 5.49±2.34 in group A and 6.33±2.15 in group B (p=0.117), and obstructive subscores were 11.81±3.90 and 10.53±4.52 in group A and group B (p=0.213), respectively. QoL scores were 3.74±1.05 in group A and 3.70±1.18 in group B (p=0.87). Qmax values were 6.91±3.35 and 7.14±3.10 (p=0.771), and PVR values were 18.00±26.82 and 19.55±26.81 (p=0.809) in group A and group B, respectively (Table. 1).

At 4 weeks (V1) after surgery, the IPSS scores of group A and group B showed irritative subscores of 3.74±1.62 and 3.17±1.97 (p=0.191), and obstructive subscores of 1.51±1.40 and 2.13±1.59 (p=0.090), respectively. QoL scores were 1.35±1.09 in group A and 1.23±0.94 in group B (p=0.629). Qmax values were 20.76±8.43 in group A and 20.82±9.28 in group B (p=0.975), and PVR values were 16.77±25.14 and 10.28±10.46 in group A and

group B, respectively (p=0.135). VAS pain scores were 0.67±0.76 and 3.60±1.52 in group A and group B, respectively (p<0.001), and the degree of satisfaction was 0.67±0.60 in group A and 1.47±1.07 and group B (p<0.001).

At 12 weeks (V2) after surgery, the IPSS scores of group A and group B showed irritative subscores of 3.91±1.85 and 3.50±2.19 (p=0.410), and obstructive subscores of 1.26±1.24 and 1.67±1.30 (p=0.179), respectively. QoL scores were 1.47±1.05 in group A and 1.60±0.93 in group B (p= 0.566). Qmax values were 21.68±10.79 in group A and 20.15±6.24 in group B (p=0.446), and PVR values were 10.08±8.42 and 13.43±9.22 in group A and group B, respectively (p=0.119). VAS pain scores were 0.84±0.90 and 2.33±1.61 in group A and group B, respectively (p<0.001), and the degree of satisfaction was 0.58±0.63 in group A and 1.20±0.81 in group B (p<0.001).

At 24 weeks (V3) after surgery, the IPSS scores of group A and group B showed irritative subscores of 5.09±4.82 and 5.87±6.06 (p=0.563), respectively, and obstructive subscores of 1.44±1.30 and 1.87±1.33 (p=0.180), respectively. QoL scores were 1.44±1.03 in group A and 1.27±0.94 in group B (p=0.455). Qmax values were 21.26±8.42 in group A and 20.26±10.08 in group B (p=0.659), and PVR values were 16.67±26.54 and 14.23±10.64 in group A and group B, respectively (p=0.588). VAS pain scores were 1.05±0.95 and 1.17±1.05 in group A and group B, respectively (p=0.620), and the degree of satisfaction was 0.28±0.50 in group A and 0.80±0.81 in group B (p=0.001) (Table 2).

6 of 53 subjects in Group A and 7 of 48 subjects in group B showed no improvement of symptoms, which we interpreted as failure of the surgery (p=0.473). Five cases of recurrence were observed in group A and 11 in

group B (p=0.029) (Table 3). Postoperative complications including urethral bleeding, extravasation, chordee, incontinence and infection were not seen.

Discussion

In the present study, the intra-urethral instillation of Guardix-sol® during EIU led to a reduction in recurrence of urethral stricture after surgery. Guardix-sol® was effective without noticeable side effects, and also helped to reduce pain after surgery.

Conventional methods to treat urethral stricture include urethral dilatation and blind urethrotomy. As access to EIU increased, its use increased in parallel because it is relatively safe, convenient and reproducible. However, the success rate of EIU is low, at about 40%, and the recurrence rate is high.[10] Although the mechanisms of urethral stricture recurrence after EIU are not clearly understood, fibrosis and adhesion of epithelial and sub-epithelial spongy tissues during healing are likely involved.[11] Holm-Neilsen et al. reported the post-EIU rate of urethral stricture recurrence to be 23-80%.[12] In the present study, the low rate of recurrence in the control group (22.9%) corresponds to a shorter follow-up period than in previous studies. By comparison to this control group, the post-EIU rate of urethral stricture recurrence in the experimental group (9.4%) was significantly reduced.

As one of many techniques used to reduce the recurrence rate, LASER has advantages over conventional surgery in the control of bleeding, which improves working visibility, and the capability to remove fibrotic tissues by vaporization during incision of the urethra. In spite of a high success rate and low recurrence, no significant differences from conventional methods in long-term outcomes have been reported.[5, 13]

Another method used to reduce recurrence is post-operative self-catheterization. This comparatively simple method takes advantage of the clearing effect of periodic urethral dilation; however, one study found no significant difference in recurrence of urethral stricture as compared with the control group.[6] Use of an

antifibrotic angiotensin-converting enzyme-inhibitor (ACE-I) gel after performing EIU may also reduce the rate of urethral stricture recurrence,[7] possibly by inhibiting fibrosis.[14, 15] Injection of a steroid at the stricture point during EIU was recently reported to postpone, but not reduce recurrence of urethral stricture.[8] Physiologically, corticosteroids may decrease scar formation by reducing the synthesis of collagen, glycosaminoglycans and inflammatory mediators.[16]

Urethral stricture occurs through scar formation and fibrosis, and in post- EIU recurrence of urethral stricture, the urethrotomy wound initiates the same process of tissue remodeling and healing that leads to fibrosis and scarring. Extracellular matrix regulation plays a prominent role in this process, which sodium hyaluronate may inhibit to reduce unwanted scar tissue by 50% or more.[17] In an animal study, Hong et al. observed tissue development, remodeling and wound healing after surgery through histological examination in the group treated with Guardix-sol®.[18]

In the human body, several natural barriers, including the peritoneum, omentum and amnion, serve to prevent adhesion between neighboring tissues.[19] When surgery breaches these barriers, synthetic physical barriers may be introduced to separate injured tissue surfaces and reduce adhesion to surrounding organs.[20] Synthetic physical barriers include films, solutions, and recently developed sol-gel transition barriers,[21] the latter two types may be instilled after performing EIU. Guardix-sol® is a fluid synthetic sol-gel barrier with a viscosity of 2500 to 3500 cP, similar to that of honey.[18] Use of Guardix-sol® in the present study to reduce post-EIU urethral stricture recurrence was based on previous studies showing that instillation of synthetic solutions as tissue barriers during EIU inhibits scar formation.

In the present study, patients treated with Guardix-sol®, who did not experience recurrence, and patients treated with lubricant (the control group) did not differ significantly in IPSS, OABSS score, QoL or uroflowmetry results. Although Guardix-sol® did not significantly affect post-operative voiding symptoms, significant differences in the post-operative pain scale and recurrence rate were observed. Guardix-sol® effectively coats wound surfaces, and maintains a long contact time through its high viscosity. Guardix-sol® instillation during EIU may reduce post-operative urethral stricture recurrence through its capacity to prevent fibrosis and scar formation during healing of the urethrotomy wound. As compared with the control group treated with lubricant, the group treated with high-viscosity Guardix-sol® experienced significantly less post-operative pain. We attribute this to the extended presence of a lubricating barrier between the urethra, urethrotomy wounds and the Foley catheter.

Limitations of the present study include a short follow-up period and the absence of post-operative histological examinations in the experimental and control groups. The present study is significant as it is the first prospective, randomized controlled study of the efficacy of Guardix-sol® in reducing the recurrence rate of urethral stricture following treatment with EIU. The long-term effects of Guardix-sol® instillation during EIU should be confirmed through extended follow-up, and the histological effects should be defined through animal experimentation.

Conclusion

The instillation of Guardix-sol® into the urethra during EIU decreased the incidence of urethral re-stricture after surgery. Use of Guardix-sol® also reduced postoperative pain effectively without significant side effects.

Figure 1. This 26-week study involved a 2-week screening period and a 24-week treatment phase.

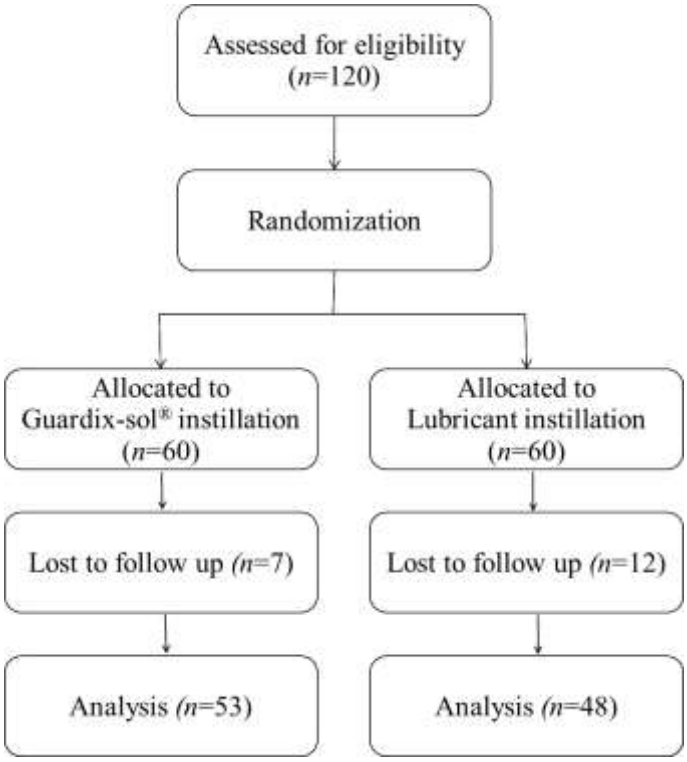

Table 1. Characteristics of patients

		Group A (n=53)	Group B (n=48)	p-value
Age, yrs		58.63±15.97	54.57±18.69	0.337
BMI, kg/m^2		25.42±2.28	25.93±2.87	0.423
Stricture location, %	Bulbar	62.26	64.58	0.957†
	Penile	33.96	31.25	
	Both	3.78	4.17	
Stricture causes, %	Trauma	33.96	31.25	0.956†
	Infection	11.32	12.50	
	Iatrogenic	16.98	20.83	
	Unknown	37.74	35.42	
IPSS	Irritative subscore	5.49±2.34	6.33±2.15	0.117
	Obstructive subscore	11.81±3.90	10.53±4.52	0.213
QoL		3.74±1.05	3.70±1.18	0.870
Qmax, mL/s		6.91±3.35	7.14±3.10	0.771
PVR, mL		18.00±26.82	19.55±26.81	0.809

Student t-test
† Chi-square test
BMI: body mass index; IPSS: international prostate symptom score
; QoL: quality of life; PVR: post voiding residual urine volume

Table 2. The follow-up of surgical outcome after EIU

		Group A (n=43)	Group B (n=30)	p-value
V1	IPSS			
	Irritative subscore	3.74±1.62	3.17±1.97	0.191
	Obstructive subscore	1.51±1.40	2.13±1.59	0.090
	QoL	1.35±1.09	1.23±0.94	0.629
	Qmax	20.76±8.43	20.82±9.28	0.975
	PVR	16.77±25.14	10.28±10.46	0.135
	VAS pain score	0.67±0.76	3.60±1.52	0.000
	Satisfaction	0.67±0.60	1.47±1.07	0.000
V2	IPSS			
	Irritative subscore	3.91±1.85	3.50±2.19	0.410
	Obstructive subscore	1.26±1.24	1.67±1.30	0.179
	QoL	1.47±1.05	1.60±0.93	0.566
	Qmax	21.68±10.79	20.15±6.24	0.446
	PVR	10.08±8.42	13.43±9.22	0.119
	VAS pain score	0.84±0.90	2.33±1.61	0.000
	Satisfaction	0.58±0.63	1.20±0.81	0.000
V3	IPSS			
	Irritative subscore	5.09±4.82	5.87±6.06	0.563
	Obstructive subscore	1.44±1.30	1.87±1.33	0.180
	QoL	1.44±1.03	1.27±0.94	0.455
	Qmax	21.26±8.42	20.26±10.08	0.659
	PVR	16.67±26.54	14.23±10.64	0.588
	VAS pain score	1.05±0.95	1.17±1.05	0.620
	Satisfaction	0.28±0.50	0.80±0.81	0.001

Student's-test
IPSS: international prostate symptom score; QoL: quality of life; PVR: post voiding residual urine volume; VAS: visual analogue scale

Table 3. Comparison of recurrence rate of urethral stricture after EIU

	Group A (n=53)	Group B (n=48)	p-value
Failure (%)			
V1 (no improvement)	5 (50.00)	7 (61.11)	0.473
Recurrence (%)	5	11	0.029
V2	1 (20.00)	5 (45.45)	0.052†
V3	4 (80.00)	6 (54.55)	

Student's t test, †Chi-square test

Table 4. Additional intervention during EIU for reduce recurrence rate of urethral stricture

References	Additional intervention	Case (n)	Length (cm)	Follow-up (months)	Recurrence rate (%)
Bodker et al. [22]	self-catheterization	28	-	12	78
Roosen et al. [23]	self-catheterization	19	-	6	0
Kjaergaaed et al. [24]	self-catheterization	21	-	12	19.05
Mkony et al. [25]	hydraulic urethral dilatation	23	<0.5	6	8.7
Tunc et al. [26]	self-catheterization	19	0.5 to 2	12	10.5
Lin et al. [27]	self-catheterization	6	-	51.5	0
Mazdak et al. [28]	urethral submucosal mitomycin C injection	20	-	6	10
Shirazi et al. [7]	intraurethral captopril gel	17	<2	16	35.3
Hosseini et al. [29]	self-catheterization and triamcinolone ointment	30	-	12	30
Rijal et al. [30]	self-catheterization	262	-	57.68	16.9
Gucuk et al. [31]		45	<1.5	16.4	
	steroid-coated hydrophilic cathter self-catheterization				20
	hydrophilic catheter self-catheterization				46.7
	silicone catheter self-catheterization				60
Kim et al. [32]	hyaluronic Acid instillation	28	-	12	47.1
Mazdak et al. [33]	urethral submucosal triamcinolone injection	23	0.6 to 1.5	12	21.7
Tabassi et al. [8]	urethral submucosal triamcinolone injection	34	0.8±1.40	9.55	12
Present study	hyaluronic Acid instillation	53	<1.5	6	10

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