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A prospective, randomized trial to evaluate the efficacy of clean intermittent catheterization versus triamcinolone ointment and contractubex ointment of catheter following internal urethrotomy: long-term results

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Abstract
Purpose Our aim was to evaluate clean intermittent catheterization (CIC) results in combination with triamcinolone ointment and contractubex ointment for lubrication of the catheter after optical internal urethrotomy (OIU).
Methods Ninety patients who underwent OIU were randomized into three groups. Two weeks after operation, patients were treated with CIC (group A), triamcinolone ointment CIC (group B), and contractubex ointment CIC (group C). Follow-up continued for 24 months after the OIU. Postoperative results were compared between the three groups.
Results There were no significant differences in the baseline characteristics of the patients or the etiology of the urethral stricture between the three groups. The mean preoperative Q_{max} was 4.31 ml/s. The average score of preoperative international prostate symptom score (IPSS) was 23.1 points. In both groups, after treatment, significant improvements in Q_{max} and IPSS were noted at all follow-up period ($p < 0.05$). But for Q_{max} and IPSS, there were not any significant differences between groups at all follow-up period ($p > 0.05$). Overall recurrence rate was 28.9 % (26 out of 90 patients) at the end of the study. Recurrence rates were, however, not found to be statistically significant between these three groups ($p > 0.05$).
Conclusion Our results indicate that the urethral dilation protocol with CIC after first OIU is a safe, simple, well-tolerated, office-based procedure. Triamcinolone or contractubex ointments of the CIC do not provide an additional benefit. Currently, urethral dilation with CIC after first OIU seems to be the only proven procedure that decreased the recurrence rate.

Keywords Urethra · Urethral stricture · Urinary catheterization · Triamcinolone · Contractubex · Recurrence · Optical internal urethrotomy

Abbreviations

CIC	Clean intermittent catheterization
OIU	Optical internal urethrotomy
US	Urethral stricture
IPSS	International prostate symptom score

Introduction

Urethral stricture (US) is a common condition with dire consequences such as urinary infection and renal insufficiency secondary to urinary retention. Underlying causes

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of US might be trauma, infection, ischemia, inflammation, or unknown causes. Stricture can be observed in any part of the urethra ranging from the prostatic urethra till the meatus [1]. Anterior urethra classically is divided into bulbar and penile parts. Strictures of the bulbar urethra are more common compared to penile urethra [2]. The decision of an intervention depends upon surgeons' preference and on factors, such as stricture length, location, and etiology. In strictures <1.5 cm, optical internal urethrotomy (OIU) is the most common intervention procedure; however, in 46–76 % of all cases, there are recurrent strictures within 2 years and treatment of recurrent strictures presents even higher recurrence risk [3, 4].

OIU does not provide an epithelial approximation but rather aims to separate the epithelium scarred for a more effective secondary healing. OIU is successful if epithelialization progresses before wound contraction that narrows the lumen significantly that will lead to recurrent stricture [5]. A number of complementary procedures including clean intermittent catheterization (CIC) have been proposed to minimize the recurrence rate of US after OIU. Likewise, corticosteroids decrease scar formation by reducing collagen and glycosaminoglycan synthesis and expression of inflammatory mediators [6]. Local corticosteroid injection (triamcinolone) after urethrotomy was proposed for the first time by Hebert [7]. Tavakkoli et al. [8] recommended intralesional steroid injection as a means to reduce the recurrence rate of US. In recent years, antifibrinolytic agents used in hypertrophic scar and keloid treatment are also employed in US therapy. Contractubex gel, containing cepae extract, heparin, and allantoin, used mainly in hypertrophic scar and keloid treatment for more than 30 years, is for the first time employed in US treatment in the present study.

Randomized controlled trials about the use and impact of CIC on US are quite rare. Moreover, they present a difficulty to determine US recurrence due to varying stricture length, location, and follow-up time. Therefore, standardized trials randomized controlled in particular are required. In the present study, the effect of CIC, triamcinolone ointment CIC, and contractubex ointment CIC on US recurrence rate in the aftermath of OIU are compared.

Materials and methods

This prospective, randomized, double-blind, and placebo-controlled study included 90 patients, aged 19–74 years (mean = 59.6), with primary symptomatic bulbomembranous US. US diagnosis was based on international prostate symptom scores (IPSS), quality of life, clinical history, uroflowmetry, ultrasonography, and urethrography. Patients with previous urethroplasty, urethral manipulation (urethrotomy or urethral dilatation), US longer than 2 cm, neurogenic bladder, urinary tract infection, history of systemic or immune disease, and corticosteroids treatment history were excluded from the study.

All US patients, with urethral strictures <2 cm, underwent OIU by the same urologist. Postoperative urethral catheter was left in place for 3 subsequent days. Two weeks after OIU, hydrophilic ureter catheters used as CIC was placed by the urologists once a week throughout a 6-week period in a rapid sequence beginning with 14 F until 20 F. Participants of the study were divided into three groups as Group A as CIC only, Group B as triamcinolone ointment CIC, and Group C as contractubex ointment CIC. Approximately one peanut size triamcinolone or contractubex ointment was used for lubrication of the 20-F urethral catheter applied at the end of the procedure beginning with 14 F and kept for 5 min in the urethra. Laboratory tests, ultrasound, post-voiding residual volume, and uroflowmetry (Q_{max} and Q_{ave}) as well as IPSS and QL were determined before OIU. Patients were evaluated at the end of the 1st, 3rd, 6th, 12th and 24th postoperative month. During follow-up period, recurrent US requiring urethroscopy was determined based on reduced urine flow, urine retention, dilatation inability due to US, and burning micturition. The procedure was considered successful if the patient did not report any voiding difficulty and had a maximum flow rate of 12 ml/s for at least 150 ml urine. US stabilization was established if the patients remained without recurrent stricture for 24 months following urethrotomy. Informed consent was obtained from all the eligible patients after the approval of the local ethics committee.

Statistical analyses for the descriptive parameters were made using SPSS 15 package program. Results were presented in form of average, standard deviation, minimum and maximum values for measurable variables, and the percentages for nonmeasurable variables (qualitative). Mann–Whitney *U* test and Kruskal–Wallis variance analysis were used in the comparison of independent groups and Friedman variance analysis and Wilcoxon signed-rank test for dependent groups.

Results

There were no significant differences in the baseline characteristics and in the etiology of the stricture among the three groups (Table 1). The etiology of US was iatrogenic in 74 (82.3 %) and idiopathic in 16 (17.7 %). Iatrogenic causes were attributed to endoscopic urologic surgery, urethral catheterization (for various nonurologic diseases), and posterior urethral trauma (not lead to complete urethral rupture) in 28 (31.1 %), 30 (33.3 %), and 16 (17.7 %) patients, respectively. The mean preoperative white blood

Table 1 Baseline characteristics of groups

Characteristics	CIC (*n*:30)	Triamc (*n*:30)	Contrac (*n*:30)	*p*
Age (years)	61.2	60.7	57.8	>0.05
Cause of urethral stricture				
Iatrogenic				
Endoscopic urologic surgery	9 (30 %)	10 (33.3 %)	9 (30 %)	>0.05
Urethral catheterization	10 (33.3 %)	8 (26.7 %)	12 (40 %)	>0.05
Posterior urethral trauma	6 (20 %)	5 (16.6 %)	5 (16.6 %)	>0.05
Idiopathic	5 (16.6)	7 (23.3 %)	4 (13.3 %)	>0.05

CIC Clean intermittent catheterization, *Triamc* Triamcinolone, *Contrac* Contractubex

Table 2 Evaluation of intergroup Q_{max} and IPSS values, compared to the preoperative period

Comparison follow-up period	CIC ($p =$)	Triamc ($p =$)	Contrac ($p =$)
Q_{max}			
Preoperative 1 month	0.003	0.002	0.001
Preoperative 3 months	0.003	0.003	0.001
Preoperative 6 months	0.004	0.003	0.003
Preoperative 12 months	0.005	0.005	0.005
Preoperative 24 months	0.005	0.004	0.005
IPSS			
Preoperative 1 month	0.004	0.005	0.003
Preoperative 3 months	0.002	0.002	0.001
Preoperative 24 months	0.003	0.003	0.002

CIC Clean intermittent catheterization, *Triamc* Triamcinolone, *Contrac* Contractubex, *p* Friedman variance analysis and Wilcoxon signed-rank test

cells in urine samples were 4.04 ± 2.5. Preoperative urine culture was negative in all patients. Mean white blood cells in urine samples, 1 month after OIU, were 7.08 ± 3.43. All patients' urine cultures were negative 1 month after the intervention. The mean white blood cells in urine samples 3 months after the operation were 4.22 ± 2.97. Urine cultures were negative in all patients 3 months after OIU. No febrile urinary tract infection episodes or any other local or systemic complications dependent on CIC, triamcinolone, and contractubex ointments usage were seen in the participants.

The mean preoperative Q_{max} was 4.31 ml/s. The average score of preoperative IPSS was 23.1 points. In all the three groups, on evaluating intergroup Q_{max} and IPSS values, there were statistically significant improvements compared to the preoperative period (Table 2). However, there

Table 3 Values of Q_{max} and IPSS, comparison among groups

Observation stage (months)	CIC (*n*:30)	Triamc (*n*:30)	Contrac (*n*:30)	*p*
Q_{max}				
Before operation	3.9 ± 3.2	4.8 ± 4.1	4.3 ± 3.9	>0.05
1	17.5 ± 3.3	18.9 ± 3.9	18.7 ± 4.2	>0.05
3	12.8 ± 4.3	13.4 ± 5.1	13.8 ± 6.8	>0.05
6	12.1 ± 7.1	13.3 ± 6.2	13.5 ± 7.4	>0.05
12	11.9 ± 9.4	11.4 ± 8.4	11.6 ± 8.2	>0.05
24	8.9 ± 6.5	9.6 ± 5.1	9.8 ± 6.5	>0.05
IPSS				
Before operation	23.6 ± 7.2	23.2 ± 7.6	22.6 ± 6.8	>0.05
1	17.2 ± 8.2	17.4 ± 7.9	16.9 ± 8.7	>0.05
3	9.5 ± 1.8	9.3 ± 3.1	8.8 ± 2.3	>0.05
24	11.4 ± 5.1	11.1 ± 4.1	11.7 ± 3.6	>0.05

CIC Clean intermittent catheterization, *Triamc* Triamcinolone, *Contrac* Contractubex, *p* Kruskal–Wallis variance analysis and Mann–Whitney *U* test

was no statistically significant difference among the groups in terms of Q_{max} and IPSS scores during the postoperative period (Table 3). Overall recurrence rate was 28.9 %. Recurrence was determined in 26 out of 90 patients at the end of the study. US recurrence was noted in 10 (33.3 %), 9 (30 %), and 7 (23.3 %) of the patients in the CIC, triamcinolone, and contractubex group, respectively. However, these were not statistically significant between the groups ($p > 0.05$). Majority of recurrences (16/26, 61.5 %) occurred in the first 6 months.

Discussion

US disease, mainly classified as anterior and posterior according to localization, posed always a challenge for urologists [9]. Posterior US can be further stratified as bulbous, membranous, and prostatic strictures. US modalities are simple dilatation, urethrotomy, and various urethral reconstructive techniques. The site, length and the underlying pathology of the stricture and presence of previous surgery will determine the treatment modality preference of the urologist [10]. For example, OIU is more successful for strictures of the bulbar urethra than those of pendulous urethra because of more abundance of corpus spongiosum of the former. Bulbomembranous US is usually associated with transurethral manipulation, trauma, and infection, providing satisfactory results with endoscopic treatment [9, 11, 12]. In the present study, iatrogenic causes made up 82.3 % of the etiologic factors and were attributed to endoscopic urologic surgery, urethral catheterization, and

posterior urethral trauma 31.1, 33.3, and 17.7 %, respectively. The stricture was considered idiopathic in 17.7 % of the US patients.

The first known form of US management in history is dilatation [11]. Urethral dilatation is used for localized and posturethroplasty US. However, this procedure, never reported as a curative method per se, has high recurrence rate and requires ultimately repair [10]. OIU, considered as a day care procedure, is performed using cold knife or laser to incise stricture ring at 12 o'clock. At the end of the procedure, the patient is catheterized and the catheter is removed within 24–48 h. Healing occurs by subsequent epithelialization of the constriction ring [13]. OIU, although associated with higher recurrence rates, is recommended in US <1.5 cm. A success rate of 20–40 % was reported for OIU that could be repeated at maximum for 2 or 3 times [14]. Factors associated with OIU failure are stricture length and severity, characterized by the depth of scar tissue and spongiofibrosis, etiology, previous stricture treatment, and location [11, 15, 16]. OIU recurrence rate in strictures <2 cm is 40 % and in strictures >4 cm is 80 % within 12 months of the postoperative period [11]. Recurrence rates of 50–75 % within 2 years after OIU with greater recurrence risk posing greater difficulties have also been reported with a higher incidence within the first 6 months [11, 17]. Idiopathic and post-traumatic strictures are reported as more successfully treated compared to those caused by post-transurethral manipulation (resection and long-term catheterization) and inflammation [18]. Overall, recurrence frequency was determined 28.9 % in the present study. In line with the relevant literature, the majority of recurrences (61.5 %) occurred in the first 6 months.

The low success rate and the recurrence of stricture despite treatment have prompted the search for alternative treatment methods. Self-urethral dilatation following OIU was reported as effective in reducing stricture recurrence rate and prolonging the time for stricture recurrence [19]. Hereby, the aim is to prevent fibrous tissue and contraction formation at the site of incision by stretching, but not tearing, the urethral lumen without producing more scarring. Soft material is more appropriate and less traumatic for stretching the urethra. Stretching prevents contraction of the incised mucosal edges and probably increases the blood flow around the incision site and thus tissue oxygenation while decreasing several cytokine levels such as transforming growth factor-beta, playing a major role in fibrosis pathogenesis of [20]. In our study, urethral dilations following OIU were performed using hydrophilic catheters with a polymer coating that binds on the surface of the catheter. When the polymer coating is submersed into water, it absorbs and binds the water to the catheter. Hence, the surface becomes smooth and very slippery in order to reduce friction, while the catheter is inserted into the urethra.

Several adjuvant therapies, including brachytherapy, injection of captopril, mitomycin C, and steroids, have been proposed to minimize the recurrence rate of US after OIU. Hradec et al. [21] reported that steroid injection decreased recurrence rate from 19.4 to 4.3 %. Hosseini et al. [22] showed that adding triamcinolone ointment to CIC regimen after OIU slightly decreased the recurrence of stricture after the first and second internal urethrotomies. On the other hand, Tabassi et al. [8] did not demonstrate a decrease in recurrence rate of stricture formation; yet, they showed that triamcinolone injection significantly delays the time to recurrence of US after OIU. The lack of significant decrease in the recurrence rate is attributed in their study to the lack of CIC use.

Chung et al. [23] reported that HA/CMC (hyaluronidase and carboxymethylcellulose) instillation after OIU decreased recurrence rate to 9.4 %. The underlying mechanism in US treatment is unclear; however, hyaluronidase ameliorates pulmonary fibrosis and is also used in treatment of hypertrophic scar and keloid. In treatment of hypertrophic scar and keloid, intralesional injection decreases fibroblast proliferation, collagen, and glycosaminoglycan synthesis and suppresses proinflammatory mediators in wound-healing process [24]. Contractubex gel is used in treatment of hypertrophic scar and keloid. It contains cepae extract, heparin, and allantoin and has been widely used for more than 30 years. Clinical studies were conducted in order to prove the safety and efficacy of contractubex gel to evaluate the efficacy and pharmacokinetics of each active ingredient and their combination. Scar-relevant anti-proliferative effect on fibroblasts and its effect on glycosaminoglycan synthesis have been proven in various experimental studies [25].

Relevant literature review revealed that urethral dilation after OIU decreased the recurrences rates [19, 20]. Moreover, several studies, indicated above, have argued that adding agents such as steroids and various antifibrosis agents to CIC regime after OIU decreased recurrences rates or prolongs the recurrence time [8, 22, 26]. In the present study, we compared the effect of three different techniques (CIC, triamcinolone ointment CIC, contractubex ointment CIC) on the recurrence rate of the stricture following OIU. Compared with the preoperative scores, there were significant improvements in Q_{max} and IPSS during the follow-up period in all groups. However, there was not any statistically significant difference among the groups in terms of recurrence throughout the postoperative period.

During the follow-up period (24 months), recurrences rates were 33.3 % in the CIC group, 30 % in the triamcinolone ointment group, and 23.3 % in the contractubex ointment group. Overall, recurrence rate was 28.9 % at the end of the study in line with the rate observed in previously published studies. Adding triamcinolone or contractubex

ointment to CIC regimen after OIU slightly decreased the recurrence of stricture (especially in contractubex ointment group) after the first internal urethrotomies. Recurrence rates were, however, not statistically significant among the three groups ($p > 0.05$). Hence, the present study proves that adding triamcinolone and contractubex gel to CIC regime does not increase the efficacy of CIC in the aftermath of OIU. In the participants of the study, neither febrile urinary tract infection episodes, nor any CIC, triamcinolone, and contractubex ointments related local or systemic complications were diagnosed. Thus, it can be assumed that CIC use per se following internal urethrotomies is an easy, cost-effective, and safe method.

Conclusion

Our results indicate that the urethral dilation protocol with CIC after first OIU is a safe, simple, well-tolerated, office-based procedure. Triamcinolone or contractubex ointments added to CIC do not provide an additional benefit. Currently, urethral dilatation with CIC after first OIU seems to be the only proven procedure in decreasing recurrence rates.

Conflict of interest The authors declare that they have no conflict of interests.

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