Long-term Effect of Colchicine Treatment in Preventing Urethral Stricture Recurrence After Internal Urethrotomy

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Purpose: Urethral stricture, known as a scar formation leading to urethral lumen stricture in sub-epithelial tissue, is the most common late complication of transurethral prostate resection (TURP). The aim of study is to evaluate efficacy of colchicine treatment in preventing urethral stricture recurrence in patients after internal urethrotomy, and to determine whether colchicine treatment had a sustained effect in decreasing stricture recurrences in patients with concomitant diseases.

Methods: Patient data with weak urine stream and/or voiding difficulty, and who had internal urethrotomy in Urology Department of Maltepe University Hospital between dates 01 January 2011 and December 2016 were collected. They were randomized to colchicine receiving, and non-receiving arms. Colchicine was given 1 g/day orally for two months, and primary efficacy point was defined as urethral stricture development in 3, 6, and 12 months after internal urethrotomy.

Results: The study was conducted on 84 males with the mean age of 67.7 ± 7.5 years. The mean ages of colchicine receivers and non-receivers were 68.2 ± 7.6 and 67.1 ± 7.6 years, respectively. Recurrence rate of urethral stricture was significantly lower in colchicine receivers ($P = .044$) than non-receivers. In overall evaluation, recurrence rate of urethral stricture was significantly low, if there was only one comorbidity ($P = .006$), but rates were significantly higher in presence of three ($P = .010$) and four ($P = .040$) comorbidities. No significant difference in recurrence rates was determined in patients without comorbidities or with two comorbidities ($P > .05$).

Conclusion: Combination of oral colchicine with internal urethrotomy reduces recurrence rates of urethral stricture significantly.

Keywords: urethral stricture; colchicine; Peyronie's disease; male; fibrosis; recurrence.

INTRODUCTION

Urethral stricture, the oldest and most difficult disease to treat in urology, is known to be caused by scar formation leading to urethral lumen stenosis in sub-epithelial tissue. It is observed with the incidence of 2.7% in late phase of endourological interventions such as transurethral prostate resection.[1,2] It was first reported in 1974, and direct visual internal urethrotomy (DVIU) was performed more commonly than blinded urethrotomy methods such as periodic urethral dilation in urethral stricture treatment, because it was easy to perform and had a short recovery duration. The curative rate of internal urethrotomy was reported as 20% with the most common complication high recurrence rate. During the procedure, scarred tissue could not be taken, and thus internal urethrotomy might be curative in strictures shorter than 1 cm, and with minimal spongiofibrosis.[1] Pansadoro and Heyns reported recurrence rates as 61%, 100% and 100% in their 4-year patient follow-up studies reciprocally.[3] On the other hand, studies indicated that mean recurrence rates of 68% after a single urethrotomy intervention, 58% after a bulbar stricture, and 89% after a penile urethral stricture.[3] In general, the usual disease initiation occurs after urethral mucosal lesion and infection which is followed by a scar tissue. Today, most urethral strictures are resulted from trauma such as endoscopic urological interventions.

Although Peyronie's disease is an uncommon condition in middle aged men, inflammation is observed in the tunica causing ultimately scarring and penile curvature. It is believed that fibrin intravasation occurs from blood circulation into tunica albuginea after a trauma. Fibrin reaching tunica albuginea stimulates profibrotic TGF-1 compound release, then induces formation of reactive oxygen species (ROS). Thus, irregular collagen accumulation is observed, and destruction of newly formed collagen mass is hindered, which leads eventually to plaque calcification.[4]

It is assumed that etiopathogenesis of urethral stricture and Peyronie's disease may have the common background as trauma and fibrosis as well. Patients at early stages of Peyronie's disease are candidates for medical treatment. In the literature, there are studies conducted with various biological agents for the disease such as calcium channel blockers, corticosteroids, vitamin E, and colchicine.[5] Although the most effective treatment has not been determined for Peyronie's disease yet, combination of verapamil with vitamin E and col-

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Table 1. Evaluation of Descriptive Characteristics According to Groups

		Colchicine receivers (n=41)	Colchicine non-receivers (n=43)	*p*
Age (year)	Min-Max (Median)	55-82 (66)	54-84 (66)	[a]0.488
	mean±SD	68.2 ± 7.6	67.1 ± 7.6	
Etiology; n (%)	TURP	31 (75.6)	38 (88.4)	[c]0.127
	Open prostatectomy	10 (24.4)	5 (11.6)	
Residual urine amount (cc)	Min-Max (Median)	0-800 (160)	0-800 (160)	[b]0.939
	mean ± SD	224.88 ± 212.85	207.44 ± 179.60	
Mean urine flow rate (ml/sec)	Min-Max (Median)	0-8 (4)	1-8 (4)	[a]0.754
	mean ± SD	4.24 ± 1.93	4.12 ± 1.79	
Maximum urine flow rate (ml/sec)	Min-Max (Median)	0-14 (8)	3-13 (8)	[a]0.729
	mean ± SD	8.20 ± 3.33	7.95 ± 3.03	

[a]Student-*t* Test [b]Mann Whitney *U* Test [c]Pearson Chi-Square Test
SD; Standard deviation

chicine has shown better pain control while reducing penile curvature, dimensions of calcification and the degree of erectile dysfunction, thus improving the quality of life.[5]

Considering the similar etiological and pathophysiological backgrounds for both diseases, the present study was conducted to evaluate efficacy of colchicine treatment in preventing urethral stricture in patients after internal urethrotomy, and to determine whether colchicine treatment had a sustained effect in decreasing recurrence of urethral strictures in patients with multiple comorbidities. To our knowledge, colchicine treatment in the prevention of urethral stricture has not been investigated yet, this is the first study evaluating the effect of oral colchicine against this common long-term complication of TURP.

PATIENTS AND METHODS

Study Population

Medical data of patients who applied to Urology Department of Maltepe University Hospital with complaints of weak urine stream or difficulty on urination following a past TURP operation between dates 01 January 2011 and December 2016 were collected, and after internal urethrotomy patients were randomized either to colchicine receiver or non-receiver study arms. Random numbers were obtained from computer software. The treatment modality for each patient was inserted in envelopes. When the eligible patient agreed to participation, the envelopes were opened by one of the researchers and allocated treatment started as described below. The outcomes were evaluated by investigators who were blind to treatment assignments.

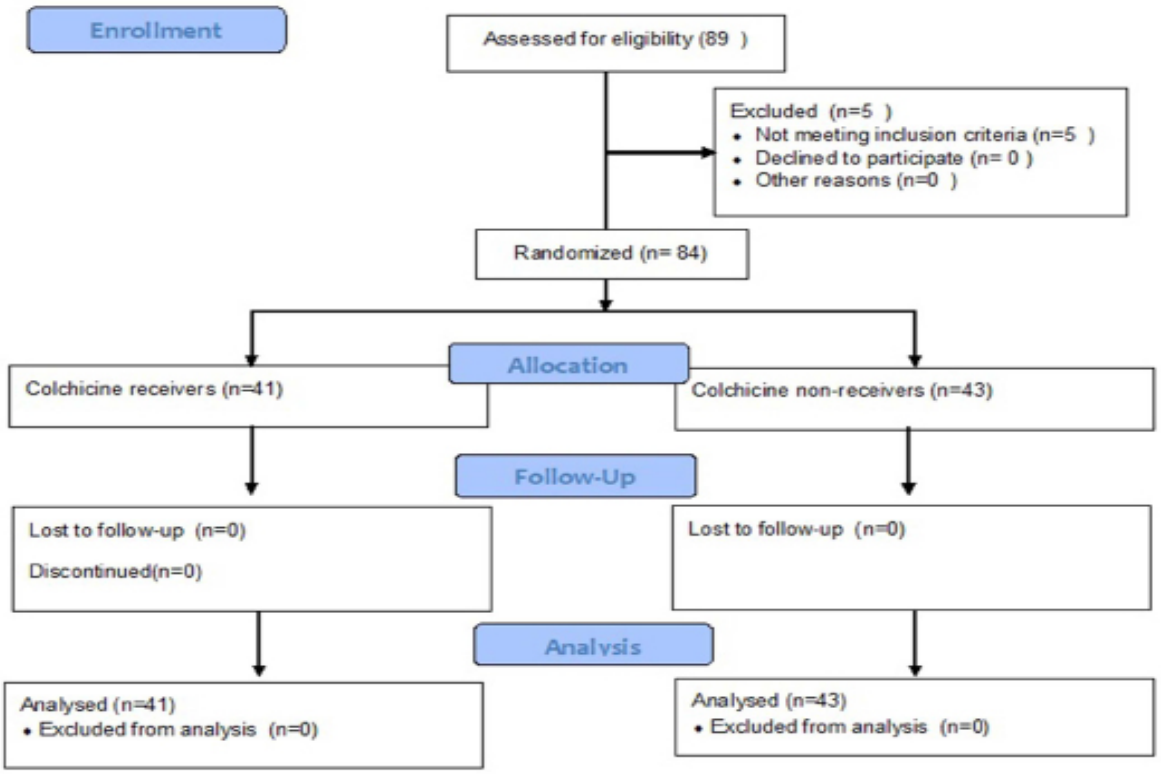

Figure 1. Study flow diagram

Table 2. Evaluation of Urethral Stricture Recurrence According to Groups

		Colchicine receivers (n=41)	Colchicine non-receivers (n=43)	cp
Recurrence of urethral stricture; n (%)	Recurrence (+)	6 (14.6)	14 (32.6)	0.044*
	Recurrence (-)	35 (85.4)	29 (67.4)	

[c]PearsonChi-Square Test *$p < 0.05$

Procedures

Urethrography-uroflowmetry was performed to assess the presence and extent of urethral stricture. Colchicine was given 1 g/day orally (2x0.5 mg) for two months, and primary efficacy point was defined as whether urethral stricture recurrence was developed or not in 3, 6, and 12 months after internal urethrotomy in both study arms.

Inclusion and exclusion criteria

Patients undergoing TUR-P having urethral stricture complication which is shorter than 1.5 cm, treated with internal urethrotomy were included in the study.

Patients who had urethral stricture longer than 1.5 cm and/or multiple urethral strictures, and developed urethral stricture after external trauma were excluded from the study. Patients who have previous history of hypersensitivity to colchicine, twice as high AST or ALT as the hospital's reference value, creatinine level of 2.0 mg/dL or higher, past history of malignant tumor, peptic ulcer, serious hematological disorder, serious cardiac disorder, aspirin induced asthma and patients who are ineligible for the study as judged by the investigator were exluded. Flow diagram of the study are summarized in **Figure 1** .

Evaluations

Hospital Information Management Systems (MediPro Software and Pusula) determined medical information of eligible patients, such as demographic and investigation results, comorbidities, etiologies, preoperative IPSS scores, results of uroflowmetry, and stricture recurrences. Hospital Information Management Systems (MediPro Software and Pusula) determined medical information of eligible patients, such as radiological and laboratory results, comorbidities, etiologies, preoperative IPSS scores, results of uroflowmetry, and stricture recurrences. The comorbidities were also confirmed by combining history taking, previous consultations.

The study was initiated after obtaining approval of Local Ethics Committee (Maltepe University Medical Faculty Ethics Committee Number 2017/900/08).

Statistical Analysis

The external statistician remained blind to outcomes variables. NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. The continuous variables; the urinary flow rate, residual urine and IPPS scores were measured to assess urethral stricture and were expressed as means and standard deviations. Variables in terms of comorbidities between colchicine receiver and non-receiver groups were compared using Pearson Chi-Square Test and Fisher's Exact Test. Comparisons of groups with normally distributed quantitative data were performed by using Student t test. If the distribution was abnormal, comparisons were performed by using Mann Whitney *U* test. The level of significance was determined as $p < 0.05$.

RESULTS

The study was conducted on 84 males with the mean age of 67.7 ± 7.5 (range = 54-84) years. The mean ages of colchicine receivers and non-receivers were 68.2 ± 7.6 and 67.1 ± 7.6 years, respectively (**Table 1**). Groups were age matched ($P > .05$). The average diameter of male urethra without stricture was 9-10 mm.

In colchicine receiver group, TURP was performed in 75.6% (n = 31), and open prostatectomy was performed in 24.4% (n = 10) patients. In colchicine non-receiver group, TURP was performed in 88.4% (n = 38) patients, whereas open prostatectomy was performed in 11.6% (n = 5) patients. Residual urine amount, mean urine flow rate, and maximum urine flow rate were compared between the groups, and no significant difference was determined ($P > .05$) (**Table 1**).

Recurrence rate of urethral stricture was significantly lower in colchicine receivers (14.6%) than non-receivers (32.6%) ($P = .044$) (**Table 2**).

The recurrence rates were significantly different according to number of comorbidities ($P = .001$). According to paired comparisons to determine number of

Table 3. Evaluation of Relationship Between Comorbidity and Urethra Stricture Recurrence Rates According to Groups

		Colchicine receivers (n = 41) US Recurrence (+)	(-)	*p*	Colchicine non-receivers (n = 43) US Recurrence (+)	(-)	*p*
Comorbidity	Positive	3 (50.0)	24 (68.6)	d0.393	14 (100)	18 (62.1)	d0.008**
	Negative	3 (50.0)	11 (31.4)		0 (0)	11 (37.9)	
DM	Positive	1 (16.7)	13 (37.1)	d0.645	12 (85.7)	8 (27.6)	c0.001**
	Negative	5 (83.3)	22 (62.9)		2 (14.3)	21 (72.4)	
COPD	Positive	2 (33.3)	3 (8.6)	d0.148	6 (42.9)	2 (6.9)	d0.009**
	Negative	4 (66.7)	32 (91.4)		8 (57.1)	27 (93.1)	
HT	Positive	3 (50.0)	20 (57.1)	d1.000	12 (85.7)	12 (41.4)	c0.006**
	Negative	3 (50.0)	15 (42.9)		2 (14.3)	17 (58.6)	
CAD	Positive	2 (33.3)	6 (17.1)	d0.578	7 (50.0)	2 (6.9)	d0.003**
	Negative	4 (66.7)	29 (82.9)		7 (50.0)	27 (93.1)	

[c]PearsonChi-Square Test dFisher'sExact Test **$p < 0.01$

Abbreviations: US, Urinary stricture; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; HT, hypertension; CAD, coronary arterial disease.

comorbidity which caused difference, recurrence rate of urethra stricture was significantly low if there was only one comorbidity (P = .006), but the rates were significantly higher if there were three (P = .010) and four (P = .040) comorbidities. There was no significant difference in the rates in patients without comorbidities and with two comorbidities (P > .05) (**Table 3**).

DISCUSSION

The average lifespan in elderly men has been extended with advances in diagnostic and treat-ment modalities in the past decades therefore, in recent years, the number of elderly patients having benign prostate hyperplasia (BPH) with several comorbidities who meet the criteria for recommended sur¬gery has increased.[2] However, surgical procedures including the widely used TURP have complications such as hemorrhage, electrolyte disturbances and long-term urethral strictures particularly in elderly patients with concomitant cardiovascular, pulmonary, and another organ diseases.[6]

In the present study, we evaluated patients suffering from urethral stricture following prostatectomy procedures, and determined that colchicine may be an effective option to decrease stricture recurrence rate after internal urethrotomy during 1-year follow-up. To the best of our knowledge this study is the first one, where combination of internal urethrotomy and oral colchicine treatment was employed to prevent recurrence of urethral stricture. The underlying conditions are still not clearly known how the process follows after internal urethrotomy, but it is assumed by some authors that if epithelialization progresses completely before wound contraction, urethrotomy may be successful.[2,6] Therefore, if wound contraction is delayed by any drug or procedure, then the recurrence rate of urethral stricture will decrease.

Mazdak et al.[1] conducted a prospective study on 50 patients with anterior urethral stricture, who underwent internal urethrotomy, and randomized to 40 mg submucosal triamcinolone injection receivers and non-receivers. After a mean follow-up of 13.7 ± 5.5 months, they reported that recurrence rate was significantly decreased in triamcinolone receiving arm. The urethral stricture was (21.7 %) in the triamcinolone group and in 11 patients (50 %) in the control group. In our study recurrence rate of urethral stricture was significantly lower in colchicine receivers (14.6 %) compared to the studies combining urethrotomy with local medication. Corticosteroid injections are a well-established pharmacological treatment for skin scars, mucosal strictures, and in a few cases of urethral strictures to decrease collagen production.[1,7] However, the reported success rates were not very promising especially for urethral stricture recurrence rates. Korhonen et al. indicated that total success rate was only 11 % at the end of the first year in patient group that received internal urethrotomy plus methylprednisolone.[8] Tavakkoli Tabassi K et al. performed a double-blind, randomized,
placebo-controlled study in which experimental group (34 patients) received triamcinolone acetonide injection and the control group (36 patients) received an injection of sterile water after internal urethrotomy. Complication and recurrence rates in experimental group were lower than the control group, but the difference was not statistically significant. However, time to recurrence decreased significantly in triamcinolone group suggesting that intralesional corticosteroid injection may delay the recurrence.[10]

These lower success rates with corticosteroids may be explained with the fact that routine urethral instrumentation destroys the wound and simultaneous subepithelial or intralesional medication with short duration of action may not reverse the fibrotic process. Moreover, Ye Tian et al. report that active surveillance is a better option for preventing stricture recurrence as compared with routine invasive manipulations as shearing force caused by them splits the epithelium. Urine extravasates through these fissures or ulcers leading to subepithelial fibrosis.[10]

Therapeutic potential of colchicine was recently recognized in Peyronie's disease. Its mechanism of action was described by blocking the path of arachidonic acid lipoxygenase, thus preventing leukotriene formation by reducing inflammation and chemotaxis and interferes with procollagen transcellular migration. Therefore, procollagen formation was decreased, and collagenase production was increased. Its mechanism of action would lead to antifibrotic, antimitotic and anti-inflammatory effects.[4,5]

In the present study, we inspired from promising results of colchicine in Peyronie’s disease treatment. Data of patients with anterior urethral stricture who underwent internal urethrotomy and received oral colchicine treatment in the subsequent 2 months were collected. It was most probable that significant decrease in recurrence rate of stricture in the colchicine receivers was related to antifibrotic and anti-inflammatory effects of colchicine. When demographic characteristics of our study group was considered, presence of multiple comorbidities were expectable.[6] They could decrease the success rate of urethrotomy, and thus recurrent interventions would be required. Comorbidities in the study cohort were mainly diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and coronary arterial disease. Combined treatment of internal urethrotomy with oral colchicine had positive influences in decreasing recurrence rates of urethral stricture in patients with three or four comorbidities.

There are some limitations in our study. Firstly, the sample size was small and could not be increased. However, it could be accepted as a pilot study, which would help to design new prospective randomized studies about the same issue. Secondly, we presented here 1-year follow-up results of the study. Five-year follow-up results would be more helpful in interpreting efficacy of this combination treatment, as it was frequently reported in the literature. Thirdly, data about cost-effectiveness and patient’s quality of life would show whether this treatment modality could reach secondary endpoints.

CONCLUSIONS

Combination of oral colchicine with internal urethrotomy reduced the stricture recurrence rate significantly. Further prospective randomized studies with larger sample sizes are required to determine efficacy and safety of this new treatment approach in more detail.

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None

CONFLICT OF INTEREST

The authors report no conflict of interest.

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