

Full Length Research Paper

Long-term effect of colchicine treatment in preventing urethral stricture recurrence after internal urethrotomy: A Retrospective Trial

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Urethral stricture is known to be caused by scar formation leading to urethral lumen stricture in sub-epithelial tissue. It is the most common late complication following transurethral prostate resection (TURP). The aim of this study is to evaluate the efficacy of colchicine treatment in preventing recurrence of 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 concomitant diseases. Medical data of patients who had anuria or voiding difficulty and internal urethrotomy in Urology Department of Maltepe University Hospital between January 1, 2011 and December 2016 were collected, and were randomized to colchicine receiver and no-receiver arms. Colchicine was given 1 g/day orally (2x0.5 mg) for two months, and primary efficacy point was defined as whether urethral stricture was developed in 3, 6, and 12 months after internal urethrotomy in both study arms. 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. Recurrence rate of urethral stricture was significantly lower in colchicine receivers (14.6%) than non-receivers (32.6%) (p=0.044 and p<0.05, respectively). In overall evaluation, recurrence rate of urethral stricture was not correlated with an individual concomitant disease, but the rates were increased in the presence of three or four comorbidities. Combination of oral colchicine with internal urethrotomy reduces recurrence rates of urethral stricture recurrence rate significantly.

Keywords: Urethral stricture, colchicine, internal urethrotomy, peyronie disease, male.

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.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

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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 an 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 colchicine has showed 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.

MATERIAL AND METHOD

In the present retrospective study, medical data of

patients who applied to Urology Department of Maltepe University Hospital with complaints of anuria or urination difficulty 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. Colchicine was given 1 g/day orally (2x0.5 mg) for two months, and primary efficacy point was defined as whether urethral stricture was developed in 3, 6, and 12 months after internal urethrotomy in both study arms.

Patients who were sensitive to colchicine, 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.

Hospital Information Management Systems (MediPro Software and Pusula) determined retrospectively medical information of eligible patients, such as demographic and investigation results, comorbidities, etiologies, preoperative IPSS scores, results of uroflowmetry, and stricture recurrences.

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

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum); 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. Pearson Chi square test and Fisher's exact test were used in comparisons of quantitative data. 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 ($p > 0.05$).

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

Table 1. Evaluation of Descriptive Characteristics According to Groups.

		Colchicine receivers (n=41)	Colchicine non-receivers (n=43)	p
Age (year)	<i>Min-Max (Median)</i>	55-82 (66)	54-84 (66)	^a 0.488
	<i>mean±SD</i>	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)	<i>Min-Max (Median)</i>	0-800 (160)	0-800 (160)	^b 0.939
	<i>mean±SD</i>	224.88±212.85	207.44±179.60	
Mean urine flow rate (ml/sec)	<i>Min-Max (Median)</i>	0-8 (4)	1-8 (4)	^a 0.754
	<i>mean±SD</i>	4.24±1.93	4.12±1.79	
Maximum urine flow rate (ml/sec)	<i>Min-Max (Median)</i>	0-14 (8)	3-13 (8)	^a 0.729
	<i>mean±SD</i>	8.20±3.33	7.95±3.03	

^aStudent-t Test
SD; Standard deviation

^bMann Whitney U Test

^cPearson Chi-Square Test

between the groups, and no significant difference was determined ($p>0.05$) (Table 2).

Recurrence rate of urethral stricture was significantly lower in colchicine receivers (14.6%) than non-receivers (32.6%) ($p=0.044$ and $p<0.05$, respectively) (Table 3) (Figure 1).

The recurrence rates were significantly different according to number of comorbidities ($p=0,001$) (Figure 2). According to paired comparisons to determine number of comorbidity which caused difference, recurrence rate of urethra stricture was significantly low if there was only one comorbidity ($p=0.006$), but the rates were significantly higher if there were three ($p=0.010$) and four ($p=0.040$) comorbidities (Figure 3). There was no significant difference in the rates in patients without comorbidities and with two comorbidities ($p>0.05$).

DISCUSSION

The average lifespan in elderly men has been extended with advances in diagnostic and treatment 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 surgery 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 retrospectively reviewed 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 retrospective 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. 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 Therapeutic potential of colchicine was recently recognized in Peyronie's disease. Its mechanism of action was described by blocking the path of arachidonic acid lipoygenase, thus preventing leukotriene formation

Table 2. Evaluation of Urethral Stricture Recurrence According to Groups.

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

^cPearsonChi-Square Test

*p<0.05

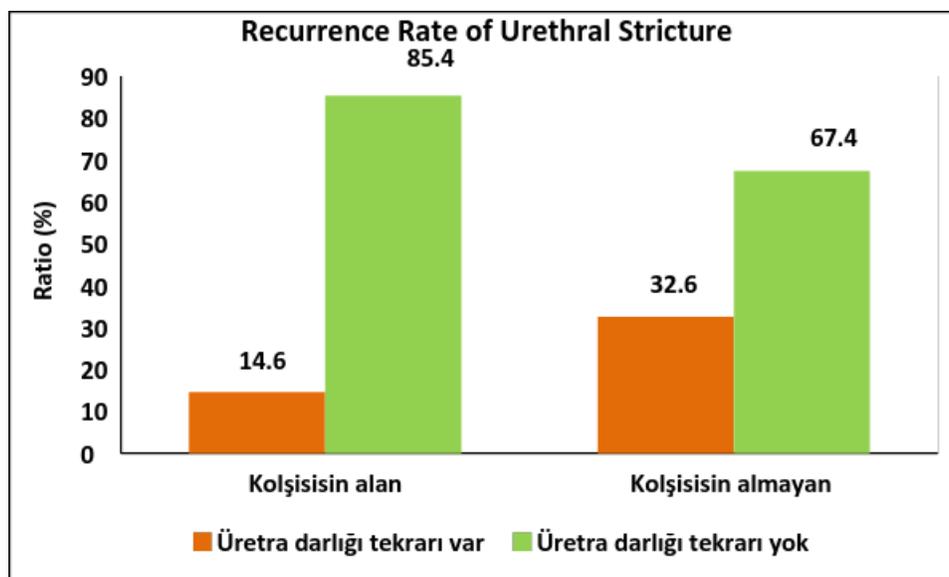
Table 3. Evaluation of Relationship Between Comorbidity and Urethra Stricture Recurrence Rates According to Groups.

		Colchicine receivers (n=41)			Colchicine non-receivers (n=43)		
		US Recurrence		p	US Recurrence		p
		(+)	(-)		(+)	(-)	
Comorbidity	Present	3 (50.0)	24 (68.6)	^d 0.393	14 (100)	18 (62.1)	^d 0.008**
	Negative	3 (50.0)	11 (31.4)		0 (0)	11 (37.9)	
DM	Present	1 (16.7)	13 (37.1)	^d 0.645	12 (85.7)	8 (27.6)	^c 0.001**
	Negative	5 (83.3)	22 (62.9)		2 (14.3)	21 (72.4)	
COPD	Present	2 (33.3)	3 (8.6)	^d 0.148	6 (42.9)	2 (6.9)	^d 0.009**
	Negative	4 (66.7)	32 (91.4)		8 (57.1)	27 (93.1)	
HT	Positive	3 (50.0)	20 (57.1)	^d 1.000	12 (85.7)	12 (41.4)	^c 0.006**
	Negative	3 (50.0)	15 (42.9)		2 (14.3)	17 (58.6)	
CAD	Positive	2 (33.3)	6 (17.1)	^d 0.578	7 (50.0)	2 (6.9)	^d 0.003**
	Negative	4 (66.7)	29 (82.9)		7 (50.0)	27 (93.1)	

^cPearsonChi-Square Test^dFisher'sExact Test

**p<0.01

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

**Figure 1.** Recurrence rates of urethral stricture according to groups.

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}

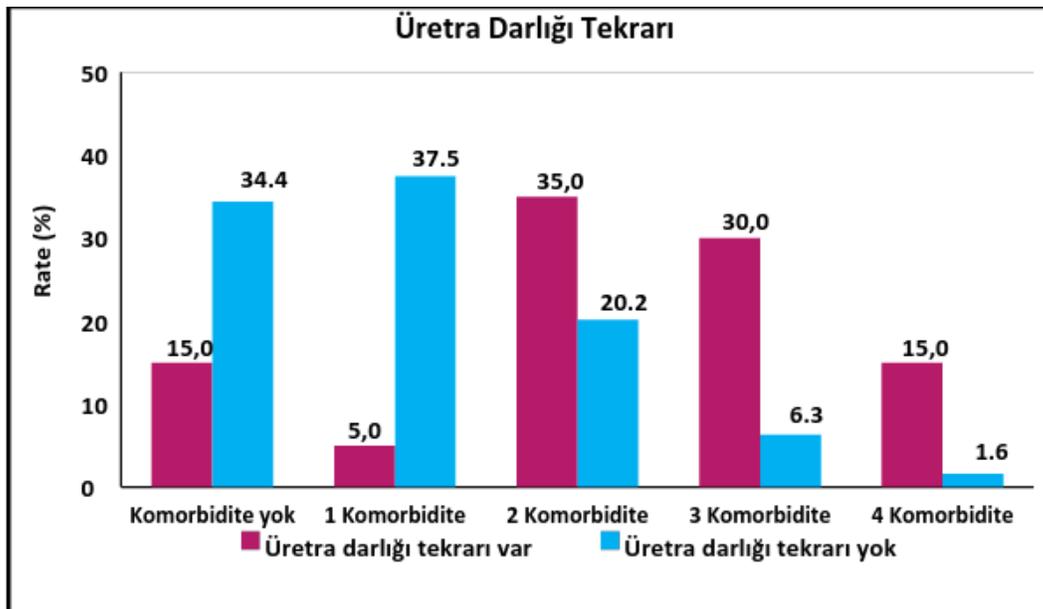


Figure 2. Recurrence rates of urethral stricture according to number of comorbidities.

In the present retrospective 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 is 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, as it was a retrospective study, 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.

CONCLUSION

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.

The authors declare no conflict of interest.

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