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ORIGINAL PAPER

Minimal invasive treatment of urethral strictures: An experimental study of the effect of Paclitaxel coated balloons in the wall of strictured rabbit's urethra

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Summary ***Purpose: The aim of this study is the evaluation of the distribution of Paclitaxel (PTX) released by a coated balloon in the layers of rabbit's urethra. Methods: 18 rabbits were included. A Laser Device was used for the stricture formation. After two weeks, dilation of the strictured urethra was performed by using Advance 35LP PTA balloons and Advance 18 PTX PTA balloons. The experimental models were divided into 3 groups. The group A included two rabbits without any intervention except for the stenosis procedure. Group B compromised six rabbits that underwent dilation with Advance 35LP PTA balloons. Group C consisted of 10 rabbits to which dilation with both Advance 35LP PTA balloons and Advance 18 PTX PTA balloons was applied. Histological evaluation and Immunohistochemistry were performed on all specimens.***

Results: Inflammation, fibrosis and ruptures were detected in the specimens of the study. In specimens of Group C the decrease of inflammation and fibrosis rate was greater. Anti-PTX antibody was detected in the epithelium, lamina propria and smooth muscle layer of all specimens of urethras that have been harvested immediately and 1 day after the dilation with Advance 18 PTX PTA balloon and it was not observed in any layer of the urethral wall of the rest of the examined specimens of Group C. Conclusions: PTX's enrichment was detected in the smooth muscle layer of all specimens that have been harvested immediately and 24h after the dilation with Advance 18 PTX PTA balloons. PTX may play an inhibitive role in the recurrence of the stenosis.

KEY WORDS: Urethra; Stricture; Balloon; Dilation; Paclitaxel.

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INTRODUCTION

Urethral strictures constitute a significant urological disease that presents a high incidence in the male population (1). The available minimally invasive approaches are associated with high recurrence rates (2). *Drug Coated Balloons* (DCBs) that release cytostatic substances have been used for the prevention of vascular stenosis (3). In the same concept, these balloons can be used for the reduction of the recurrence rates after the management of the urethral strictures with balloon dilation (4). The successful effect of the drug requires its distribution to the muscle layer of the urethra where the smooth muscle cells are present (5). These cells are responsible for restenosis through their proliferation and production of inappropriate collagen (6). Paclitaxel has been proven to inhibit the proliferation of these cells and reduce the production of collagen (7, 8). Thus, the use of paclitaxel-coated balloons for the prevention of restenosis after balloon dilation seems to be a promising approach. The distribution of paclitaxel in the normal rabbit urethra has already been evaluated (9). The aim of this experimental study is to provide evidence about the benefits of the application of DCBs in urethral strictures. The current protocol aims to provide evidence on the distribution of *paclitaxel* (PTX) in the wall of the strictured urethra of rabbits. The drug should be distributed to the muscle layer of the urethra in order to achieve maximal efficiency. Moreover, data regarding the efficacy of this approach on the recurrence of the urethral strictures treated by the paclitaxel-coated balloons will be presented.

Materials and Methods

Ethical standards

The current experimental trial was pre-approved by the Veterinary Administration of the Prefecture of Western Greece and the animals were treated according to the current veterinary protocols.

Experimental models

Eighteen domestic male rabbits weighing between 3-4 kg were included in the conduction of the current experimental study.

Sedation

The rabbits were sedated by intramuscular injection with a combination of ketamine and xylazine.

Intervention

The experimental models were placed in the supine posi-

tion. A urethroscopy was conducted on each rabbit by using a 7FR pediatric nephroscope (Storz 27095AA Pediatric Nephroscope Set, Karl Storz SE & Co. KG, Tuttlingen, Germany) . Stricture formation took place by using the Thulium fiber laser device (Quanta Fiber Dust, Samarate, Italy) with a 200-μm fiber and power settings 8W (0.5J x 16Hz). Strictures were formed in the penile urethra approximately 1-2 cm before the sphincter (Figure 1). After 2 weeks, an urethrography and an urethroscopy of each model were held. The presence of a urethral stricture of approximately 1 cm in length in all experimental models was confirmed by these procedures. Dilation of the stricture with Advance 35LP- high pressure balloon (HPB) (Cook Medical, Cook Ireland Ltd., Limerick, Ireland - 16, diameter 6 mm/ length 40 mm) and Advance 18PTX- DCB (Cook Medical, Cook Ireland Ltd., Limerick, Ireland – 16, diameter 6 mm/ length 40 mm) depending on the study group was conducted in the same session (Figure 2). A 0.035" inch hydrophilic guidewire was inserted into each urethral lumen under fluoroscopic guidance. A stiff guidewire exchanged the hydrophilic wire over a 7 Fr ureteral catheter (Cook Medical, Cook Ireland Ltd., Limerick, Ireland). The balloon dilator was placed over the stiff guidewire and inflated to its maximum pressure of 8 atm for at least 5 minutes and then was emptied and removed. Follow-up to 6 weeks with urethrography every 2 weeks depending on the study group took place.

Study groups

The experimental models were divided into 3 main groups (groups A, B, and C). The rabbits were sacrificed on specific time periods and the whole length their urethra was obtained. Group A: The control group included 2 experimental models where stricture formation was performed without any other intervention. These specimens were obtained two weeks after the stricture formation.

Group B: 6 rabbits were included in this group. Two weeks after the stricture formation, dilation with HPB took place. The subgroups were divided based on the postoperative duration until the harvesting of the urethras to provide information on the stricture condition after conventional balloon dilation. All subgroups included 2 rabbit's urethras and were defined as:

Group B.1: Harvested urethras 2 weeks after the dilation procedure.

Group B.2: Harvested urethras 4 weeks after the dilation procedure.

Group B.3: Harvested urethras 6 weeks after the dilation procedure.

Group C: 10 experimental models were included in this study group. Two weeks after the stenosis formation, dilation with HPB, at first, and then with DCB took place at the same time. The subgroups were divided in the same way as in Group B. 2 rabbit's urethras were included in each subgroup. The subgroups of group C were defined as:

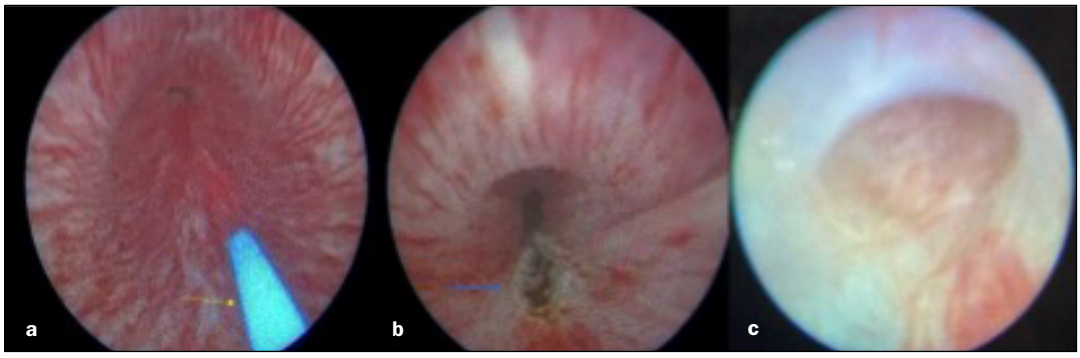
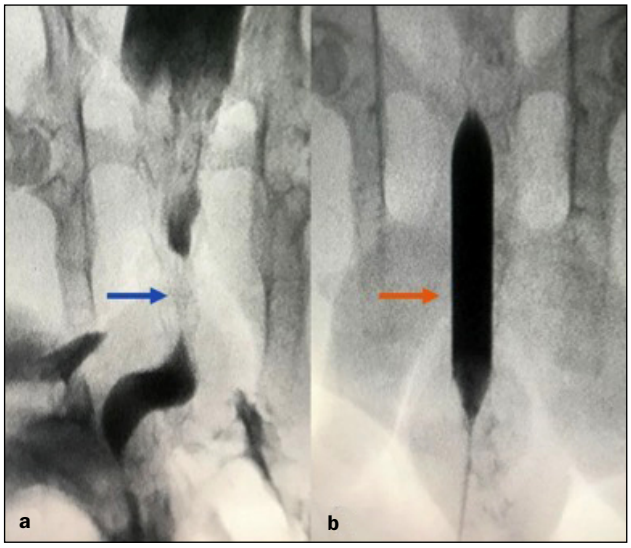


Figure 1.
Endoscopic images before and after the stricture formation
a. The laser fiber inside the urethral lumen during urethoscopy.
b. The initiation of stricture formation.
c. Urethral stricture 2 weeks after the initial intervention.



Group C.1: Harvested urethras immediately after the dilation procedure with both HPB and DCB.

Group C.2: Harvested urethras 1 day after the dilation procedure with both HPB and DCB.

Group C.3: Harvested urethras 2 weeks after the dilation procedure with both HPB and DCB.

Group C.4: Harvested urethras 4 weeks after the dilation procedure with both HPB and DCB.

Group C.5: Harvested urethras 6 weeks after the dilation procedure with both HPB and DCB.

Figure 2.
Fluoroscopic images
a. Antegrade urothrography. Recognition of the stricture (blue arrow).
b. Dilation with Advance 18 PTX PTA balloon on the previously depicted stricture (orange arrow).

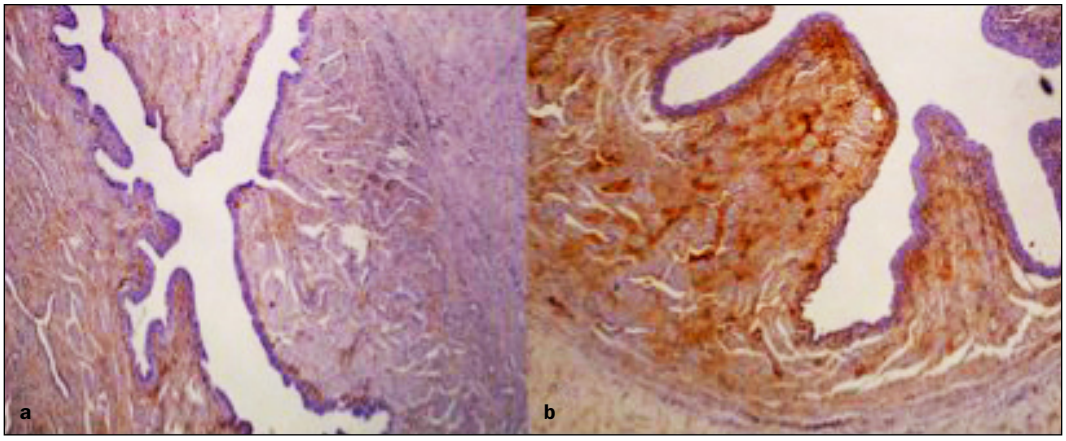


Figure 3.
Histolpathological Images from the urethral wall of the experimental models.
a. *Specimen from Group C.4*
b. *Specimen from Group C.1*

Pathology process

The specimens of urethras were embedded in formalin and standard fixing process with paraffin was performed. 4μm-thick sections were enriched with hematoxylin/eosin and were placed on gelatin-eluting glass slides.

Histological evaluation of the specimens

All glass slides were tested by the same expert uropathologist. This procedure is conducted by using a standard light microscope with an attached camera (*Nikon ECLIPSE 50i and Nikon HD color camera head DS-Fi2, Nikon GmbH, Dusseldorf, Germany*). Slides were received from each urethral specimen for the conduction of histology and immunohistochemistry.
Morphological alterations (stricture, connective tissue formation) and inflammation were microscopically evaluated. The inflammation rate of the urethral layers was estimated according to Nakada classification (10). Normal appearance of the urethra after microscopic examination was graded as 0 and severe inflammation was graded as 3.

Immunohistochemistry (IHC)

IHC was performed by using the monoclonal anti-body for IHC (Anti-Taxol antibody from Abcam). This process aimed into elucidating the enrichment of PTX in different layers of urethral wall. The PTX's presence and the location of the agent in the examined slides was evaluated with IHC (Figure 3).

Results

Histology

Ruptures across the urethral wall and inflammation were observed in all specimens. In Group A the inflammation grade was 3 (according to Nakada classification), fibrosis was observed in all layers (squamous epithelium, submucosa, smooth muscle layer) of the urethra. In Groups B.1 and B.2 the inflammation grade was 2 and fibrosis was observed in all layers of the urethral tissue. In Group B.3 fibrosis in all layers of the urethral wall and inflammation (Grade 1) were observed. As for the Group C.1 and C.2, the inflammation Grade was 3 in both groups and fibrosis was observed in the epithelium tissue, submucosa and smooth muscle layer. Blood clots were found in both groups. In Group C.3 and C.4 the inflammation grade of the urethral wall was 2 and 1, respectively. Fibrosis was observed only in the squamous epithelium and submucosal layer in both groups. In Group C.5 the inflammation grade was 1 and fibrosis was observed only in the epithelium tissue of the urethral wall.
These results are presented in Table 1.

Table 1.
Histological findings of the harvested urethral specimens regarding the Inflammation Grade, Fibrotic Formation, and the integrity of the urethral lumen.

Experimental Model	Study Group	Inflammation Grade (Nakada Classification)	Fibrosis
1	A (stricture formation-no intervention)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
2	A (stricture formation-no intervention)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
3	B.1 (stricture formation-dilation 35LP PTA balloon-2 weeks)	2	· Squamous epithelium · Submucosa · Smooth Muscle Layer
4	B.1 (stricture formation-dilation 35LP PTA balloon-2 weeks)	2	· Squamous epithelium · Submucosa · Smooth Muscle Layer

5	B.2 (stricture formation-dilation 35LP PTA balloon-4 weeks)	2	· Squamous epithelium · Submucosa · Smooth Muscle Layer
6	B.2 (stricture formation-dilation 35LP PTA balloon-4 weeks)	2	· Squamous epithelium · Submucosa · Smooth Muscle Layer
7	B.3 (stricture formation-dilation 35LP PTA balloon-6 weeks)	1	· Squamous epithelium · Submucosa · Smooth Muscle Layer
8	B.3 (stricture formation-dilation 35LP PTA balloon-6 weeks)	1	· Squamous epithelium · Submucosa · Smooth Muscle Layer
9	C.1 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-immediately)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
10	C.1 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-immediately)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
11	C.2 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon -24h)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
12	C.2 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-24h)	3	· Squamous epithelium · Submucosa · Smooth Muscle Layer
13	C.3 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-2 weeks)	2	· Squamous epithelium · Submucosa
14	C.3 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-2 weeks)	2	· Squamous epithelium · Submucosa
15	C.4 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-4 weeks)	1	· Squamous epithelium · Submucosa
16	C.4 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-4 weeks)	1	· Squamous epithelium · Submucosa
17	C.5 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-6 weeks)	1	· Squamous epithelium
18	C.5 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-6 weeks)	1	· Squamous epithelium

IHC

The specimens of Group C were examined for the presence of the antibody of PTX. In all specimens examined of Group C.1 and C.2, the anti-PTX antibody was found in the squamous epithelium, submucosa and smooth muscle layer of rabbit's urethra. In one specimen of group C.1, the anti-PTX antibody was observed, also, in the corpus cavernosum and the connective tissue of the rabbit's penis. In the rest examined specimens of Group C the antibody wasn't detected in any layer of the urethral wall. The results of the IHC are summarized in Table 2.

Table 2.

Paclitaxel (PTX) distribution in the layers of the examined specimens of the urethral wall based on the Immunohistochemical report.

Experimental Model	Study Group	Squamous Epithelium	Submucosal Tissue	Smooth Muscle Layer
9	C.1 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-immediately)	+	+	+
10	C.1 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-immediately)	+	+	+
11	C.2 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon -24h)	+	+	+
12	C.2 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon -24h)	+	+	+
13	C.3 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-2 weeks)	-	-	-
14	C.3 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-2 weeks)	-	-	-
15	C.4 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-4 weeks)	-	-	-
16	C.4 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-4 weeks)	-	-	-
17	C.5 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-6 weeks)	-	-	-
18	C.5 (stricture formation-dilation 35LP PTA balloon+18 PTX PTA balloon-6 weeks)	-	-	-

Discussion

DCBs contribute to the treatment of atherosclerosis, instent recurrence of stenosis and the reduction of the risk of thrombosis without the placement of a permanent foreign object (11-14). DCB is a standard angioplasty balloon coated with a drug, which is embedded in the matrix coating by using a hydrophilic spacer in order to allow the drug to be released after the expansion of the balloon into the vessel lumen. Then, the drug is absorbed in the layers

of the vessel wall and reduces the tissue formation which is the normal effect in cases of either balloon expansion or stent placement in the lumen of a vessel (15). The effect of DCBs is attributed to the cytostatic drugs which are coated onto the balloons (16). The currently drug of choice is PTX. PTX constitutes the most tested anti-proliferative drug for the urinary tract (17). The aim of our study is the distribution of PTX in the different layers of the urethral strictured wall. *Barbalias et al.* evaluated the distribution of PTX in the normal rabbit urethral wall (9). The researchers investigated the distribution of PTX in the layers of normal rabbit's urethra after the inflation of a PTX-coated balloon. They proved that PTX was detected to the epithelium, submucosal, and muscle layers of the normal rabbit's urethra immediately after the dilatation procedure by using DCB. Also, PTX was found 24 and 48 hours after the dilatation process. Nonetheless, there is no evidence in this study if the substance is adequately distributed in the case of strictured urethra or the effectiveness of the approach. Another difference between the two studies was the timeline. In our study the experiment was conducted in 8 weeks and the follow up of the experimental models lasted up to 6 weeks. However, both studies proved that the smooth muscle layer was enriched by PTX in both normal and strictured urethras, even 6 weeks after the dilatation with DCBs. *Fu et al.* investigated the impact of docetaxel (PTX's synthetic analogue) in management of urethral strictures (18). They randomly separated forty rabbits in 2 equal groups of 16 rabbits which received high and low dose of docetaxel respectively and a control group of 8 rabbits. Retrograde urethral irrigation was used for the administration of docetaxel, once per day for 28 days. Normal saline was administrated in the control group. The urethral diameters and the histological findings were evaluated. The diameter of the urethral lumen was significantly lower and the fibrosis and collagen concentration rate was greater in the control group compared to the other groups. These results are similar to the results of our study. Nevertheless, the researchers didn't use any antibody for testing the exact distribution of docetaxel in the different layers of rabbits' urethras. *Wikan et al.* tested the role of docetaxel and captopril in RNA expression of TGF-β1, MMP-1, CTGF, PAI-1. These genes play an important role in the formation of fibrotic tissue. They tested four groups of rabbit's urethra: a control group, a docetaxel group, a combined docetaxel/captopril group and a captopril group. They proved that, only, single docetaxel could decrease the expression of the 3 out of 4 prereferred genes. Consequently, this PTX's synthetic analogue could, also, contribute to the inhibition of fibrotic formation. *Ji Hoon et al.* evaluated the effect of PTX-coated stents in dog's canine urethra (19). They placed two stents (one PTX-coated stent and one polyurethane-coated stent) in each urethral model, one in the proximal and one in the distal urethra. They separated the dogs in 2 equal groups of 10 individuals. First group's models were sacrificed 4 weeks after the stent's placement and second group's models were sacrificed 8 weeks after the stent's placement. In the first group, they placed the drug-coated stent and the polyurethane-coated stent in the proximal urethra and the distal urethra respectively in 5 dogs and, also, placed the same stents reversely in the remaining five dogs of the group. Retrograde urethrography was performed in each model just before the sacrifice of the models and proved that tissue hyperplasia was significantly less in PTX-coated stenting part of the urethra in both groups. The histological evaluation of their experimental study showed that the granulation formation, the papillary projection and the submucosal inflammatory were significantly less in PTX-stenting specimens in both the 4-week and the 8-week group. Even if they tested different parameters in different experimental models, their outcomes strengthen theoretically the results of our study and provide evidence about the efficacy of PTX in the urethral tissue.

Other experimental studies were, also, conducted in the past for the efficacy of PTX in other parts of the urinary tract. *Liourdi et al.* conducted an experimental study in porcine ureteral wall by using DCBs (20). The aim of this study was the elucidation of the possibility of the clinical use of DCBs in ureteral strictures. As for the results, we concluded that PTX was distributed in the urothelium, submucosal, and smooth muscle layers of porcine ureter. Also, the inflammation rate was lower in the PTX groups of the study. This result comes to agreement with the results of our study and proves the efficacy of PTX. Nevertheless, it is worth mentioning that the experimental models and the anatomical structures of the urinary tract were different. In addition, in our experimental study the urethral wall was already strictured, in contrast with the normal tissue of the ureter of porcine models in the previous mentioned experiment. *Liatsikos et al.* presented an experimental study for the comparison of the efficacy of standard bare metal stents and PTX-coated metal stents in the ureteral wall of porcine models (21). Ten standard stents were placed randomly in the right or left ureter of 10 female pigs and ten PTX-coated stents placed in the other ureter of the same porcine models. After a follow-up period of 21 days all experimental models were sacrificed. After the histological evaluation, they concluded that PTX-coated stents contributed to less inflammation and hyperplasia of the ureteral wall compared to standard stents. Another important study about the effect of PTX-coated stents in the ureteral tissue's hyperplasia was presented by *Kram et al.* (22). They compared the efficacy of uncoated polyurethane stents and PTX-coated stents in a rat ureteral model after the conduction of ureteroureterostomy. Their outcomes indicated that PTX contributed to decreasing hyperplastic proliferation and postoperative restenosis rate.

Consequently, PTX-coated balloons or stents may be a promising approach for the management of strictures even in the upper or in the lower urinary tract.

A plethora of drugs has been tested regarding the efficacy in the restenosis formation of the urothelial lumen, such as poly-DL-lactic acid, zotarolimus, captopril, halofuginone, protein nanofilm-controlled drugs, rapamycin, insulin-like growth factors, Clostiridium histolyticum and others (23-26). However, only PTX proved its feasibility both in experimental and clinical aspects. *Virasoro et al.* presented a prospective, multi-center, clinical study about the usage of Optilume® PTX-coated balloon (*Laborie Medical Technologies, Mississauga, Ontario, Canada*) for the

management of patients with urethral stricture (27). The follow-up of the patients lasted 3 years and included the measurement of IPSS score, maximum flow rate, post-void residual urine volume and the evaluation of erectile function. All parameters of the study were improved after the intervention with PTX-coated balloons in most of the participants and there was no influence in the sexual function of the patients. Elliott and colleagues prepared a randomized controlled trial where 127 patients separated in 2 groups (28). First group included patients treated by Optilume® PTX-coated balloon and second group patients treated by urethral dilation or optical internal urethrotomy. After 6 months they evaluated the anatomic success by a simple passage of a flexible cystoscope. 1 year after the primal intervention they measured the IPSS score and the maximum flow rate in all participants. They, also, investigated in which of the participants a repeated intervention was necessary. All results of the study were in favor of Optilume® PTX-coated balloon group except of minor complications, such as minor hematuria and dysuria which were observed more frequently in patients treated by PTX-coated balloons.

There are some limitations related to our experimental trial which should be mentioned. First of all, human anatomy and tissue differs from the experimental rabbit's model that was used in the current experimental study. Moreover, the follow up period of the models lasted until only six weeks. Longer-term outcomes are needed for the evaluation of the distribution of PTX in different layers of the urethral wall. In the current study, we have some clues about the efficacy of DCBs in the treatment of strictured urethral lumen as we evaluated the inflammation and fibrosis of the strictured rabbit's urethras.

Nonetheless, it is not possible to do flow studies to the rabbits to obtain more information on the efficacy of the approach.

Conclusions

PTX-coated balloons seem to be an effective approach for the treatment of urethral stenosis. When PTX was released in the strictured rabbit's urethra, its distribution included all layers of the urethral wall and most importantly the smooth muscle layer, which related to the fibrosis and the restenosis of the lumen. The results showed reduced inflammation and fibrosis.

Consequently, DCBs may play an important inhibitive role in the restenosis formation.

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