LECTURE

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THE USE OF A URETHRAL CATHETER WITH AN ULTRASOUND-INDUCED BIOPOLYMER DRUG COATING FOR THE PREVENTION OF RECURRENT BLADDER NECK SCLEROSIS IN PATIENTS AFTER ENDOSCOPIC TREATMENT OF BENIGN PROSTATE HYPERPLASIA

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Recurrent bladder neck sclerosis is one of the common complications of endoscopic treatment of benign prostate hyperplasia, which often leads to multiple re-operations, including complex open and laparoscopic reconstructive procedures. One of the most promising minimally invasive methods for preventing recurrence of bladder neck sclerosis is balloon dilatation under transrectal ultrasound guidance. To improve the results of using this technique, a urethral catheter with a biopolymer coating, capable of depositing a drug and eluting it under the influence of diagnostic ultrasound, was proposed.

Key words: BPH, TURP, bladder neck sclerosis

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Bladder neck sclerosis (BNS) is characterized by the development of scar tissue due to inflammation in the area of the bladder neck with partial involvement of the urethra and the bladder wall [1]. BNS was first described by the American urologist F. M. Denslow in 1918 as a complication of open surgical treatment of benign prostatic hyperplasia [2]. Currently, BNS is the most common complication of endoscopic procedures on the prostate [3–5]. Among complications after transurethral resection of the prostate (TURP), the incidence of BNS is in the range from 4.9 [5] to 12.3% [6], while after simple prostatectomy, according to the European Association of Urology, is 6% [7]. According to an analysis of more than 2000 patients with BNS, there was no significant difference between TURP and enucleation [8].

For the treatment BNS, cold knife incision, bipolar and monopolar electroresection, laser incision, and prostatic stent placement are suggested [5]. As a rule, the first-line option is endoscopic treatment, and its efficiency does not exceed 72% [9]. If a recurrence occurs, patients are considered resistant to endoscopic treatment, then more radical treatment can be performed, including open or laparoscopic reconstruction, in some cases up to prostatectomy [10, 11].

Taking into account the high incidence of development of BNS, as well as the low efficiency of primary treatment, many alternative techniques have been proposed, among which are a combination of endoscopic treatment with subsequent administration of antiproliferative agents (mitomycin C, triamcinolone), regenerative agents (hyaluronidase, collagen preparations), and also the use of endourethral brachytherapy. The efficiency of combination treatment does not exceed 72–93% [9, 12–14].

One of the most promising minimally invasive methods for preventing recurrence of BNS is balloon dilatation of under transrectal ultrasound guidance. The method was developed and proposed by the team of the Department of Urology and Andrology, Faculty of Fundamental Medicine, Moscow State University named after M.V. Lomonosov in 2019 [15].

Balloon dilatation of BNS under transrectal ultrasound guidance

Balloon dilatation of BNS is a minimally invasive procedure that can be performed on an outpatient basis as a method of preventing recurrence after the endoscopic treatment.

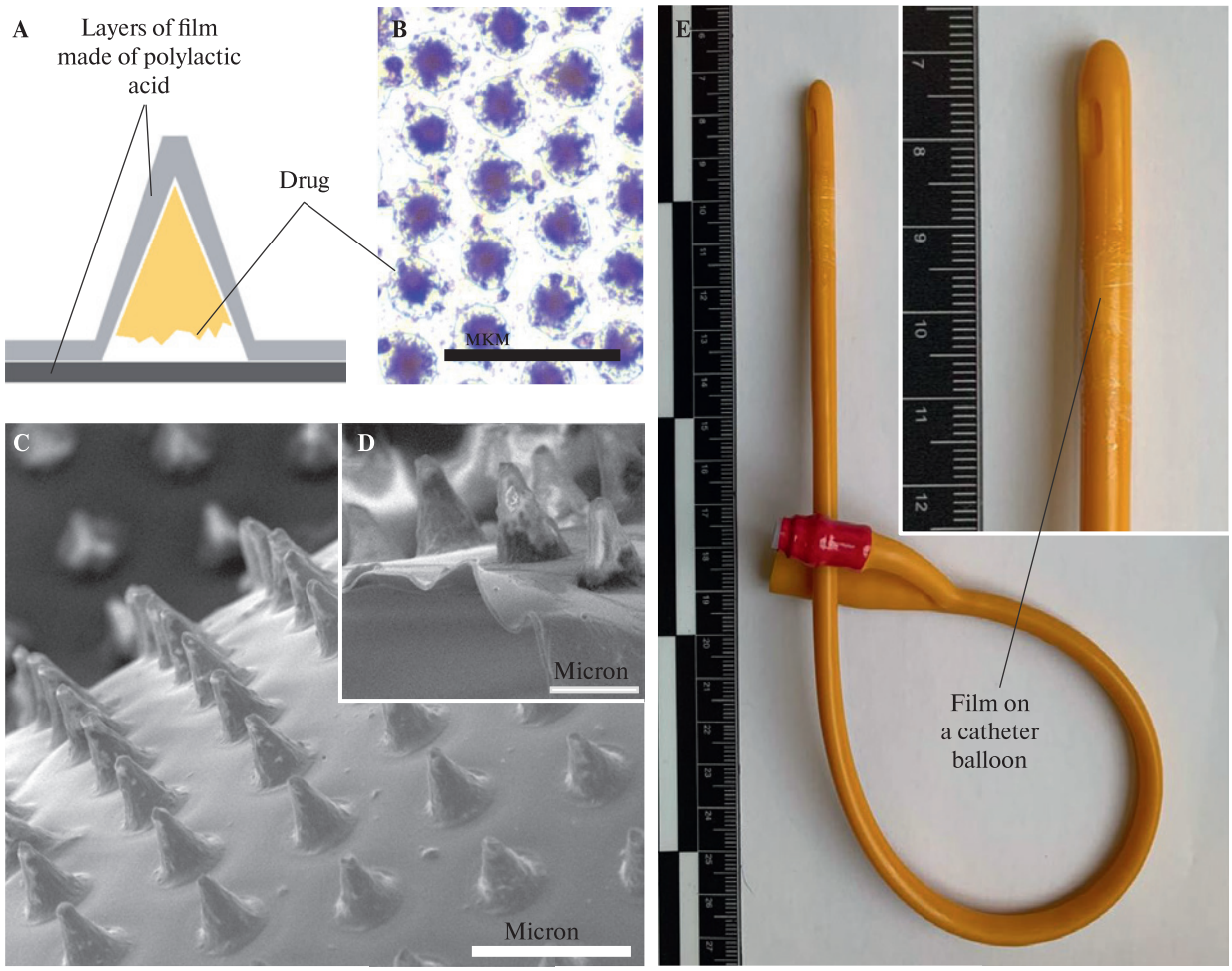


Fig. 1. Modification of urethral catheters using a biopolymer film made of polylactic acid
A – diagram of the structure of a microcontainer with a medicinal substance; B – microcontainers after saturation with the drug; C, D – electron micrographs of the film surface; E – coated urethral catheter [18].

This technique involves putting a urethral Foley catheter under transrectal ultrasound, positioning the balloon across the scar ring and inflating it until it forms a "waist". This allows for gradual elastic stretching of the bladder neck, protecting it from excessive trauma and aggressive scarring, after which a similar inflation is performed directly in the bed of the prostate bed with exposure duration in both cases for 5 minutes. The therapeutic effect in this case is achieved by stabilizing the scar ring at a urodynamically acceptable level with systematic and non-aggressive stretching with a balloon. The procedure is carried out in several sessions until the desired effect is achieved and stretching the bladder neck is preserved. The optimal time to start treatment is 3 weeks from the endoscopic treatment. Repeated sessions are carried out according to the scheme once every 3–6 weeks with a gradual increase in the interval between sessions, with at least 4 procedures [16].

According to an open, randomized, prospective, parallel-groups, single-center study [17], the efficiency of endoscopic treatment of BNS in combination with standard drug therapy in a group of 75 patients was 72.0% compared to 86.7% in the group of endoscopic treatment in combination with standard drug therapy and programmed balloon dilatation of the bladder neck under ultrasound control (n=45).

Our data showed high effectiveness of this technique compared to existing alternative methods, however, the percentage of recurrence in the main group remained quite high, up to 13.3%.

Modification of the surface of urethral catheters using ultrasound-induced drug coating

In order to improve the results of treatment, a urethral catheter with a biopolymer coating, capable of depositing a drug and releasing it under the influence of diagnostic ultrasound, was proposed. This coating is a thin biopolymer film (from one to several microns) made of polylactic acid (PLA) with many ordered, hermetically sealed microcontainers containing the drug substance [18] (*Fig. 1*).

Using in vitro and in vivo models, it has been proven that such a method of encapsulation allows to preserve the biologically active properties of the drug, as well as release it under the influence of ultrasound [19–24]. According to one of the experimental studies, when a biopolymer film with encapsulated adrenaline hydrochloride was implanted under the skin of the thigh of a laboratory animal, extracorporeal exposure of low-intensity therapeutic ultrasound on the implant area led

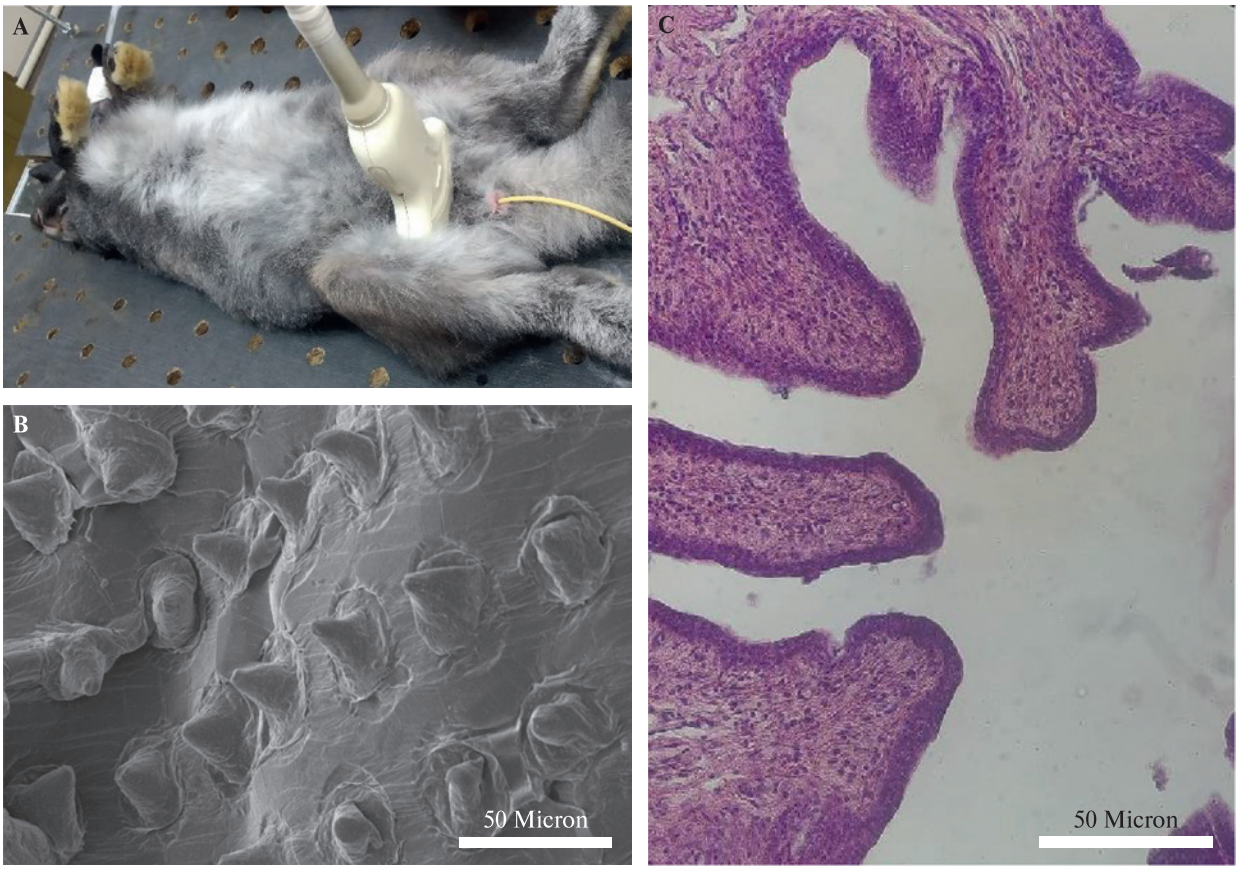


Fig. 2. Experimental safety assessment of a urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone in an animal model [18]

A – position of the laboratory animal when targeting diagnostic ultrasound at the balloon of the urethral catheter; B – electron micrograph of the PLA coating after the experiment; B – histological picture of the urethra of a laboratory animal 24 hours after putting of a drug-coated urethral catheter.

to the release of the drug from microcontainers, which was confirmed by pronounced vasoconstriction recorded on the implantation side [25].

Methylprednisolone in the form of a lyophilizate was used as a deposited substance for coating urethral catheters, which is a highly water-soluble low-molecular drug with high bioavailability, as well as a pronounced antiproliferative and anti-inflammatory effect.

The safety of using the urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone to perform balloon dilatation of the bladder neck was experimentally assessed in vivo in rabbits [18]. For this experiment, 12 healthy adult male rabbits were divided into two groups: experimental and control, 6 individuals in each. Under general anesthesia, studied animals underwent inserting of urethral catheter 6 Ch with an inflation inside the bladder neck. In the experimental group, urethral catheters with a coating were used, while in the control group standard uncoated catheter were put. The exposure duration in both groups was 10 minutes, while in the experimental group, during the entire exposure time, a local impact by ultrasound on the urethral catheter balloon was done (*Fig. 2*).

A histological study of the urethra and bladder neck of laboratory animals 24 hours after putting urethral catheters did not show significant differences between groups and demonstrated the absence of negative consequences of using a urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone compared to an uncoated catheter.

Introduction into clinical practice

The novel technique, in comparison with standard balloon dilatation of the bladder neck under transrectal ultrasound control, differs only in the sequence of inflation of the catheter balloon, since to create a high concentration of the drug directly in the scarring area, it is most advisable to perform the first inflation of the balloon directly in the area of the prostate bed. Next, the balloon is deflated and moved to the area of the scar ring, after which it is inflated again in the narrowest place. The exposure duration in both positions is 10 minutes in total (5 minutes each). The improved effect compared to standard balloon dilatation of the bladder neck is ensured by the delivery of the drug to the area of the scar ring under the influence of ultrasonic waves and the antiproliferative effect on fibrous tissue (*Fig. 3*).

The proposed methodology received approval from the local ethical committee of the Moscow State University named after M.V. Lomonosov, after that an open, prospective, single-center study was launched in 2021.

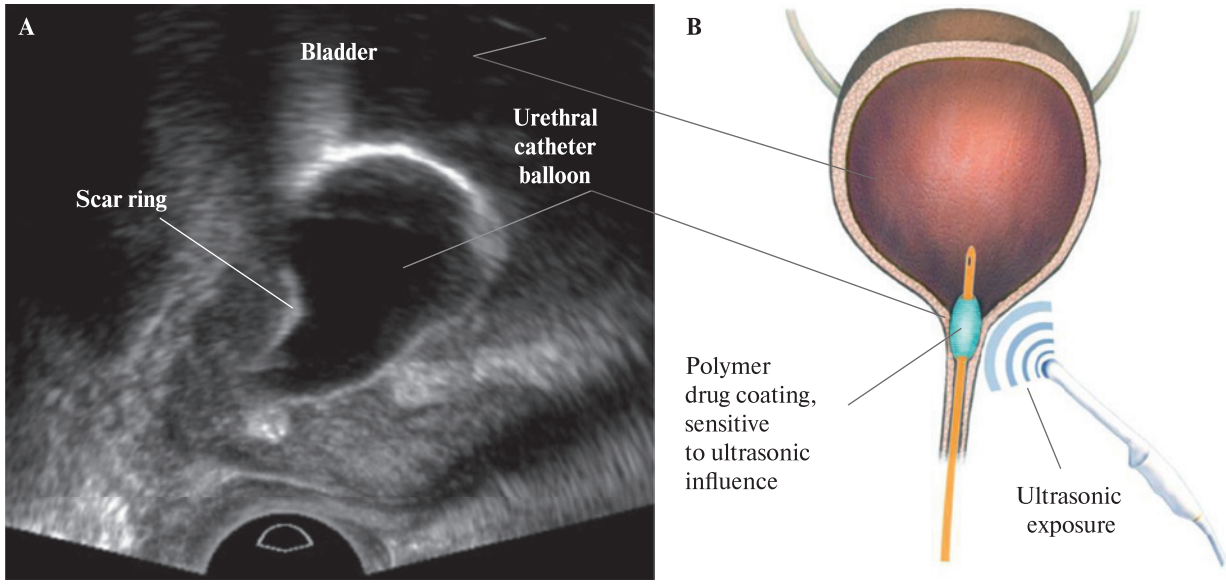


Fig. 3. A balloon dilation of bladder neck sclerosis under transrectal ultrasound control using a urethral catheter with an ultrasound-induced biopolymer drug coating

A – Transrectal ultrasound of the bladder neck and urethral catheter balloon during the procedure;
B – Schematic representation of the process of balloon dilatation of the bladder neck using a urethral catheter with an ultrasound-induced biopolymer drug coating.

To date, the study has included 13 patients with two or more recurrences of BNS after endoscopic removal of benign prostatic hyperplasia. The planned number of participants is 40 patients, and currently recruitment is ongoing.

The existing experience has demonstrated the high potential of the balloon dilatation of the bladder neck using a standard urethral Foley catheter. Literature data on the combination of endoscopic treatment with local and systemic use of antiproliferative agents, including corticosteroids, allow to expect improved results of treatment of recurrent BNS while maintaining minimally-invasiveness and the possibility of performing the procedure on an outpatient basis.

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