Background: Benign prostatic hyperplasia (BPH) and chronic prostatitis (CP) are disorders with high prevalence and have a great impact on overall morbidity in men. The patients that do not respond to medical therapy for lower urinary tract symptoms (LUTS) related to BPH are candidates for surgery. However, the number of men with BPH/LUTS seeking for non-surgical, or for less invasive treatment is growing. Aim: To present the basic information about minimally invasive treatment modalities for BPH and CP: intraprostatic injections, urethral lift procedures, modifications of transurethral microwave thermotherapy (TUMT), prostatic artery embolization etc. Conclusion: The majority of these techniques is still in experimental phase and not widely accepted. However, it is very likely that new, safe and minimally invasive techniques will appear in the near future.

Key words: benign prostatic hyperplasia; intraprostatic injections; minimally invasive treatment; urethral lift procedures

INTRODUCTION

Prostate gland, which is a relatively small organ in the human body, has a significant impact on overall morbidity and mortality of men. Benign prostatic hyperplasia (BPH) associated with lower urinary tract symptoms (LUTS) is the fourth most common disease, after coronary artery disease and hyperlipidemia, hypertension and diabetes type-2. With the overall prevalence of 8%, chronic prostatitis is the most common urological disorder in men under 50 years. Finally, prostate cancer (PCa) is among the three most common malignant diseases in the world.

Although urology and related disciplines offer a huge range of different treatment modalities, there is a constant need for new, safe and effective treatments for prostate diseases. In addition, the majority of patients would choose a treatment which is less invasive, anesthesia-free and without side effects.

In this text, some of new emerging techniques and treatment modalities are briefly described. Still, the majority of these techniques are not widely accepted.

INTRAPROSTATIC INJECTIONS

Intraprostatic injections of antibiotics for chronic prostatitis

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is very common disorder of modern man, with a high tendency to recur. The significant percentage of CPs recurs, due to the formation of intraprostatic bacterial biofilms that obstruct the antibiotic diffusion into prostatic glands. This is why a number of urologists tried to inject the antibiotics directly into prostatic tissue in men with CP. In 1983, Baert et al. described positive effects of intraprostatic injection of the combination of amikacin, cefazolin, gentamicin, and thiamphenicol glycinate with lidocaine. Leonard (1988), Jimenez-Cruz (1988), Yamamoto (1996) and others, also advocated direct injection of antibiotics into the prostate. Jimenez-Cruz et al reported 51 patients with gram-negative CP treated successfully with amikacin (500 mg) and tobramycin (100 mg) weekly for 2-4 weeks. The antibiotics were injected into the peripheral zone under ultrasonographic control, via perineal route. Guercini et al. (2000, 2005) added steroid betamethasone to the combination of antibiotics. The trial included 320 patients with CP with severe and recurrent symptoms. All patients received the intraprostatic cocktail at the beginning of the study, than after 7 and 14 days. At the end of the study, 68% of patients were classified as “cured”, while 13% were non-responders. Hemorrhage was the most common adverse effect, while perineal or prostatic pain was relatively rare.

So far, the majority of urologists think that intraprostatic injections are as effective as intramuscular injection of antibiotics and that its wide use is not likely, due to significant adverse effects. The most common complications of intraprostatic injections are infections (transrectal...
route), severe pain (transperineal route), hemospermia and hematuria. In the future, steroids in the injection could be replaced with some new immunomodulatory, or anti-inflammatory agents effective for the abacterial prostatitis, as well. On this way, immunosuppression would be delivered only to the prostate, with the avoidance of side effects. In addition, if complication rates can be reduced this treatment could be potentially beneficial for patients with CP/CPPS.

**Intraprostatic injections for the treatment of benign prostatic hyperplasia**

The idea of BPH/LUTS treatment by simple injection of active drug is relatively old. In India, Sir James Roberts was first to use intraprostatic injection to relieve retention of the urine due to enlargement of the prostate. Talwar (1966), Shipman (1967) and Sharma (1977) described successful treatment of patients with BPH and severe comorbidities using the intraprostatic injections composed of phenol 2%, glacial acetic acid 2%, and glycerin 4%, in distilled water. The injections of a volume from 2 to 3 mL were given via transperineal route. Intraprostatic injections can be performed using the transrectal, transurethral, or transperineal route. (Figure 1).

**INTRAPROSTATIC INJECTIONS OF ABSOLUTE ETHANOL**

In the canine prostate, absolute (dehydrated, 95-98%) ethanol causes inflammation, coagulative necrosis, cell membrane lysis and ablation of prostatic tissue, resulting in cavity formation.

The first attempt to treat patients with BPH with intraprostatic ethanol injection (IEI) was made by Goya et al. in 1999. The group of 10 patients underwent IEI transurethrally, with 3.5 to 12 mL of ethanol given at 4 to 8 sites in the prostate. The authors noted significant improvement in urinary symptoms and urinary flow.

So far, the effects of IEI were studied in several trials. Ethanol was usually injected in a liquid state, or as a gel, using a 20 to 22 gauge needles. The volume of the injected ethanol depended on total prostate volume (TPV) and ranged from 2 mL to 25 mL. The average duration of the procedure was 30 minutes; after the procedure, the majority of patients needed a urethral catheter. After a mean follow up ranging from 3-48 months, the majority of trials demonstrated a significant reduction in symptoms, improvement in the maximum urinary flow rate (Qmax) and a significant TPV decrease. However, there was a significant number of retentions within the first year after the procedure; after three years, the retreatment rate was up to 41%. The most common adverse events were perineal pain, bladder storage symptoms, hematuria, urinary tract infection and urinary retention.

In the recent paper, Li et al. tested the group of 70 men with BPH and poor response on medical therapy of LUTS. In addition, all patients had significant comorbidity, or refused surgery for BPH. After 24 months of treatment, TPV, International prostate symptom score (IPSS) and postvoiding residual urine (PVR) were significantly reduced, while Qmax significantly increased. In the group which received high dose of ethanol, four patients had severe complication- liquefaction necrosis and urinary tract injury. However, in the group which received reduced dose of ethanol, no patient had complications.

Alcohol gel composed of 97% denatured alcohol and a polymer to cause viscosity seems to have some advantages over liquid alcohol. The viscosity of the gel allows precise imaging under the ultrasound and prevents the dispersal of the alcohol out of the prostate. Larson published the results from 65 patients which underwent IEI of average 8 mL of ethanol gel. All patients showed statistically significant improvements in urinary symptoms and urinary flow.

**INTRAPROSTATIC INJECTIONS OF BOTULINUM TOXIN A**

Botulinum toxin A (BT-A, Botox) injected into the rat prostate induced selective denervation and the prostatic involution. BT-A induces the apoptosis of prostatic stromal and epithelial cells and decreases smooth muscle contractility.
In a group of 30 patients with BPH, Maria et al. injected 4 mL of solution with 200 units of BT-A. Two months later, 13 patients reported subjective relief. In a group of 77 men with BPH, Brisinda injected 200 units of BT-A. After one year of follow up, approximately 60% of men had the improvement of urinary symptoms and a reduction of prostate volume [13, 14]. (Figure 2).

**INTRAPROSTATIC INJECTIONS OF CARDIOTOXIN D**

The main lethal component of cobra toxin is the basic polypeptide cardiotoxin, which produces cell membrane depolarization and definitive cytolysis. Omran et al. investigated the action of cobra venom on prostate cancer cell lines. They found that snake venom produced cell fragmentation, cytosol condensation, the swelling and finally, destruction of the cells [15]. Becker et al. injected cardiotoxin D in ventral prostates of the laboratory rats. After two weeks the animals were sacrificed; prostatic weight decreased and prostatic tissue showed signs of atrophy. No systemic effects were noted [16].

**INTRAPROSTATIC INJECTIONS OF PSA-ACTivated Pore-FormING TOXIN (PRX302)**

Prostate specific antigen (PSA)-activated pore-forming protein toxin, PRX302 is a potential novel agent for intraprostatic injection therapy. Denmeade et al injected PRX302 into the right and left transition zone to the subjects with BPH/LUTS. After one year of follow up, approximately 60% of men had the improvement of urinary symptoms and a reduction of prostate volume [17]. Figure 3.

**INTRAPROSTATIC INJECTIONS OF NX-1207 PROTEIN**

New potential agent for intraprostatic BPH therapy, NX-1207 is a protein with selective pro-apoptotic properties, which can be administered in an office-based procedure by transrectal intraprostatic injection under ultrasound guidance. NX-1207 induces focal cell loss in prostate leading to prostate volume reduction and the improvement of the urinary symptoms. In a rat model, NX-1207 produced a 40–47% decrease in prostate volume. In four US clinical trials, NX-1207 has shown evidence of symptomatic improvement substantially better than currently approved BPH medications with no significant safety issues [18, 19].

Nymox Pharmaceutical Corporation announced the satisfactory safety profile of NX-1207 in the treatment of BPH. In addition, NX-1207 showed the reduction in prostate cancer progression in an ongoing phase II trial. The trial enrolled 146 patients with localized low-risk prostate cancer which received intraprostatic injections of NX-1207 and the patients in active surveillance only. The drug was injected in the area of the prostate where the cancer was detected. In the follow up of up to 22 months, repeated biopsies found the significant reduction in cancer volume and Gleason score progression in the group with NX-1207, compared to the group with active surveillance. The investigators hope that the drug will offer men with low-risk prostate cancer a real chance to avoid radiation and/or surgery.

**HISTOTRIPSY**

The term “histotripsy” denotes tissue destruction produced by high intensity ultrasound pulses. Lake et al. treated 11 anesthetized dogs with high-intensity ultrasound pulses. After treatment, pathological examination revealed the presence of the cavity containing liquefied material, at the ablation site. Interestingly, a narrow margin of cellular injury was noted, beyond which no tissue damage was evident [20].

**URETHRAL LIFT PROCEDURES**

Prostatic Urethral Lift (PUL) represents a new, minimally invasive treatment for symptomatic BPH. The action of PUL is mechanical opening of the prostatic urethra, without tissue ablation or resection. The first experiences regarding the effectiveness of the procedure, as well as its safety and feasibility, are encouraging.
Woo et al. were among the first investigators which performed PUL procedure. In a series of 19 men, they implanted small suture-based implants transurethrally under cystoscopic visualization, to take apart encroaching lateral prostatic lobes. Postoperative adverse effects were mild and transient and included dysuria and hematuria. Chin, Woo et al. treated 64 men with PUL. Inclusion criteria included IPSS >13, Qmax of 5-12 mL/second, and prostate specific antigen (PSA) < 10 ng/mL. All patients were tested for sexual dysfunction, using male sexual health questionnaires. They concluded that urethral lift improved LUTS and urine flow without compromising sexual function. No patient reported retrograde ejaculation at any follow-up visit.

Roehrborn and other investigators engaged in multicenter L.I.F.T. study inserted 140 urethral lifts in men with a prostate volumes ranging from 30 to 80 mL. The subjects were followed to one year and assessed for LUTS, urinary flow and sexual function. They concluded that PUL provides rapid and sustained improvement in symptoms and flow, while preserving sexual function. In the extension of the L.I.F.T. study, McVary et al. confirmed the previous conclusions.

The same inclusion criteria were included in the following prospective multicentric studies: IPSS=12, Qmax =12 mL, and TPV between 30 and 80 mL. Shore et al. treated 51 men; by one month, 86% of subjects achieved high quality recovery, measured by a score of = 80 on the Quality of Recovery Visual Analog Scale. Ninety percent of subjects reported improvement in their condition and 75% of subjects would recommend the procedure to a friend. Symptom response, flow rate improvement, and sexual function preservation were comparable to published studies. There were no serious adverse events.

In the multicentric study in 19 centers in the USA, Canada and Australia, Cantwell et al. placed permanent PUL implants into the lateral lobes of the prostate to enlarge the urethral lumen. Urinary symptom relief, health-related quality of life (HRQL) impact, urinary flow parameters, sexual function, and adverse events were assessed. Symptom, flow, HRQL and sexual function assessments showed response improvements from baseline results, similar to results from other published studies. In addition, symptom, flow, and HRQL improvements were durable over the 12 months of the study. Adverse events were transient and mild to moderate; one patient (2%) required reintervention with transurethral resection of the prostate in the first year. There were no occurrences of ejaculatory or erectile dysfunction.

In conclusion, PUL is minimally invasive procedure that can be performed under local anesthesia, allows patients to quickly return to normal activity, provides rapid and durable improvement in symptoms, and preserves sexual function. The PUL offers better IPSS improvement when compared to medical therapy, but worse than surgical therapy. Additional advantages of the PUL in comparison to other surgical therapies are the use of a local anesthesia and, in some cases, postoperative period without catheterization. However, it is very unlikely that PUL will replace traditional ablative surgical techniques; its use could be indicated only in strictly selected cases.

**NEW MODIFICATIONS OF TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT)**

Microwave thermolabilation system (Prolieve®) consists of the special catheter, with a heating antenna and a small balloon. The system simultaneously compresses the prostate with a 46F balloon and delivers microwave energy into the prostate. The procedure lasts approximately 45 minutes. If the temperature reaches the heating limit, the system will shut off automatically. In a clinical trial, 74% (68/92) of Prolieve® System patients experienced a 30% improvement of their AUA total score at one year. Larson et al. found that the necrotic zones appeared after the temperature exceeds 45°C. In addition, peak temperatures of 51.8°C appeared at 7 mm away from the prostatic urethra. The average temperatures were greater near the bladder neck and mid-gland than near the prostatic apex. One hour after the treatment, voiding cystourethrogram showed widely patent prostatic urethras.

High energy TUMT followed by intraprostatic injections of mepivacaine and adrenaline (MA) showed significant reduction of TPV, with reduced pain and shortened treatment time. In a recent study, Stenmark et al. treated 283 men with LUTS/BPH by intraprostatic injections of MA, followed by HE-TUMT. Approximately 87% patient responded to therapy. The average TPV was 74 mL and average treatment time was 13 minutes. The reduction of TPV was 26% for the prostates with TPV < 100 mL and 31% for the prostates with TPV = 100 mL.

Cooled thermo therapy (CTT) consists of the heating antenna and the small channels which provide the circulation of the cooled fluid, to protect surrounding healthy urethral tissue. Usually, the significant symptom improvement is noticed within 6-12 weeks after the procedure.

**PROSTATE ARTERY EMBOLIZATION**

Prostate artery embolization (PAE) is a non-surgical way of treating a BPH/LUTS by blocking off the arteries that feed the prostate gland. The procedure is performed by an interventional radiologist. PAE was first performed in 2009, and since then over 200 men have had the procedure performed predominantly in Portugal and Brazil. The procedure is usually performed under local anesthesia, using the microcatheter 1mm in diameter and 300- to 500 im large microspheres.

Carneval et al. reported the prostate volume reduction of up to 48%, if the bilateral PAE was performed. Recent findings from a prospective United States clinical trial to evaluate the efficacy and safety of PAE showed that embolization was technically successful in 18 of 20 patients and unsuccessful in two patients with atherosclerotic occlusion of prostatic arteries. Prostate volume decreased 18% after six months, while the urinary symptom scores and the sexual function, improved significantly (Figure 4).

**DISCUSSION**

Benign prostatic hyperplasia (BPH) and chronic prostatitis significantly influence on overall morbidity of male population. In modern era, the number of men with these
conditions is growing, together with the average life span. Therefore, there is a constant need for new, effective and minimally invasive treatments followed by mild side effects.

Intraprostatic injections can be applied as simple, outpatient procedures and are potentially ideal for the treatment of BPH and prostateitis. Fifty years ago the first attempts have been made in this subject. Intraprostatic injections can be performed using the transrectal, transurethral, or transperineal route. The greatest series included the subjects treated with intraprostatic ethanol injections. However, greater randomized studies are needed to confirm the effectiveness and the safety of this method. According to 2012 EAU Guidelines, intraprostatic ethanol injections should be performed only in clinical trials.

There is a growing evidence of positive effects of other agents injected into the prostate, like botulinum toxin A, cardiotoxin D, PSA-activated pore-forming toxin (PRX 302) and NX-1207 protein. All these therapeutic modalities will prove its efficacy in the near future. While histotripsy and urethral lift procedures are still experimental, TUMT is well known procedure and its new modifications (thermodilatation, cooled etc.) will probably increase its popularity. Finally, prostate artery embolization can be performed under local anesthesia and allows patients to quickly return to normal activity. Although PUL offers better results than medical therapy, it is still inferior to surgery and could be considered only in strictly selected cases.

SUMMARY

NOVE I EKSPERIMENTALNE TEHNIKE U LEÇENJU BENIGNIH BOLESTI PROSTATE

Uvod: Benigna hiperplazija prostate (BHP) i hronični prostatitiz (HP) su bolesti sa visokom prevalencijom, koje imaju veliki uticaj na ukupni morbidity kod muškaraca. Bolesnici kod kojih je medikamentozna terapija za simp- tome donjeg urinarog trakta (LUTS) koji su posledica BHP, neuspešna, zahtevaju hirurško lešenje. Medjutim, vrlo je verovatno da će se invazivnih metoda još u eksperimentalnoj fazi i nije zacije arterija prostate itd. Suretralne mikrotalasne termoterapije (TUMT), embolizacije, pro McC edure podizanja uretre, novije modifikacije transuretranalne termoterapije (TUMT), embolizacije arterija prostate itd. Zaključak: Vecina minimalno invazivnih metoda je još u eksperimentalnoj fazi i nije široko prihvaćena. Medjutim, vrlo je verovatno da će se novije, efikasnije i sigurnije tehnike pojavljivati u bliskoj budućnosti.

Kljucne reci: benigna hiperplazija prostate; intraprostatine injekcije; minimalno invazivno lešenje; procedure podizanja uretre.

REFERENCES


