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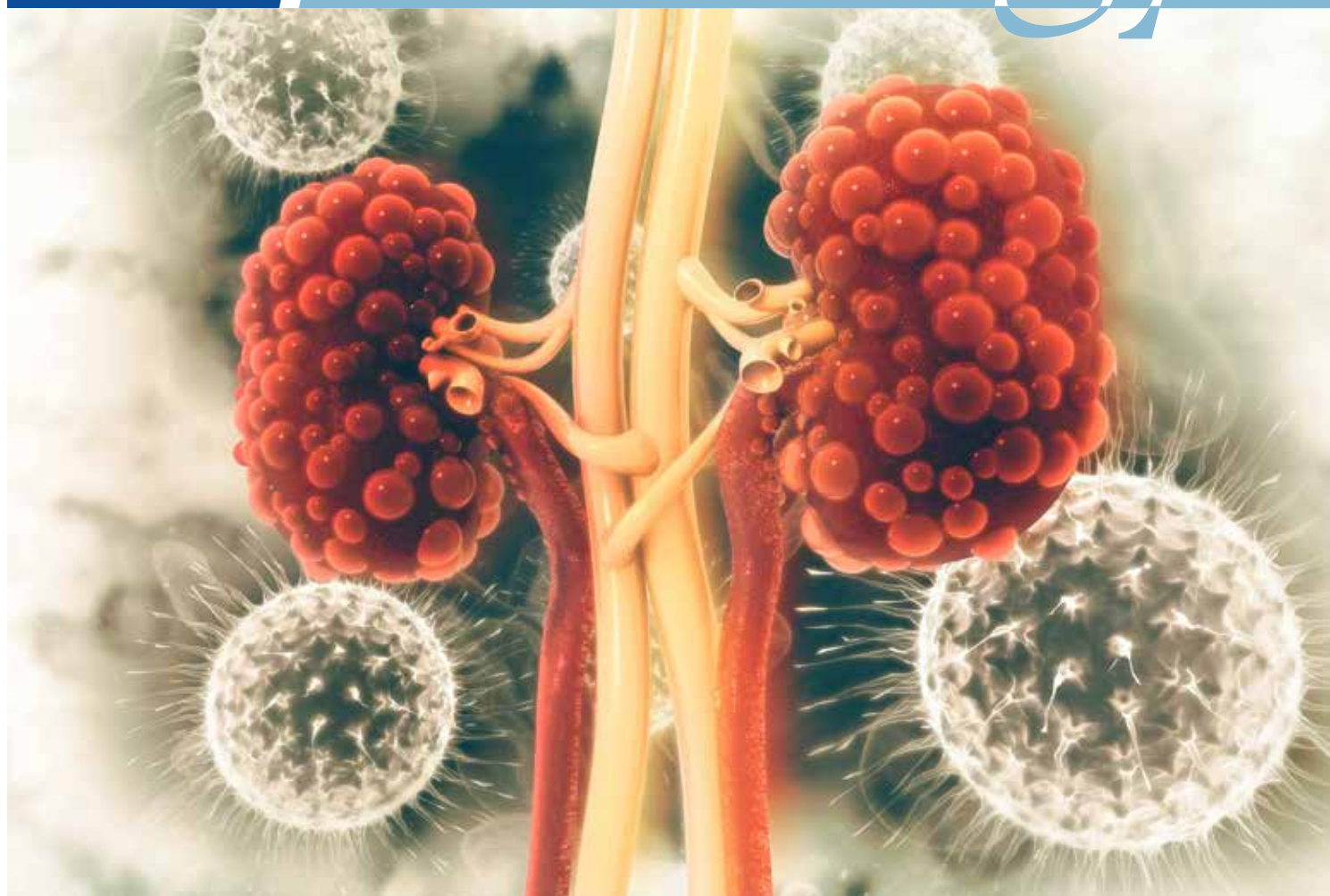
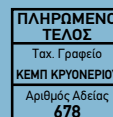
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Original Articles

- Trends of bacterial susceptibility in chronic bacterial prostatitis. A retrospective study
- The contribution of modified Marmar technique to achieve improvement in spermiogram and to achieve pregnancy in couples with infertile men with varicocele

- Is There a role for b3 agonists or anticholinergics in the treatment of the lower urinary tract symptoms in patients with multiple sclerosis?

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- New imaging technologies in the diagnosis and staging of Non-Muscle Invasive Bladder Cancer

Case Reports

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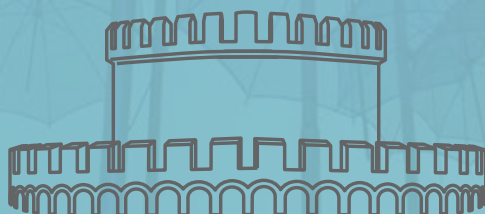
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Instructions to Authors

Hellenic Urology is the official scientific journal of the Hellenic Urological Association. Its main objective is to publish original articles, reviews and case reports on diseases of the genitourinary system. The journal Hellenic Urology is also concerned in the continuous education of the Urologists and aims at promoting the science of Urology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations as well as basic and applied laboratory research; new data and recent developments of urological interest are also welcomed. Papers published in another journal are not accepted.

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ORIGINAL ARTICLE

Trends of bacterial susceptibility in chronic bacterial prostatitis. A retrospective study

Konstantinos Stamatiou¹, Georgios Christopoulos², Rafail Mantzioros³, Vaia Papadouli⁴, Nektaria Rekleiti⁴, Olympia Zarkotou⁴, Kate Themeli Digalaki⁴

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Abstract

INTRODUCTION/AIM: Chronic bacterial prostatitis (CBP) is an inflammatory condition of the prostate, characterized by relapses and remissions. Due to trends in bacterial susceptibility, persistence, recurrence and reinfection are considered frequent. The aim of our study was to investigate recurrences and reinfections rate and to determine bacterial susceptibility in our environment.

MATERIAL: The clinical sample used in the study consisted of bacterial isolates obtained by CBP patients who visited our clinic from 03/2009 until 03/2015. Bacterial identification was performed using the Vitek 2 Compact system and the sensitivity test with the disc and the Vitek 2 system.

RESULTS: A total of 389 bacterial isolates constituted the material of the study. A wide array of different Gram-positive and Gram-negative species was isolated from CBP patients. Notable variations in susceptibility levels between pathogens were observed, with that of *Enterococcus* being the most emerging. Bacterial persistence occurred in 111 cases. Relapses occurred in 53 patients. Pathogens commonly associated with relapses were *Enterococcus faecalis*, *CoNS* and *E. coli*.

CONCLUSIONS: Wide variations in susceptibility levels between pathogens exist. While bacterial persistence is frequent, microbiological relapses are less common with the true reinfections being the most usual cause of CBP recurrence.



Konstantinos Stamatiou, Georgios Christopoulos, Rafail Mantzioros, Vaia Papadouli, Nektaria Rekleiti, Olympia Zarkotou, Kate Themeli Digalaki
Trends of bacterial susceptibility in chronic bacterial prostatitis. A retrospective study
Hellenic Urology 2019, 31(4): 13-19

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Introduction/Aim

Chronic bacterial prostatitis (CBP) is an inflammatory condition of the prostate, characterized by relapses and remissions. Due to trends in bacterial susceptibility, recurrences and reinfections are considered frequent. The aim of our study was to investigate recurrences and reinfections rate and to determine bacterial susceptibility in our environment.

Methods

Material

The material of this retrospective study consisted in bacterial isolates from urine and/or prostatic secretions or sperm cultures (total ejaculate) obtained from individuals with CBP, visiting our clinic from 03/2009 to 05/2015. Patients suffering from conditions that influence bacterial virulence or host response (eg. immunodeficiency, abnormalities of the urogenital system) and patients who received antibiotics or immunosuppressive treatment within 4 weeks of the visit were excluded from the study.

Microbiological assessments

Included patients were clinically evaluated and underwent the Meares-Stamey "4-glass" test, based on cultures of first-void (VB1), midstream/pre-prostatic massage (VB2), expressed prostatic secretions (EPS) and post-prostatic massage urine (VB3) specimens. Few cases underwent the "two-glass" test [1], assessing the sole VB2 and VB3 specimens. Depending on medical history and specific symptoms, urethral and total ejaculate cultures (TEC) were additionally obtained from several patients. Patients presenting with febrile prostatitis were investigated by a midstream urine culture (MUC) only. Appropriate antimicrobials were administered to confirmed cases of CBP accordingly to antibiogram for a period of 4 weeks. Follow-up included interview, physical examination and the Meares-Stamey test

Microbiological evaluation

The Meares-Stamey test was considered positive when: 1) bacteria grew in the culture of expressed prostatic secretion (EPS) and VB3 urine sample and did not in VB1 and VB2 sample; 2) bacterial colonies in VB3 were higher in number compared to VB1 and VB2 samples.

Key words

chronic prostatitis, prostate, infection, antibiotics, susceptibility, Stamey-Meyers

Given that no standard cut-off level of the number of bacteria in both urine and prostate secretion samples is defined by consensus for the diagnosis of chronic bacterial prostatitis, we defined no lower acceptable level for either one. Cultures, identification and semi-quantitative assay for *Mycoplasma hominis* and *Ureaplasma urealyticum* were performed using the Mycoplasma IST 2 kit (bioMérieux). *Chlamydia trachomatis* was detected by direct immune-fluorescence (monoclonal antibodies against lipopolysaccharide membrane, Kallestad). Urine samples were cultured undiluted in blood and MacConkey agar plates (Kallestad Lab., TX, USA) and subjected to centrifugation for microscopic examination of the sediment. Evaluation of culture results was performed by two specialist microbiologists, who not informed about patient records. Identification of traditional pathogens was performed by conventional methods and the Vitek-2 Compact (bioMérieux, France) system and susceptibility testing was performed by disc diffusion and/or the Vitek-2 system. Interpretation of susceptibility results was based on Clinical and Laboratory Standards Institute (CLSI) guidelines [2].

The local Ethical Committee approved the research protocol for the present retrospective study.

Results

The material of the study constituted of 389 cultures (316 EPS/VB3, 27 MUC, 46 TEC). Only 92 out of 316 Meares-Stamey test provided sufficient amounts of expressed prostatic secretions (EPS); thus, in the remaining 224 cases the microbiological diagnosis was based only on VB3 cultures. Demographic and microbiological data for the present study are presented in Table 1. A vast variety of bacteria was found, with *Escherichia Coli* being the most common monomicrobial isolate. Coagulase negative staphylococci (CoNS) (mainly *S. hominis* and *S. haemolyticus*) and *Enterococcus faecalis* were also common isolates.

Twenty nine out of 46 TEC were performed complementary to EPS/VB3. In 13 out of 29 cases were identical to EPS/VB3 cultures. The remaining 16 cultures allowed to diagnose bacterial infection cases, while the EPS/VB3 cultures were negative. The most frequently assessed isolates were *Enterococcus spp.* (19 monomicrobial and 3 polymicrobial).

Table 1 <i>Patient demographic and microbiological data</i>	
Clinical sample	Number
Number of Patients	389
Median Age	40.2
Microbiological sample	
Cultures of prostatic secretions	92
Urine samples collected after prostate massage	224
Mid-stream urine only cultures (febrile cases)	27
Sperm cultures (total ejaculate)	46
monomicrobial infection	297
polymicrobial infection	92

Table 2 <i>Resistance patterns and trends of Enterococcus faecalis</i>					
Resistance Patterns	macrolides	tetracyclines	aminoglycosides	quinolones	teicoplanin
N: 158	37	45	21	28	1
%	24%	29%	13.9%	18.5%	0.66%
Resistance Patterns	TMP-SMX	penicillins	cephalosporins	fusidic acid	clindamycin
N: 158	NA	19	NA	NA	NA
%	NA	12.5%	NA	NA	NA

Table 3 <i>Resistance patterns and trends of Escherichia coli</i>						
Resistance Patterns	quinolones	TMP-SMX	aminopenicillins Beta-lactams +beta-lactamases inhibitors	tetracyclines	aminoglycosides	cefalosporines 1 st & 2 nd generation
N: 84	15	19	14	18	12	6
%	17.8	22.6	16.6	21.4	14.2	1.14

Susceptibility of pathogen isolates

Enterococcus spp. strains were found in 66 monomicrobial and 36 polymicrobial isolates. Twenty-one out of 66 (43.4%) monomicrobial isolates and 8 out of 25 (38.8%) polymicrobial isolates were sensitive to all tested antimicrobials (Resistance patterns and trends of *Enterococcus faecalis* are presented in Table 2).

E. Coli strains were found in 104 monomicrobial and 38 polymicrobial isolates. Ninety-six out of 104 (92.3%) monomicrobial isolates and 22 out of 38 (57.8%) polymicrobial isolates were sensitive to all tested antimicrobials

(Resistance patterns and trends of *E. Coli* are described in Table 3).

Regarding CoNS strains, 64 monomicrobial isolates and 44 polymicrobial isolates were found. Thirty five out of 64 (54.6%) monomicrobial isolates and 25 out of 44 (56.8%) polymicrobial isolates were sensitive to all tested antimicrobials (Resistance patterns and trends of CoNS are described in Table 4).

The small number of other isolates and their combinations does not allow reliable comparisons (Tables 5,6). In general, relatively high resistance levels to antibacterial agents used in CBP therapy (quinolones, TMP-SMX,

Table 4 Resistance patterns and trends of *Staphylococcus CoN*

Resistance Patterns	macrolides	TMP-SMX	methicillin	tetracyclines	quinolones
N: 129	30	17	21	28	7
%	23.2	13.17	16.27	21.7	5.42
Resistance Patterns	fusidic acid	clindamycin	Amino glycosides	cefalosporins	rifampicin
N: 129	7	3	3	6	3
%	5.42	2.3	2.3	4.6	2.3

Table 5 Resistance patterns and trends of *Proteus spp.*

Resistance Patterns	cefalosporines	quinolones	TMP-SMX	penicillines	tetracyclines	colistin	aminoglycosides
N: 43	5	10	8	2	10	NA	5
%	11.6	23,25	18.6	4.6	23,25	NA	11.6

Table 6 Resistance patterns and trends of *Streptococcus spp.*

Resistance Patterns	tetracyclines	macrolides	penicillins	aminoglycosides	quinolones
N: 8	4	2	1	1	NA
%	50	25	12.5	12.5	–

tetracycline) was observed. In some cases, we couldn't observe cross-resistance between ciprofloxacin and new-generation quinolones.

Of note, contrary to the EPS/VB3 isolates, most *Enterococcus spp.*, isolates from TEC were susceptible to all tested antibacterials (63.1%). In general, TEC were comparable to EPS/VB3 cultures, though the small number of most isolates does not allow reliable comparisons.

Follow-up visits

Bacterial persistence occurred in 111 cases. In 17 patient's white blood cells were found in EPS and/or VB3 in the absence of symptoms. In 6 cases EPS/VB3 cultures were negative despite the presence of bacteria in the same samples. Six patients were diagnosed with another disease during follow-up (Table 7). In most non-treated cases, the pathogens found in the follow-up cultures were different from those isolated in the initial visit (usually *Enterococcus faecalis*, CoNS and *E. coli*). Relapses occurred in 53 patients and almost half of them were caused by microorganisms other than those

causing the initial infection. The average time interval between episodes of chronic prostatitis is 13.9 months (minimum 2 and maximum 56 months). The pathogens most commonly associated with clinical relapses were *Enterococcus faecalis*, CoNS and *E. coli*.

Discussion

Notable variations in susceptibility levels between pathogens were observed in this study. In monomicrobial isolates, *Staphylococcus aureus* and *Escherichia coli* showed the highest susceptibility rates (92.4 and 93.4% respectively). However, both became resistant to antimicrobials when coexisted with each other and with other pathogens in polymicrobial isolates. This fact can be attributed to gene exchange between species coexisting in polymicrobial isolates [3] Research has revealed that horizontal gene transfer and biofilm formation are connected processes. Urinary tract infection biofilms are polymicrobial in nature [4] and provide excellent conditions for bacterial interactions because of (i) the high-density and well-organized diverse mi-

Table 7 <i>Clinical and microbiological outcome</i>	
Cured	146
Bacterial persistence - Symptom persistence	63
Bacterial eradication - Symptom persistence	54
Clinical improvement -Unknown microbiological outcome	53
Elimination of symptoms - Bacterial persistence	44
Developed asymptomatic chronic nonbacterial prostatitis	17
Non-recognizable bacteria in EPS/VB3 cultured samples	6
Diagnosed with another disease during follow-up	6
Developed cystitis (VB3 cultures were identical to VB2)	4
TOTAL	389

crobial community allowing physical cell–cell contact and (ii) the matrix that concentrates various chemical compounds [5]. Polymicrobial infections often involves one or more Gram-positive bacteria and recent data demonstrated that they can impact the pathogenic phenotype of co-infecting organisms [6].

Enterococci may contain or develop resistance determinants to multiple antibacterial agents, with the most important resistance profiles being to beta-lactams, aminoglycosides and glycopeptides. According to the ECDP 2017 report, the proportion of high-level aminoglycoside resistance in *E. faecalis* is 12.2% in Greece and 45.9% in Italy, whereas high-level vancomycin resistance in *E. faecium* is 30.8% in Greece and 14.6% in Italy. Currently, different degrees of resistance in *Enterococci* are frequently found among other antibiotics such as trimethoprim-sulfamethoxazole, macrolides, tetracyclines or fluoroquinolones [7,8]. In our study *Enterococcus* showed higher resistance trends against tetracyclines (29%), macrolides (24%) and fluoroquinolones (18.5%). This trend is emerging, given that *Enterococci* are tolerant microorganisms that develop biofilms on abiotic surfaces such as prostatic calcifications, rendering their eradication difficult [9].

In our study, *E. Coli* showed higher resistance trends against TMP-SMX (22.6%), tetracyclines (21.4%) and fluoroquinolones (17.8%). In fact, resistance in *Escherichia coli* to the most widely used medicines for the treatment of urinary tract infections is widespread. A study from Sweden reported increase in norfloxacin, ciprofloxacin and cotrimoxazole resistance over a ten-year period [10] though a study from England showed a slight increase in resistance to amoxicillin and significant fall in resistance to ciprofloxacin over a five-year period [11].

Resistance in CoNS seems to evolve due to positive selective pressure following antibiotic treatment. A study from the US showed that over the course of a 13 years study period *S. epidermidis* resistance to ciprofloxacin and clindamycin increased steadily from 58.3% to 68.4% and from 43.4% to 48.5%, respectively. Resistance to levofloxacin increased rapidly from 57.1% in 1999 to 78.6% in 2005, followed by a decrease to 68.1% in 2012. Multidrug resistance for CoNS followed a similar pattern, and this rise and small decline in resistance were found to be strongly correlated with levofloxacin prescribing patterns [12]. In a study from Ghana the highest frequency of resistance to CoNS was observed for penicillin V (98%), trimethoprim (67%), and tetracycline (63%) [13]. Although Greece is among the greatest consumers of quinolones, in our study *Staphylococci* CoN showed higher resistance trends against macrolides (23.2%) and tetracyclines (21.7%), compared to quinolones (5.42%).


As far as our bacterial eradication rate (68.15%) is concerned, its value is close to that reported in a previous Greek study (64.7%) [14] whilst is lower of that reported in clinical trials [15-17]. These facts may reflect the antibiotic susceptibility status in our country. Outcome was also associated with the severity of CBP: usually patients with a shorter duration and less severe symptoms will have resolution of prostatitis-like symptoms within 1 year after treatment while those with persistent chronic prostatitis may remain relatively unchanged over the year [18].

Relapse was relatively low in this study (13.6%). Relapse episodes were caused by incomplete eradication of causative pathogens in almost 50% of the cases. In the remained cases they were caused by microorganisms other than those causing the initial infection. Relapse



was found to be a complex multifactorial phenomenon mostly associated with short-lasting antibiotic therapy. Busetto et al., found twice as many relapses (27.6%) as in our study following 21 days treatment [19]. Interestingly, higher doses for shorter durations seem not to be helpful in extending the relapse-free interval in patients with CBP [20].

Conclusions

Notable variations in susceptibility levels between pathogens were observed in this study. Enterococcus resistance trends against tetracyclines, macrolides and fluoroquinolones is emerging, given that Enterococci are tolerant microorganisms that develop biofilms on abiotic surfaces such as prostatic calcifications, rendering their eradication difficult. 

Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Η χρόνια βακτηριακή προστατίτιδα (ΧΒΠ) είναι μια φλεγμονώδης κατάσταση του προστάτη, που χαρακτηρίζεται από υποτροπές και υφέσεις. Λόγω των τρεχουσών τάσεων στην βακτηριακή ευαισθησία, η βακτηριακή παραμονή, η κλινική υποτροπή και η επανεμφάνιση της λοίμωξης θεωρούνται συχνές. Σκοπός της μελέτης μας

ήταν να διερευνήσουμε το ποσοστό υποτροπών και της επανεμφάνισης και να προσδιορίσουμε την βακτηριακή ευαισθησία στο περιβάλλον μας.

ΥΛΙΚΟ: Το κλινικό δείγμα που χρησιμοποιήθηκε στη μελέτη περιλάμβανε βακτηριακές απομονώσεις που ελήφθησαν από ασθενείς με ΧΒΠ που επισκέφθηκαν την κλινική από 03/2009 έως 03/2015. Διεξήχθη βακτηριακή ταυτοποίηση χρησιμοποιώντας το σύστημα Vitek 2 Compact και δοκιμή ευαισθησίας με δίσκο και το σύστημα Vitek 2.



**Λέξεις
ευρετηριασμού**
χρόνια προστατίτιδα,
προστάτης, λοίμωξη,
αντιβιοτικά, ευαισθησία,
Stamey-Meyers

ΑΠΟΤΕΛΕΣΜΑΤΑ: Συνολικά 389 προϊόντα βακτηριακής απομόνωσης αποτέλεσαν το υλικό της μελέτης. Μια ευρεία ποικιλία θετικών κατά Gram και αρνητικών κατά Gram ειδών απομονώθηκε από ασθενείς με ΧΒΠ. Παρατηρήθηκαν αξιοσημείωτες μεταβολές στα επίπεδα ευαισθησίας μεταξύ των παθο-

γόνων, με εκείνη του *Enterococcus* να είναι η πιο εμφανής. Βακτηριακή παραμονή παρατηρήθηκε σε 111 περιπτώσεις. Υποτροπές εμφανίστηκαν σε 53 ασθενείς. Τα παθογόνα που συσχετίζονται συνήθως με υποτροπές ήταν *Enterococcus faecalis*, CoNS και *E. Coli*. **ΣΥΜΠΕΡΑΣΜΑΤΑ:** Υπάρχουν μεγάλες διαφορές στα επίπεδα ευαισθησίας μεταξύ των παθογόνων. Ενώ η βακτηριακή παραμονή είναι σχετικά συχνό φαινόμενο, οι μικροβιολογικές υποτροπές είναι λιγότερο συχνές. Οι επαναμολύνσεις τείνουν να είναι η συνηθέστερη αιτία επανεμφάνισης της ΧΒΠ.

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ORIGINAL ARTICLE

The contribution of modified Marmar technique to achieve improvement in spermiogram and to achieve pregnancy in couples with infertile men with varicocele

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Abstract

Varicocele is the most common cause of male infertility. The goal of varicocele treatment is to prevent backflow into the internal spermatic veins. The aim of this study is to investigate the hypothesis that varicocele repair with a modified Marmar technique, using Valsalva maneuver intraoperatively to better identify the varicose veins in infertile men, not only contributes to the postoperative improvement of the spermiogram, but also to the achievement of pregnancy.

Between March 2017 and March 2019 a total of 169 infertile men, aged 18 to 44, underwent varicocele repair with the modified Marmar technique. Men with co-existing other causes of infertility or with varicocele and normal spermiogram were excluded. Postoperatively, normalization of the number of spermatozoa was present in 109 cases (64.5%), of the sperm motility in 92 cases (54.4%) and of the sperm morphology in 147 cases (87%), while simple improvement of the number



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of spermatozoa was found in 151 cases (94.1%), of the sperm motility in 161 cases (95.3%) and of the sperm morphology in 149 cases (88.1%). During follow up, 70 patients reported constant efforts to achieve a pregnancy. Spontaneous pregnancy rate was 45.7% (32 cases). Only three patients (1,8 %) presented hydrocele formation.

Based in our findings Modified Marmar technique using Valsalva maneuver intraoperatively to identify the varicose veins is a very safe technique, with rare complications and with a high effectiveness to improve postoperatively the semen analysis parameters and the man fertility, affecting positively to spontaneous pregnancy.

Introduction

According to the World Health Organization (WHO), infertility is defined as the failure of a sexually active couple to achieve pregnancy after 12 or more months of regular, unprotected sexual intercourse and affects about 16% of the couples. The male factor is present in 50% of the cases.(1-4). Varicocele is the most common cause of male infertility and is found at 15-20% of the general population but at 35% of men with primary infertility and up to 81% of men with secondary infertility (1, 4-11). The aim of varicocele treatment is to prevent backflow into the internal spermatic veins. This can be achieved by percutaneous selective embolization, sclerotherapy, or surgical repair. There are a large number of techniques and sub-techniques for Varicocelectomy which are practiced worldwide but none of them is yet acknowledged as the "gold standard". Each technique has a different degree of complexity, success, complications, and relapse(1, 12, 13). A big advantage of Marmar technique which was first described in 1985 is the reduction of post-operative pain(13). This is due to the small incision being made, but mainly to the fact that it is avoided to open the aponeurosis of the abdominal external oblique muscle that has been associated with the occurrence of postoperative pain (1, 11, 13-15).

Most studies have shown that the repair of the varicocele leads to improvement of spermiogram parameters. However, the latest major studies showed that treatment of varicocele showed no benefit in terms of achieving pregnancy despite the ameliorating of the spermiogram (1, 4). According to Weedon et al between 233 patients with varicocele and non-occlusive azoospermia who were surgically treated there was an improvement in the spermiogram at 39% of the patients but the pregnancy ratio was only 6% (16).

The aim of this study is to investigate the hypothesis that varicocele repair with a modified Marmar

Key words

varicocele, male infertility, surgical repair, Marmar technique

sub-technique in infertile men not only contributes to the postoperative improvement of the spermiogram, but also to the achievement of pregnancy.

Material and Methods

This is a prospective study performed at Aretaion University of Athens hospital and Sismanogleio General Hospital of Athens between 01/03/2017 until 01/03/2019. In the study were included infertile men aged 18-44 years who underwent Varicocele repair with a modified Marmar technique. Men with co-existing other causes of infertility or with varicocele and normal spermiogram excluded from the study. Demographic data, location of varicocele, sperm parameters prior to surgery and 6 months later and pregnancy achievement after monitoring recorded.

The data recorded and analyzed based on Biostatistics principles and all analyses were performed with IBM SPSS 23.0 for Windows.

Surgical technique

The position of the superficial inguinal ring is recognized, and a small incision is made 2-3 cm in length just below it. The spermatic cord is recognized, detached from the surrounding adhesions and isolated with the use of a penrose drain. Then traction is applied, resulting in the spermatic cord being out of subcutaneous tissue. The external spermatic fascia is opened and the testicular artery and the vas deferens are recognized and maintained. Then Valsalva maneuver is performed to increase intrathoracic pressure, reduce cardiac output, reduce venous return and increase venous pressure. This results in the spermatic veins being filled with blood and being magnified. The stretched spermatic veins are identified and ligated while the surgical wound is



Table 1 *Entire study population characteristics*

Number of patients included in the study		169
Age		30.1 ± 6
Varicocele – Left Side		169 (100%)
Bilateral Varicocele	No	152 (89.9%)
	Yes	17 (10.1%)
Improvement to any variable of spermiogram	Yes	169 (100%)
	No	0 (0%)
Any Improvement of the number of sperm	Yes	151 (94.1%)
	No	18 (5.9%)
Improvement to the number of sperm to the normal limits according to WHO	Yes	109 (64.5)
	No	60 (35.5%)
Any improvement to the Motility of sperm	Yes	161 (95.3%)
	No	8 (4.7%)
Improvement to the Motility of sperm to normal limits according to WHO	Yes	92 (54.4 %)
	No	77 (45.6 %)
Any improvement to the Morphology of sperm	Yes	149 (88.1 %)
	No	20 (21.9%)
Improvement to the Morphology of sperm to the normal limits according to WHO	Yes	147 (87%)
	No	22 (23%)
Postoperative spermiogram	Normal	4 (2.4%)
	Abnormal	165 (97.6%)
Postoperative Hydrocele	Yes	3 (1.8%)
	No	166 (98.2 %)
Postoperative pregnancy attempt	Yes	70 (41.4%)
	No or Missing data	99 (58.6)
Postoperative successful pregnancy attempt	Yes	38 (54.3%)
	No	32(45.7%)

closed by layers. The surgery can be performed with general, local or epidural anesthesia.

Results

During the period of the study 169 consecutive patients submitted to varicocele repair with this modified Marmar technique. The mean (\pm SD) age for all patients was 30.1 \pm 6 years. Preoperative semen analysis showed simultaneously abnormal results for the number, the motility and the morphology of sperm to the whole population of the study. All the patients suffered from Left Varicocele, including 17 patients (10.1%) suffered from bilateral varicocele. Postoperatively any improvement to any variable of semen analysis was

found to all the cases but only 4 patients presented normal spermiogram postoperatively. During the follow up 70 patients reported constant efforts to achieve a pregnancy. Spontaneous pregnancy rate was 45.7% (32 cases). Demographic and clinical data of entire study are summarized in Table 1.

DISCUSSION

Varicocele is the most common and correctable cause of male infertility and is found at 15-20% of the general population but at 35% of men with primary infertility and up to 81% of men with secondary infertility (1, 4-11) Many individual studies and meta-analyses demonstrated that varicocele repair improves semen

parameters in patients with preoperative abnormal spermiogram (11). Matkov et al report a significant improvement of sperm motility and sperm count (9, 17). Kibar et al (2002) demonstrated a notable improvement in the sperm count, motility and morphology (18). Perimenis et al (2001) compared postoperative semen variables between 146 patients surgically treated with subinguinal technique and 62 patients treated with tamoxiphen and reported improvement to the 83.2% of operated patients instead of 32.3% of the non-operated patients. (19) In our series we identified improvement in at least one semen parameter to all the cases, demonstrating the effectiveness of the modified Marmar technique to improve the postoperative semen variables. According to WHO guidelines normalization of the number of sperm was present in 109 cases (64.5%), of the motility of sperm in 92 cases (54.4%) and of the morphology of sperm in 147 cases (87%). Otherwise improvement of the number of sperm was found in 151 cases (94.1%), of the motility of sperm in 161 cases (95.3%) and of the morphology of sperm in 149 cases (88.1%) Nevertheless only 4 patients identified with normal spermiogram after the varicocele repair.

Although many studies report high postoperative pregnancy ratio, there are still conflicting opinions if Varicolectomy improves fertility. Cayan et al. (2000) reported pregnancy ratio 33.57% with Palomo technique and 42.85% with microsurgical technique (20). Baazeem et al. (2009) reported a significant improvement in semen variables and a higher pregnancy ratio (38%) using microsurgical technique than only observation (30%) (5). Perimenis et al. (2001) demonstrated statistically significant higher pregnancy ratio (42,5%) in the group with surgically treated patients instead of the group of the patients who refused the surgical option (12.9%) (19). Nevertheless according to Weedon et al between 233 patients with varicocele and non-occlusive azoospermia who were surgically treated there was an improvement in the spermiogram at 39% of the patients but the pregnancy ratio was only 6% (16). According to the biggest metaanalyses published in the literature from Cayan et al. (2009) pregnancy ratio was 37.69% in the Palomo technique, 41,97% in the microsurgical


techniques, 30.7% in the laparoscopic approach and 36% in the macroscopic inguinal technique (11). In our study the pregnancy ratio was 45.7% which suggests the postoperative positive impact of modified Marmar technique to the man fertility.

The modified Marmar technique we used in our study has the advantage that during Valsalva maneuver, because of the increased intrathoracic pressure, spermatic veins being filled with blood and being enlarged. Then the stretched spermatic veins are easily identified and ligated without the use of magnification, thus artery or lymphatic vessel injury is avoided. Moreover modified technique retains the main advantages of the original technique: 1) the operation can be performed under local, general and epidural anesthesia, 2) reduced rates of recurrence and complications, 3) preservation of the spermatic artery, vas deferens and lymphatic vessels 4) reduction of post-operative pain.

Hydrocele formation postoperatively is the most common complication of varicocele repair. According to Cayan et al (2009) hydrocele rate was 8,24% in the Palomo technique, 2,84% in the laparoscopic technique 0.44% in the microsurgical techniques and 7,3 % in macroscopic inguinal of subinguinal technique (11). In our series only three patients (1,8 %) presented hydrocele after the operation which compare similarly with the rates reported to the literature for the classic and other modified Marmar techniques (1, 5, 11, 13, 20, 21).

Limitations of our study include its two-center nature and the small number of participants. In addition it is difficult to evaluate the true improvement in pregnancy ratio while an accurate evaluation must include the whole couple and not only the male factor.

CONCLUSION

Base in our findings Modified Marmar sub-technique using Valsalva maneuver intraoperatively to identify the varicose veins is a very safe technique, without the frequent occurrence of complications and with a high effectiveness to improve postoperatively the semen analysis parameters and the man fertility, affecting positively to spontaneous pregnancy. 



Περίληψη

Η κιρσοκήλη αποτελεί την συχνότερη αιτία υπογονιμότητας στον άνδρα. Ο σκοπός της αποκατάστασής της, είναι να εμποδίσει την παλλινδρόμηση αίματος στις έσω σπερματικές φλέβες. Ο σκοπός της μελέτης είναι η διερεύνηση της υπόθεσης πως η χειρουργική αποκατάσταση της κιρσοκήλης με την τροποποιημένη τεχνική κατά Marmar, όπου εκτελείται δοκιμασία Valsalva διεγχειρητικά

ώστε να γίνουν καλύτερα αντιληπτές οι ανεπαρκείς φλέβες σε υπογόνιμους άνδρες, όχι μόνο συμβάλλει στη βελτίωση του σπερμοδιαγράμματος μετεγχειρητικά, αλλά αυξάνει και τα ποσοστά εγκυμοσύνης.

Μεταξύ Μαρτίου 2017 και Μαρτίου 2019, 169 υπογόνιμοι άνδρες, ηλικίας 18 έως 44 ετών, υποβλήθηκαν σε αποκατάσταση της κιρσοκήλης τους με την τροποποιημένη Marmar τεχνική. Συνυπάρχουσες άλλες αιτίες υπογονιμότητας ή περιπτώσεις κιρσοκήλης με φυσιολογικό σπερμοδιάγραμμα ήταν αιτίες απο-

Λέξεις ευρετηριασμού

κιρσοκήλη,
ανδρική υπογονιμότητα,
χειρουργική αποκατάσταση,
τεχνική Marmar

κλεισμού. Μετεγχειρητικά, το σπερμοδιάγραμμα έγινε φυσιολογικό αναφορικά με τον αριθμό των σπερματοζωαρίων ανά ml σε 109 περιπτώσεις (64.5%), την κινητικότητα σε 92 περιπτώσεις (54.4%) και τη μορφολογία σε 147 περιπτώσεις (87%), ενώ απλά βελτιώθηκε ο αριθμός ανά ml σε 151 περιπτώσεις (94.1%), η κινητικότητα σε 161 περιπτώσεις (95.3%) και η μορφο-

λογία σε 149 περιπτώσεις (88.1%). Κατά την μετεγχειρητική παρακολούθηση, 70 ασθενείς ανέφεραν προσπάθειες για εγκυμοσύνη, η οποία επετεύχθη σε 32 περιπτώσεις (45.7%). Μόνο σε 3 ασθενείς ανεπύχθη υδροκήλη (1,8 %).

Με βάση τα ευρήματά μας, η τροποποιημένη Marmar τεχνική με τον χειρισμό Valsalva διεγχειρητικά, είναι μια ασφαλής τεχνική, με σπάνιες επιπλοκές και υψηλή αποτελεσματικότητα μετεγχειρητικά τόσο στις παραμέτρους του σπέρματος όσο και στα ποσοστά επίτευξης εγκυμοσύνης.

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ORIGINAL ARTICLE

Is there a role for b3 agonists or anticholinergics in the treatment of the lower urinary tract symptoms in patients with multiple sclerosis?

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Abstract

INTRODUCTION: Multiple Sclerosis (MS) is the most frequent autoimmune demyelinating disease of the Central Nervous System. Patients suffering from MS usually present with over-active bladder syndrome. Our objective is to study the efficacy and safety of treating patients with MS and lower urinary tract

symptoms (LUTS) using either b3 agonist (mirabegron) or anticholinergics.

MATERIAL AND METHODS: This is a randomized controlled trial including 30 patients with MS and LUTS from a single center. At baseline all patients underwent thorough clinical examination,



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urine test, urine cultivation and abdominal ultrasound. They also completed an urination diary and specific questionnaires. At second visit all patients were administered either a b3 agonist (mirabegron) or anticholinergics. Sixteen patients (the 1st group) received mirabegron 25mg or 50mg and fourteen patients (the 2nd group) received solifenacin 5mg or 10mg or fesoterodine 4mg. The treatment was always carried out alongside with the MS treatment. Reevaluation was performed 3 months after the first visit. All patients underwent the same clinical and imaging tests that were carried out at first visit.

RESULTS: We compared several clinical and imaging param-

eters between the two groups at first visit and month 3 after treatment. In both groups, improvement in LUTS was recorded. Statistical analysis was performed in both groups using the t-test. In most of the studied parameters, no statistical difference was noted between the mirabegron group and the antimuscarinic group in terms of LUTS improvement. Adverse events were reported in both groups.

CONCLUSIONS: All MS patients receiving either mirabegron or antimuscarinic therapy for LUTS showed an improvement. Nevertheless, no statistical difference was noted between the two groups in most of the tested parameters.

Introduction

Multiple Sclerosis (MS) is the most frequent autoimmune demyelinating disease of the Central Nervous System (CNS) through focal lymphocyte infiltrations which can preexist for years before the onset of clinical symptoms [1]. MS is characterized by heterogeneous clinical presentation and evolution. Most patients suffer from over-active bladder (OAB) symptoms or recurrent urinary tract infections (UTIs). Other common complaints are voiding and emptying difficulties with a smaller group of patients who cannot void at all (urinary retention) [2]. Between the various symptoms of MS, the neurogenic dysfunction of the lower urinary tract contributes notably in reducing the quality of patients' life. Most of the patients suffer from storage, OAB symptoms. These symptoms include increased frequency, urgency, incontinence and nocturia which intervene negatively in the quality of life affecting mental health and the ability to work as well [3].

MS plaques can be found anywhere in the CNS, including the spinal cord. Their exact location will profile unique features of lower urinary tract dysfunction. Lesions in cortical regions related to urinary tract regulation (medial prefrontal cortex, insula, and pons) are thought to be the cause of neurogenic detrusor overactivity (NDO) [4]. The prevalence of cervical cord plaques is almost 80% in these cases, predominantly in the lateral corticospinal (pyramidal) and reticulospinal tracts. Lumbar and dorsal cord involvement is less frequent (40% and 18%, respectively). Suprasacral spinal lesions may cause NDO by impacting the descending inhibition

Key words

multiple sclerosis;
lower urinary tract symptoms;
b3 agonists;
anticholinergics

of bladder contraction. On the other hand, damage to the reticulospinal tracts may lead to detrusor-sphincter-dyssynergia [5]. Plaques in efferent or afferent pathways may impair emptying and urinary retention [6].

The prevalence of lower urinary tract symptoms (LUTS) in patients with MS ranges from 6,9% to 95%, while especially the prevalence of over-refraction of the detrusor muscle ranges from 27% to 91% [7]. LUTS occur on average 6 years after the onset of the disease (with a range of 5 to 9,5 years) while all MS patients experience LUTS within a period of 10 years or more from the onset of the MS symptoms [7]. Such symptoms are often underestimated by attending physicians and this reflects also to the literature. As a result, many patients deal with complications arising from LUTS such as urinary incontinence, recurrent urinary tract infections, kidney and urinary bladder lithiasis and ultimately an impairment of the renal function. Detailed recording and treatment of LUTS is therefore of great importance in order to prevent complications and to offer a better quality of life [8].

The objective of the study is to evaluate the efficacy and safety of treating patients with MS and LUTS using either b3 agonist (mirabegron) or anticholinergics.

Material and methods

This is an ongoing, single center, randomized, controlled study, including initially 30 patients with MS and LUTS treated with either b3 agonist or anticholinergics. At baseline, all patients underwent thorough clinical examination including neurological examination and



Table 1 Patient baseline characteristics

	Patients treated with b3 agonist (n = 16)	Patients treated with anticholinergics (n = 14)	P value
Age years (mean, range)	54 (23-81)	49 (27-59)	0.141
Male gender pts	4 (25)	3 (21.4)	0.416
Years since MS diagnosis (mean, range)	10.5 (3-340)	15 (3-38)	0.084
Years since initiation of LUTS (mean, range)	4.3 (1-12)	6.5 (2-19)	0.084
Previous treatment pts	6 (37.5)	7 (50)	0.254
PVR (+) pts	1 (6.3)	2 (14.3)	0.241
US dilatations pts	0	1 (7.1)	0.146
Urine infection pts	3 (18.8)	3 (21.4)	0.430
MusiQoL score (mean, range)	66.3 (50-79)	68.1 (61-78)	0.258
NBSS score (mean, range)	20.1 (6-36)	22.1 (1-37)	0.278
Dairy fluid intake, ml (mean, range)	1303 (550-2300)	1321 (780-2200)	0.459
Dairy urgency episodes (mean, range)	4.2 (0-11)	10.2 (4.5-16)	0.115
Dairy number of urinations (mean, range)	10 (5.5-13.5)	6 (0-11)	0.440
Urination volume, ml (mean, range)	149 (60-350)	123 (50-250)	0.188

digital rectal examination (DRE). Extent medical history was recorded. All patients underwent urine test, urine cultivation and abdominal ultrasound with special emphasis in possible dilatations or post void residual (PVR). All patients completed an urination diary (for at least 3 consecutive days) and specific questionnaires such as MusiQoL [9] and NBSS [10].

At second visit and after all the above were completed all patients were administered either a b3 agonist (mirabegron) or anticholinergics. The choice of which anticholinergic drug to be used was random as no such drug shows any superiority compared to the others [11]. More specifically 16 patients with a mean age of 54 years (the 1st group) received mirabegron 25 or 50 mg and 14 patients with a mean age of 49 years (the 2nd group) received solifenacin 5 mg or 10 mg or fesoterodine 4 mg (**Table 1**). The majority of the patients from the 1st group (14 pts) received mirabegron 25 mg. Two of the 1st group patients received mirabegron 50 mg. Most of the patients of the 2nd group (13 pts) received solifenacin and only one patient was treated with fesoterodine. Five patients of the 2nd group received solifenacin 5 mg while eight of them received solifenacin 10 mg. The treatment was always carried out alongside with the MS treatment. Reevaluation was performed 3 months after the first visit. All patients underwent the same clinical and imaging tests that were carried out at first visit. Statistical analysis was performed in both groups using the t-test.

Results

We compared several clinical and imaging parameters such as the scores of the 2 questionnaires, potential pelvic or calyceal dilatations in the ultrasounds, increased urine residual volume, infections and the urination diary data between the two groups at first visit and month 3 after treatment.

Statistical analysis of the results showed that there was no statistical significance regarding the results of both groups before and after treatment in terms of the PVR, US dilatations, NBSS score and the dairy fluid intake.

On the contrary, the results before and after treatment were significant at $p < 0.05$ in both groups in terms of urine infection, MusiQoL score (p value < 0.001), dairy urgency episodes, dairy number of urinations and the urination volume. Improvement in LUTS was recorded and validated in the parameters written above. All adverse events of the drugs were reported in both groups (**Table 2, Table 3**).

No statistical difference was noted between the mirabegron group (1st group) and the antimuscarinic group (2nd group) in terms of LUTS improvement in all the statistically significant parameters except of the dairy urgency episodes and the dairy number of urinations. In terms of the dairy urgency episodes, a significant difference (p value = 0.027) was noted between the mirabegron group and the antimuscarinic group in favor of the mirabegron group. Similarly, the results of both groups showed a significance in the dairy number

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Table 2 <i>Patient data before and after treatment</i>			
	Patients treated with b3 agonist (n = 16)		P value
Group 1	Baseline	3 months	
PVR (+) pts	1 (6.3)	0	0.163
US dilatations pts	0	0	0.5
Urine infection pts	3 (18.8)	0	0.036
MusiQoL score (mean, range)	66.3 (50-79)	52.4 (30-65)	<0.001
NBSS score (mean, range)	20.1 (6-36)	18.7 (6-34)	0.335
Dairy fluid intake, ml (mean, range)	1303 (550-2300)	1454 (1200-2000)	0.173
Dairy urgency episodes (mean, range)	4.2 (0-11)	1.1 (0-4)	0.003
Dairy number of urinations (mean, range)	10 (5.5-13.5)	7.3 (7-9)	<0.001
Urination volume, ml (mean, range)	149 (60-350)	219 (65-400)	0.013

Table 3 <i>Patient data before and after treatment</i>			
	Patients treated with anticholinergics (n = 14)		P value
Group 2	Baseline	3 months	
PVR (+) pts	2 (14.3)	1 (7.1)	0.28
US dilatations pts	1 (7.1)	1 (7.1)	0.5
Urine infection pts	3 (21.4)	0	0.035
MusiQoL score (mean, range)	68.1 (61-78)	54.4 (42-71)	<0.001
NBSS score (mean, range)	22.1 (1-37)	17.6 (0-32)	0.093
Dairy fluid intake, ml (mean, range)	1321 (780-2200)	1439 (1200-2000)	0.185
Dairy urgency episodes (mean, range)	6 (0-11)	2.2 (0-6)	0.001
Dairy number of urinations (mean, range)	10.2 (4.5-16)	8.1 (6-10)	0.013
Urination volume, ml (mean, range)	123 (50-250)	207.1 (140-325)	<0.001

Table 4 <i>Comparison of the results of the 2 groups after treatment</i>			
	Patients treated with b3 agonist (n = 16) Group 1	Patients treated with anticholinergics (n = 14) Group 2	P value
Urine infection pts	0	0	0.5
MusiQoL score (mean, range)	52.4 (30-65)	54.4 (42-71)	0.298
Dairy urgency episodes (mean, range)	1.1 (0-4)	2.2 (0-6)	0.027
Dairy number of urinations (mean, range)	7.3 (7-9)	8.1 (6-10)	0.021
Urination volume, ml (mean, range)	219 (65-400)	207.1 (140-325)	0.309

of urinations (p value = 0.021) in favor of the 1st group (Table 4).

Discussion

Overactive bladder is the most common lower uri-

nary tract complaint in men and women with MS as defined by urgency, urge incontinence, urinary frequency and nocturia [12,13]. An established medical treatment option for patients with NDO, including those with MS, is antimuscarinic therapy, which may improve bladder compliance and reduce OAB symptoms [14,15]. The



efficacy of antimuscarinics on daytime frequency, urgency, and urgency incontinence is well established and recognized, but side effects are quite common. Data support that the most common adverse events associated with oral antimuscarinics are dry mouth and constipation. Local adverse skin reactions are the most commonly reported side effect with the oxybutynin transdermal delivery system. The potential for increasing side effects may be greater in select patient populations such the elderly and those already taking multiple medications. Many commonly prescribed drugs have anticholinergic effects that could increase the anticholinergic "load" or "burden" in OAB patients managed with antimuscarinic agents, thus potentially increasing the frequency and severity of side effects [16]. Thus, in MS patients, antimuscarinics have been associated with a relatively high risk of urinary retention, and current guidelines do not recommend these agents for patients with an increased post void residual (PVR) and advise monitoring of the PVR when antimuscarinic therapy is applied [17]. CNS related side effects, with antimuscarinics able to cross the blood-brain barrier, increases the risk of urinary tract infections due to a reduction in bladder emptying, and precipitation or exacerbation of constipation. As some antimuscarinics may affect cognitive status, patients may suffer from memory deterioration especially if cognitive status is already impaired. In such cases, antimuscarinics that do not cross the blood-brain barrier (BBB) or with selective affinity for the M3 receptor should be preferred [18]. Agents such as darifenacin, fesoterodine and trospium chloride have a low potential to cross the BBB and have shown little evidence of CNS toxicity in clinical trials [19]. Based on current literature there are several trials which compare the effects of different anticholinergic drugs for OAB symptoms in adults. In Cochrane Systematic review by Madhuvrata et al, eighty-six trials involving 31,249 adults comparing one anticholinergic drug with another or two doses of the same drug, were included. The authors' conclusions were that when the prescribing choice was between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth with tolterodine, 2 mg twice daily is the usual starting dose but a 1 mg twice daily dose might be equally effective, with less risk of dry mouth. If extended release preparations of oxybutynin or tolterodine are available, these might be preferred to immediate release preparations because there is less risk of dry mouth. Between solifenacin and immediate release tolterodine, solifenacin might be preferred for

better efficacy and less risk of dry mouth. Solifenacin 5 mg once daily is the usual starting dose, which could be increased to 10 mg once daily for better efficacy but with increased risk of dry mouth. Between fesoterodine and extended release tolterodine, fesoterodine might be preferred for superior efficacy but has a higher risk of withdrawal due to adverse events and higher risk of dry mouth. There was little or no evidence available about quality of life, costs, or long-term outcomes in these studies. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions [20]. Despite the known use of antimuscarinics on MS patients' LUTS as first line treatment, comparative studies of different anticholinergic agents specifically on MS patients are limited [1]. The efficacy, tolerability and safety of anticholinergic drugs among patients with multiple sclerosis were assessed in a Cochrane Systematic review by Nicholas et al, published in 2009 (REF15). However, this review included data from only three single-center randomized crossover trials that were either placebo-controlled or designed to compare the effects of two or more treatments. In the Cochrane review15, the authors did not find sufficient evidence to prove any significant benefit of antimuscarinics in patients with multiple sclerosis and LUTS. The authors also noted a high incidence of adverse effects (such as dry mouth or constipation) with more than one in five trial participants having to withdraw from antimuscarinic treatment. Findings of systematic reviews do not support the superiority of any drug over another [15].

In 2012, the FDA approved the first non-antimuscarinic oral medication, mirabegron, to treat patients with OAB symptoms. Mirabegron works via the sympathetic nerve pathway and stimulates beta-3 receptors, causing smooth muscle relaxation in the bladder [21, 22]. The use of a beta-3 agonist is specific to the bladder as 97% of the beta adrenergic receptor subtypes are the beta-3 subtype [23]. As mirabegron does not cause antagonism of M3 receptors, it is postulated that there is a lower risk for urinary retention compared to antimuscarinic agents [22, 23]. In addition with a mechanism of action distinct from antimuscarinics, mirabegron has a different tolerability profile and does not contribute to anticholinergic burden. While antimuscarinics are associated with low persistence rates due to bothersome adverse effects (AEs) including dry mouth and constipation mirabegron has a low incidence of these particular AEs. In addition, studies report a low incidence of CNS effects with mirabegron, a particular benefit in older patients at risk of cognitive decline [24].

To our knowledge no randomized control study exists comparing the efficacy and safety of b3 agonists and anticholinergics in MS patients suffering from LUTS.

Conclusions


All MS patients receiving either mirabegron or antimuscarinic therapy for LUTS showed an improvement. Nevertheless, no statistical difference was noted between the two groups in terms of drug efficacy except of the dairy urgency episodes and the dairy number of

urinations in which the mirabegron group had better results.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Η πολλαπλή σκλήρυνση (ΠΣ) είναι η συχνότερη απομυελινωτική νόσος του κεντρικού νευρικού συστήματος. Ασθενείς που πάσχουν από ΠΣ συνήθως εκδηλώνουν συμπτωματολογία του συνδρόμου υπερδραστικής κύστης όπως συχνουρία, έπειξη, ακράτεια, νυχτουρία (LUTS). Τα LUTS επιδρούν αρνητικά στην ποιότητα ζωής των ασθενών με ΠΣ, ξεκινούν κατά μέσο όρο έξι

έτη μετά την πρώτη εκδήλωση της νόσου, ενώ δέκα έτη μετά την αρχική διάγνωση όλοι οι ασθενείς με ΠΣ αναφέρουν LUTS. Σκοπός της μελέτης είναι να ελεγχθεί η αποτελεσματικότητα και η ασφάλεια της θεραπείας των ασθενών με ΠΣ και LUTS με την χρήση είτε β3 αγωνιστή (mirabegron) είτε αντιχολινεργικών.

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ: Πρόκειται για μία τρέχουσα, τυχαιοποιημένη, ελεγχόμενη, μονοκεντρική μελέτη στην οποία περιλαμβάνονται 30 ασθενείς με πολλαπλή σκλήρυνση (ΠΣ) και LUTS. Στην 1^η επίσκεψη όλοι οι ασθενείς εξετάστηκαν κλινικά (η κλινική εξέταση περιλάμβανε πλήρη νευρολογική εξέταση και δακτυλική) και καταγράφηκε το πλήρες ιατρικό τους ιστορικό. Επίσης όλοι οι ασθενείς υποβλήθηκαν σε γενική και καλλιέργεια ούρων και υπερηχογράφημα NOK. Επιπρόσθετα όλοι οι ασθενείς συμπλήρωσαν ημερολόγιο ούρησης (τουλάχιστον 3 ημερών) καθώς και ειδικά ερωτηματολόγια όπως το MusiQoI και το NBSS. Κατά την 2^η επίσκεψη και αφότου είχαν διενεργηθεί όλα τα ανωτέρω, σε όλους τους ασθενείς χορηγήθηκε είτε β3 αγωνιστής (mirabegron) είτε αντιχολινεργικός παράγοντας. Η επιλογή του αντιχολινεργικού ήταν τυχαία καθώς κανένας παράγοντας δεν έχει αποδειχθεί δραστικότερος των υπολοίπων στην θεραπεία ασθενών με ΠΣ και LUTS. Πιο συγκεκριμένα 16

Λέξεις

ευρητηριασμού

πολλαπλή σκλήρυνση, συμπτώματα κατώτερου ουροποιητικού συστήματος, β3 αγωνιστές, αντιχολινεργικά

ασθενείς (1^η ομάδα) έλαβαν mirabegron 25 ή 50mg και 14 ασθενείς (2^η ομάδα) έλαβαν είτε σολιφенаκίνη 5 mg ή 10 mg είτε φεσοτεροδίνη 4 mg. Η θεραπεία των ασθενών γινόταν πάντα παράλληλα με την θεραπεία για την ΠΣ. Μετά την πάροδο τριών μηνών από την 1^η επίσκεψη έγινε επαναξιολόγηση των ασθενών με τον ίδιο κλινικό και απεικονιστικό έλεγχο που είχε διενεργηθεί

κατά την 1^η επίσκεψη.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Έγινε σύγκριση διαφόρων κλινικών και απεικονιστικών παραμέτρων (τα σκόρ των 2 ερωτηματολογίων, πιθανές διατάσεις ή αυξημένο υπόλειμμα ούρων, ουρολοιμώξεις, ημερολόγια ούρησης) ανάμεσα στις 2 ομάδες ασθενών στην 1^η επίσκεψη και μετά τον 3^ο μήνα από την έναρξη της θεραπείας. Διενεργήθηκε στατιστική ανάλυση σε αμφοτέρες τις ομάδες ασθενών με χρήση του t-test. Και στις 2 ομάδες ασθενών υπήρξε στατιστικά σημαντική βελτίωση στα LUTS μετά την έναρξη της θεραπείας. Δεν ανεδείχθη στατιστικά σημαντική διαφορά ανάμεσα στην ομάδα του mirabegron και την ομάδα των αντιχολινεργικών ως προς τη βελτίωση των LUTS, με εξαίρεση τα ημερήσια επεισόδια επιτακτικότητας και τον ημερήσιο αριθμό ουρήσεων, όπου τα αποτελέσματα ήταν καλύτερα για την ομάδα του mirabegron. Οι ανεπιθύμητες ενέργειες της θεραπείας καταγράφηκαν και στις 2 ομάδες ασθενών.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Όλοι οι ασθενείς με ΠΣ που έλαβαν είτε mirabegron είτε αντιχολινεργικό παράγοντα παρουσίασαν στατιστικά σημαντική βελτίωση στα LUTS. Παρόλα αυτά δεν ανεδείχθη στατιστικά σημαντική διαφορά ανάμεσα στις 2 ομάδες ασθενών με εξαίρεση τις 2 παραμέτρους που αναφέρονται ανωτέρω.



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Review

Serenoa repens and Pygeum Africanum in the treatment of BPH

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Abstract

INTRODUCTION /AIM: Serenoa repens (SR) and Pygeum Africanum (PA) exhibit marked anti-inflammatory, anti-androgenic and anti-proliferative effects. For this reason, they have been subject of research as potential treatment of benign prostatic hypertrophy (BPH). The aim of this study is to present current knowledge on the topic.

METHODS: A non-systematic search was performed in electronic libraries for clinical trials, experimental studies and systematic reviews on the topic using the terms: "prostate", "benign prostatic hypertrophy", "lower urinary tract symptoms" combined with the key words: "phytotherapy", "Saw palmetto", "Serenoa repens", "Serenoa serrulata", "Pygeum Africanum", "Prunus africana" in various combinations.

RESULTS: A sufficient number of studies of the efficacy of SR for the treatment of LUTS and BPH exists. Most of them examine the role of saw palmetto as add-on to other agents and less as monotherapy. Few similar studies for PA have been published up to date. Almost all examine its role as monotherapy. According to our research, there is no clear evidence of clinical superiority of phytotherapy over conventional treatment however a potent synergistic effect was shown. SR seems to be more efficient than PA though non produce some of the therapeutic effects of PA.

CONCLUSIONS: Combination of SR and PA with other medications can offer significant improvements of urinary status while having a favourable safety profile and for this reason may be considered a viable therapy for treating LUTS in certain groups of patients.

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Introduction

Benign prostatic hyperplasia (BPH) is often accompanied by lower urinary tract symptoms (LUTS) that can significantly affect the quality of life (QoL) of the patients. A variety of phytotherapeutic agents are widely used in traditional and alternative medicine to treat LUTS. The most commonly used preparations originate from the species of palm-like tree *Serenoa repens* (SR), commonly known as saw palmetto (*Serenoa serrulata*) and from the African prune tree *Pygeum Africanum* (PA) also known as *Prunus Africana*. The extract of the fruits and the husk of these plants is highly enriched in fatty acids and phytosterols and exhibit anti-inflammatory anti-androgenic and antiproliferative effects [1-3]. For this reason, they have been the subject of clinical and experimental research in the treatment of symptoms of BPH. In this paper we aim to review relevant published data in order to compare their efficacy in this field.



Key words

phytotherapy,
Serenoa repens,
Pygeum Africanum

apy for men with BPH related LUTS, these of Lopatkin et al, and Giulianelli et al, showed significant improvement in symptoms (as measured in IPSS questionnaire) over the six-month treatment and follow up period. Improvement in both erectile and voiding function was also achieved [4, 5].

Sinescu et al., demonstrated a statistically significant improvement of mild or moderate LUTS and improvements in overall QoL, urinary flow (Qmax), residual urinary volume (RV) and erectile function (EF) during the long-term study period [6]. Others found that higher doses of SR cannot additionally improve neither LUTS nor EF [7, 8].

When compared with placebo, SR extract demonstrated a statistically significant difference in improvement of mild or moderate LUTS. However, SR treatment showed no measurable effect on Qmax [9]. Recently, Ye et al, in a placebo-controlled study found significant improvements in Qmax, IPSS, QoL and EF in the SR extract group. Adverse events were very rare and comparable between the two groups (1.89 and 1.18% in the study and the placebo group respectively)[10]. Finally, Giannakopoulos et al, found significant improvements in the IPSS quality-of-life scores, Qmax and RV over the placebo. In contrast, Helfand et al, found no differences between improvements in urinary symptoms between SR extract and placebo group at 72 weeks of follow-up [8, 11]. Two similar synchronous trials found no difference in the effectiveness of SR versus placebo [12-13]. In none of the abovementioned studies were observed significant side effects.

Efficacy of SR was also compared to that of established BPH treatments. Alcaraz et al, found that in real-life practice, SR shows an equivalent efficacy to alpha-blockers and 5-ARI in LUTS improvement with fewer side effects [14]. In accordance to these findings, Pytel et al. (2002 and 2004) enrolled patients with documented BPH and LUTS. Outcome was estimated upon IPSS, QoL, index of sexual function (MSF-4), size of the prostate, urodynamic and biological parameters. Follow-up lasted 24 months. Apart from the abovementioned parameters, plasma hormones (testosterone, DHT, estradiol, LH, androstenedione) did not change [15,16]. A prospective multicentre double-blind randomized study comparing tamsulosin (0.4mg/24h) with SR (320mg/24h) in a sufficient number of patients with symptomatic BPH (IPSS≥10) found no differences in IPSS improvement after 12 months of follow up. Nota-

Material and methods

A database and a manual search were conducted in the MEDLINE database of the National Library of Medicine, Pubmed, Cochrane Library and other libraries using the terms: "prostate", "benign prostatic hypertrophy", "lower urinary tract symptoms" combined with the key words: "phytotherapy", "Saw palmetto", "Serenoa repens", "Serenoa serrulata", "Pygeum Africanum", "Prunus Africana" in various combinations. Bibliographic information in the selected publications was checked for relevant publications not included in the initial search. Because of the close relationship between inflammation and prostatic hypertrophy and the fact that these two conditions share similar symptoms, we also took in consideration few studies examining the efficacy of phytotherapy in the treatment of symptoms secondary to prostatitis in BPH patients.

Results

SR in the treatment of symptoms of BPH has been tested either alone or in combination or in comparison with other phytotherapeutic, alpha-blockers and inhibitors of 5-alpha reductase (5-ARI). There are more studies examining the role of saw palmetto as add - on therapy to other agents and less as monotherapy.

With regard to studies using SR extract as monother-

bly, Qmax and PSA improvement was similar in both groups. Both treatments were equally well tolerated [17]. Ryu et al showed that the combination SR and tamsulosin was more effective than tamsulosin monotherapy, only in reducing storage symptoms after 6 months of treatment. Adverse events were comparable (16.9 and 20% for the monotherapy and combinational therapy groups) [18]. Statistically significant difference in clinical improvements in LUTS/BPH severity was found between Silodosin plus SR and SR alone, and Silodosin plus SR and Silodosin alone as well [19]. In contrast, according to Argirović and Argirović, in the treatment of BPH, none of SR and tamsulosin had superiority over another and, combined therapy (tamsulosin + SR) does not provide extra benefits. In this study, adverse events occurred only with tamsulosin [20]. Similar conclusions were provided by Glemain et al. and Hizli & Uygur [21, 22]. Finally, a multicentre study compared the efficacy of the combination SR plus alpha-blocker versus SR alone and found similar changes in the uroflowmetry after 6 months of follow-up [23].

Cai et al found greater improvement of patient's quality of life, with the combination SR, Pinus massoniana Bark Extract and Crocus sativus when compared with SR alone [24]. Morgia and colleagues evaluated the effectiveness of the combination SR, lycopene and selenium (SR, LY, SE) versus SR alone in patients with LUTS/BPH/CNBP. They found a slightly higher IPSS improvement in the group of combined therapy after eight weeks of treatment [25]. Again, Morgia and colleagues evaluated the effectiveness of the combination SR, LY, SE (group A), versus tamsulosin alone (group B) and versus the combination SR, LY, SE and tamsulosin (group C). At one year from baseline, the changes of IPSS and Qmax were greater for Group C versus monotherapies [26].

According to some authors a two-month period of treatment with PA extract 50mg twice daily induced significant improvement in IPSS and uroflowmetry parameters [27, 28]. Positive effects were accompanied by a satisfactory safety profile and a substantial improvement in QoL [28]. PA extract administration (200 mg/24h), for 60 days improved urinary sexual and and prostatic echographical parameters with no significant alteration in serum hormonal levels (testosterone, DHT) before and after therapy [29]. In contrast, a small similar study by Donkervoort et al., found no significant effect [30].

In a placebo-controlled study, Pygeum extract given for 6 weeks in a daily dose of 2x100 mg showed

significantly better improvement in IPSS over placebo [31]. In another placebo-controlled study a daily dose of 4x 50 mg provided greater improvement in all the subjective and objective parameters than the placebo [32]. A similar multicenter study found a significant difference between the PA group and the placebo group with respect to therapeutic response as measured by IPSS (55 versus 31% respectively) after two months of treatment [33]. Mild side effects (diarrhea, constipation, dizziness and visual disturbance) were observed in 2.3% of PA group patients.

Of note, comparison of once and twice daily dosage forms of Pygeum africanum showed equal effectiveness and safety at 2 months [34].

Several authors investigated the efficacy and safety of the combination of PA with other phytotherapeutic agents: An orally dosed herbal preparation containing Cucurbita pepo, Epilobium parviflorum, lycopene, Pygeum africanum and Serenoa repens provided significant reduction in IPSS median score (36% in the active group vs 8% for the placebo group), during the 3-months intervention. The day-time and night-time urinary frequency were also reduced in the active group [35]. Krzeski et al., compared the standard dose of an Urtica dioica/PA preparation (300/25mg) with half the standard dose twice daily for 8 weeks and found no difference in Qmax, RV and nycturia improvement [36].

Main outcomes of the comparative studies included in this review are displayed in table 1.

Discussion

Evaluation of SR and PA efficacy in BPH related LUTS treatment is actually difficult for two main reasons. First, the exact mechanism by which they treat BPH remains unknown. Among mechanisms proposed to explain SR's and PA's effects is the inhibition of the activity of the enzyme 5- α reductase (5- α R), the impediment of apoptotic processes in prostate's cells and the hindrance of inflammatory mediators [37, 38]. The above have been attributed by specific studies to different compounds and chemical ingredients included in the extracts. However, the mechanism of action is yet to be thoroughly and fully specified.

5- α R is a basic modulator of the conversion of testosterone to dihydrotestosterone (DHT), which is responsible for the overgrowth of the prostate's epithelial cells. When compared with the most known 5- α R inhibitor, finasteride, SR shows similar or inferior effectiveness in the treatment of mild and moderate LUTS, nocturia

Table 1 Main outcomes

	Placebo	SR	SARI	alpha-blockers	IDIProst plus SR	SR, LY, SE	alpha-blocker SR, LY, SE	alpha-blocker SR	PA
Dedhia	+	+							
Bent	+	+							
Ye	+	++							
Barry	+	+							
Alcaraz		+	+	+					
Debruyne		+		+					
Cai		+			++				
Morgia		+				++			
Morgia				+		+	++		
Ryu				+				++	
Boeri		+		+				++	
Argirović		+		+				+	
Bertaccini		+						+	
Gerber	+	++							
Helfand	+	+							
Glemain		+		+				+	
Hizli & Uygur		+		+				+	
Dufour	+								++
Bassi	+								++
Barlet	+								++

and discomfort [39-41]. However clinical trials found SR extract no more effective than placebo in blocking benign prostate growth [42]. Evidence suggests that the main activity of SR is anti-apoptotic and it is rather the association of SR with some natural compounds (such as lycopene, other carotenoids and selenium) that reduce prostate size than SR alone [43]. This happens as the Ly-Se-SR association is more effective than SR in augmenting the pro-apoptotic Bax and caspase-9 and blunting the anti-apoptotic Bcl-2 mRNA. In addition, Ly-Se-SR more efficiently suppresses the EGF and Vascular Endothelial Growth Factor (VEGF) expressions in hyperplastic prostates [44]. Finally, research suggests an anti-inflammatory activity of SR, provided by beta-sitosterols, which inhibits the production of prostaglandins in the prostate. A strong anti-inflammatory is also achieved through the inhibition of inflammatory mediators MCP-1/CCL2 and VCAM-1 [45].

Despite slight decrease in levels of testosterone associated with PA administration, inhibition of 5-αR by PA is considered minimal and not clinically significant [46]. Antiandrogenic and antiestrogenic effects

(which may block the initiation of hyperplasia), were also achieved through the activity of ferulic esters which decrease prolactin (which stimulates intraprostatic dihydrotestosterone synthesis and testosterone uptake) and cholesterol (which increases the binding sites for dihydrotestosterone), though such effects do not appear to reverse the progression of BPH [47]. An anti-inflammatory effect attributed to several contents of PA extract -such as pentacyclic triterpenes and ferulic esters- was proposed to explain -in part- the in vitro therapeutic effect of Pygeum [48]. In confirmation to the above, a significant downregulation of genes involved in inflammation and oxidative-stress pathways has been recently shown [49]. According some investigators, a powerful anti-proliferative effect on prostate cells, resulting from inhibition of epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor 1 (IGF-I) counteract the structural and biochemical changes associated with BPH [50, 51].

Research suggests that PA reverses altered myosin isoform expression and causes a decrease in the contractility of the detrusor muscle by reducing its sensitivity



to electric stimulants such as phenylephrine, adenosine triphosphate and carbachol [52].

The abovementioned properties of SR and PA explain in part their effects on BPH however remains a gap between in vivo and in vitro studies. Especially for PA most studies are old and out-dated.


Second, due to the heterogeneity of the existing herbal formulations, the short duration of most studies, the variability in study design and variation in outcome measures, the literature is somehow limited. In fact, most SR extracts vary considerably in composition, effectiveness and supporting evidence, since their activity depends on the concentration of free fatty acids and the method of extract preparation [53]. Unfortunately, most studies provided generic or inadequate descriptions of the preparations used with regards to the free fatty acid and phytosterol percentage of the extract and no study gave extra information on the method of SR extraction and the pivotal aspect of the preparation's lauric acid content that would show compliance with the European Pharmacopoeia recommendation. On the other hand, it is possible that placebo effect influenced by positive patients' expectation on phytotherapeutic agents alter the findings of questionnaire based clinical studies [54].

This review didn't find evidence of superiority of SR and PA over conventional BPH treatment and no direct comparison between the two phytotherapeutic agents exists. According to this research, both SR and PA offer improvements of urinary status while having a favorable safety profile. However, it should be also noted that most PA studies are old and include small numbers of patients while there are no studies comparing its efficacy and safety to that of established BPH treatments. For this reason, it could be assumed that SR effects on

urine flow rate and residual urine content might be better. Both have a favourable safety profile though, SR is better tolerated. On the other hand, SR seems not to produce the effects of PA on bladder detrusor.

Since initial clinical trials examining SR with other phytotherapeutic agents and micronutrients have shown a potent synergistic effect [55], the above combination with α -blockers may offer an alternative (other than finasteride and α blocker) combination therapy to patients with moderate symptoms. The combination of PA with α -blockers could be investigated as an alternative (other than anticholinergic and α blocker) combination therapy for patients with irritative symptoms. Finally, SR and PA exhibit remarkable anti-inflammatory and anti-proliferative effect and therefore they may have a crucial role in delaying the development of clinical BPH. For this reason, it could be important to study their effect in younger patients with early symptoms. Such a study may be carried out for each extract separately, depending on the method of preparation and brand.

Conclusions

Despite the amount of preclinical and clinical studies, a definite evaluation of the efficacy of SR and PA in the treatment of BPH related LUTS is actually difficult for methodological reasons. Current data provides no clear evidence of clinical superiority of phytotherapy over conventional treatment. However, combination of SR and PA with other medications can offer significant improvements of urinary status while having a favourable safety profile and for this reason may be considered a viable therapy for treating LUTS in certain groups of patients. 



Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Το εκχύλισμα των *Serenoa repens* (SR) και *Pygeum Africanum* (PA) διαθέτει αντιφλεγμονώδεις, αντιανδρογονικές και αντιπολλαπλασιαστικές ιδιότητες. Για το λόγο αυτό έχει αποτελέσει αντικείμενο έρευνας για την θεραπεία της υπερτροφίας του προστάτη. Σκοπός αυτής της μελέτης είναι να παρουσιάσει την τρέχουσα γνώση πάνω σε αυτό το θέμα.

ΜΕΘΟΔΟΙ: Πραγματοποιήθηκε μια μη συστηματική έρευνα σε ηλεκτρονικές βιβλιοθήκες για κλινικές δοκιμές, πειραματικές μελέτες και συστηματικές ανασκοπήσεις θέμα χρησιμοποιώντας τους όρους: «προστάτης», «καλοήθης υπερτροφία του προστάτη», «συμπτώματα κατώτερου ουροποιητικού» σε συνδυασμό με τις λέξεις: «φυτοθεραπεία», «Saw palmetto», «*Serenoa repens*», «*Serenoa serrulata*», «*Pygeum africanum*», «*Prunus Africana*» σε διάφορους συνδυασμούς.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Στην βιβλιογραφία υπάρχει επαρκής αριθμός μελετών για το SR στην θεραπεία των συμπτωμάτων της

**Λέξεις
ευρετηριασμού**
φυτοθεραπεία,
Serenoa repens,
Pygeum Africanum

καλοήθους υπερτροφίας. Οι περισσότερες από αυτές εξετάζουν το ρόλο του ως πρόσθετο σε άλλους παράγοντες. Λίγες μελέτες έχουν δημοσιευθεί μέχρι σήμερα για το PA. Σχεδόν όλες εξετάζουν το ρόλο του ως μονοθεραπεία. Σύμφωνα με αυτήν την έρευνα, δεν υπάρχουν σαφή στοιχεία κλινικής ανωτερότητας της φυτοθεραπείας σε σχέση με τις συμβατικές φαρμακοθεραπείες. Ορισμένες κλινικές δοκιμές που χρησιμοποιούν το SR συνδυαστικά με άλλα φυτοθεραπευτικά ή με συμβατικά φάρμακα ανέδειξαν μια ισχυρή συνεργική επίδραση. Από την άλλη πλευρά αυτό στερείται ορισμένων θεραπευτικών ιδιοτήτων του PA.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Ο συνδυασμός SR με το PA και άλλα φυτοθεραπευτικά μπορεί να προσφέρει σημαντικές βελτιώσεις στην λειτουργία του ουροποιητικού συστήματος ενώ έχει ευνοϊκό προφίλ ασφάλειας και γι' αυτό το λόγο μπορεί να θεωρηθεί ως μια βιώσιμη θεραπεία σε ορισμένες κατηγορίες ασθενών.

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Review

New imaging technologies in the diagnosis and staging of Non-Muscle Invasive Bladder Cancer

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Abstract

OBJECTIVES : Transitional cell carcinoma (TCC) of the bladder is the second most frequent urological cancer. The patients are usually diagnosed in the non-muscle invasive stage of the disease during cystoscopic examination of the bladder, using the current standard of care, which is White Light Cystoscopy (WLC). The aim of this article was to examine new imaging microscopic and macroscopic technologies in the diagnosis of bladder cancer detection.

METHODS: A customized literature search was performed on Pubmed, focusing on English articles of the last 5 years, concerning new technologies in diagnosis of non-muscle invasive bladder cancer. 36 articles appeared.

RESULTS: WLC is the gold standard in the diagnosis of bladder cancer, with significant limitations, including false – positive

findings, and residual untreated CIS in up to 20% of cystoscopy patients. Recent developments in technology resulted in macroscopic and microscopic imaging modalities for bladder cancer. Photodynamic Diagnosis and Narrow Band Imaging provide additional macroscopic contrast enhancement to traditional cystoscopy and highlight suspicious lesions. The microscopic modalities enable high resolution subsurface characterization of suspected lesions specifying tissue microarchitecture and cellular morphology which are technically impossible using macroscopic imaging technology.

CONCLUSIONS: Overall, there are a lot of new promising technologies that will eventually allow us to simultaneously visualize and stage NMIBC.



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Introduction

Transitional cell carcinoma (TCC) of the bladder is the second most frequent urological cancer, with an incidence in the countries of the European Union of 27/100 000 men and 6/100 000 women per year (1). The majority of TCC cases are detected in the non-muscle-invasive, curable stage of the disease, which highlights the need for optimum tumor detection and treatment at the point of initial recognition/detection, to ensure optimum conditions for staging, treatment, prognosis and patient care. Bladder cancer is not only frequent, but it has also very expensive treatment. The high cost is calculated by the need of frequent follow-up cystoscopic examination, intravesical therapy and surveillance imaging (2). Thorough cystoscopic examination of the bladder is a critical, indispensable component of the disease diagnosis and treatment, and the quality of the endoscopy, frequency of follow-up and completeness of bladder tumor resection may directly influence the disease outcome and patient survival.

The gold-standard in the diagnosis of bladder cancer is white light cystoscopy (WLC). Despite its pivotal role, WLC's limitations are well known and contribute to increased risk of residual tumor after resection, cancer persistence, recurrence and progression (in the case of high-grade bladder cancer and/or presence of carcinoma in situ – CIS) (3). Technology advances have introduced new imaging methods, both at macroscopic and microscopic level, thus improving bladder cancer detection and treatment, patient care and reducing treatment-related costs.

Material and Methods

A customized literature search was performed focusing on English articles of the last 5 years concerning new technologies in diagnosis of non-muscle invasive bladder cancer, using the keywords: "new technologies, non-muscle-invasive bladder cancer". 36 articles appeared and a retrospective review was conducted, after cross-matching the sources according to their validity and impact.

Results

White Light Cystoscopy

White light cystoscopy (WLC) is the gold standard

Key words

imaging technologies,
non-muscle invasive
bladder cancer,
Photodynamic Diagnosis,
Narrow Band Imaging,
Confocal Laser Endomicroscopy,
Optical Coherence Tomography

for visualizing the bladder and establishing the diagnosis of bladder cancer. Direct visual inspection using WLC and subsequent histopathologic examination through tumor biopsy are required for diagnosis and subsequent surveillance. Flexible cystoscopy is the workhorse in the outpatient clinic. WLC performs quite well for the majority of papillary bladder tumors. Experienced urologists can discriminate benign from malignant lesions.

Cina et al demonstrated that urologists can reliably distinguish cancerous from noncancerous lesions using WL alone with 100% sensitivity and specificity (4).

Nevertheless WLC is associated with false-positive findings, leading to unnecessary and potentially excess intervention with bladder biopsies. False-negative cystoscopy, in turn, can lead to residual, untreated, microscopic cancer and a missed diagnosis of carcinoma in situ (CIS) which is not visible by WL cystoscopy in up to 20% of patients (5). Visual appearance by WLC is unreliable for grade staging of the bladder tumor or its level of invasion, thus most patients needing a re-TUR, to re-assess resected areas and completely resect all lesions, in this way resulting in more accurate grade staging, risk of progression and recurrence staging and better treatment and follow-up of the patient (6).

In order to face the weak points of WLC and to improve detection and characterization of suspected bladder tumors, new optical imaging technologies have been developed. These new technologies are intended to improve, rather than replace WLC and boost its diagnostic yield. Table 1 summarizes the characteristics and properties of the technologies reviewed.

Imaging technologies are classified based on macroscopic or microscopic field of view. The macroscopic modalities, Photodynamic Diagnosis (PDD) and Narrow Band Imaging (NBI), survey a large area of bladder mucosa in a manner similar to WLC and provide additional contrast enhancement, highlighting suspicious lesions and distinguishing them from surrounding, presumably non-cancerous mucosa. The microscopic modalities, Confocal Laser Endomicroscopy (CLE) and Optical Coherence Tomography (OCT), enable high resolution sub-surface characterization of suspected lesions, specifying tissue microarchitecture and cellular morphology which is impossible using macroscopic imaging technology.

Table 1 *New imaging technology specifications and technical considerations*

New imaging technology specifications				
	PDD	NBI	CLE	OCT
Field of view	Macroscopic	Macroscopic	Microscopic	Microscopic
Contrast medium	HAL	No	Fluorescein	No
Scope/probe size (mm)	5-7	5-7	1-2.8	2.7
Depth	Surface	Surface	120/μm	1-3 mm
Resolution	mm-cm	mm-cm	2-5 μm	10-20 μm
Vendor	GE Healthcare/Karl Storz	Olympus	Mauna Kea Technologies	Imalux

Photodynamic diagnosis (PDD)

The Photodynamic Diagnosis (PDD), known as blue-light cystoscopy and fluorescence cystoscopy, require preoperative intravesical instillation of a fluorophore that is taken up by the urothelium and preferentially is accumulated by dysplastic cells. Subsequently, when exposed to blue light (380-480 nm), dysplastic cells emit a characteristic red fluorescence. Currently, PDD is the most well validated method of enhanced cystoscopy in improvement of bladder tumor detection (7).

Drugs currently available for the use in PDD are 5-aminolevulinic acid (5-ALA) and the derivative of hexyl ester, hexaminolevulinate (HAL). A prospective phase III trial demonstrated a 16% reduction of relative risk of recurrence at 9 months post-transurethral resection for patients treated with HAL compared with WLC. HAL was subsequently approved by the Food and Drug Administration (FDA) in 2010 (8). HAL has been reported to have superior pharmacological characteristics (9).

A meta-analysis of 2,949 patients presented 92% sensitivity of tumor detection for PDD, compared to 71% for WLC (10). Evidence exists that PDD reduces residual tumor in NMIBC compared with WLC alone, especially in flat lesions such as CIS and dysplasia. These findings result into reduced disease recurrence rates and this is confirmed by most, but not all randomized controlled studies, thus suggesting to accept results with caution (7, 11, 12). Moreover, O'Brien et al. showed that PDD using HAL in patients with primary presenting bladder cancer did not lead to lower recurrence rates in comparison to standard WLC resection, both arms using postoperative single-shot instillation of mitomycin C (13). A delay in time to tumor recurrence after PDD- assisted TURBT was found significant (16.4 vs 9.4 months with WLC) (14). PDD seems to significantly improve CIS detection in a

recent meta-analysis of 551 patients (87% for PDD and 75% for WLC) (15). Jocham et al showed that more accurate diagnosis and better postoperative treatment was possible using PDD in >20% of bladder-cancer patients (16). PDD does not seem to reduce disease progression rates. If PDD is used, it should be applied at initial resection or with an adequate interval to previous treatments, in order to avoid false positive findings (17, 18). Patients with multifocal or recurrent tumors seem to benefit the most from PDD – guided TURBT (19).

False-positive diagnoses are common with PDD and potentially lead to over-use of bladder biopsies. They appear as often as up to 40% on a per-lesion basis and range between 10% - 12% on a per-patient basis in recent clinical trials. There is a learning curve to successful use of this novel imaging modality, and thus surgeon's experience seems to be of high significance (8). False-positive PDD results are produced by auto fluorescence, which is caused by activation of the tissue's endogenous fluorophores in response to blue light. Moreover, adjacent imaging and inflammation, associated with post-intravesical therapy mucosal changes (mainly recent treatment with bacillus Calmette Guérin – BCG) (20) and post-transurethral resection of tumors result in false-positive PDD. PDD during TURB using either ALA or HAL exhibits a limited depth of penetration to bladder lesions, thus restricting the evaluation of more invasive lesions. Another serious disadvantage of PDD is the limiting time of examination to approximately 30 minutes due to "photobleaching", or loss of fluorescence (21).

A limited number of cost-effectiveness studies have been performed evaluating the use of PDD assisted TURBT with WLC. Overall, these studies show a significant cost reduction in bladder cancer follow-up and treatment when PDD is used, compared to WLC alone

in a 5-year period (\$25,921 vs \$30,581, respectively) (22). A study in Germany in 99-month period reported similar results (1597€ lower cost compared to WLC) (23).

Other potential fluorophores used together with PDD included hypericin, which is a derivative of St. John's wort. It seems less susceptible to photobleaching, with higher specificity than HAL/ALA. D'Hallewin et al. reported 94% sensitivity and 95% specificity for hypericin-induced fluorescent detection of CIS (which was superior to 5-ALA and HAL), excellent patient tolerability and extended time of bladder fluorescence after instillation (24-27). A potential downside of hypericin is its low water solubility, which may be controlled using solvents, such as polyvinylpyrrolidone (PVP) and albumin. In preclinical animal models, PVP-hypericin accumulated 3.5 times more in malignant lesions compared to benign urothelium (28).

Narrow band imaging

Narrow band imaging (NBI) is a relatively new macroscopic - imaging technology, which aids at the identification of bladder tumor sites. It filters out the red light spectrum of white light, thus resulting in blue and green bands at 415 and 540 nm, which are well absorbed by hemoglobin. In this manner NBI differentially penetrates the mucosa, enhancing the mucosal and submucosal vasculature. Because of the higher density of the vasculature, NBI accentuates the visual appearance of tumors or CIS by displaying them in a dark green or brown color. The use of NBI assisted TUR, as well as PDD or WLC, cannot differentiate between tumor grades or invasion, but overall, it improves detection of NMIBC (29).

Advantages of NBI are its simple integration to flexible and rigid cystoscopy, thus allowing facile switch between white light and NBI allowing for rapid real-time evaluation and avoiding the need for pre-cystoscopic intravesical administration of an imaging agent.

A recent meta-analysis by Xiong YQ., et al. showed that NBI-assisted TURBT detected 9.9% more NMIBC lesions at per-patient level and 18.6% more NMIBC at per-lesion level (30). A study by Naselli A., et al. showed that NBI-assisted TURBT decreased 1-year recurrence, compared to WLC (32.9% vs 51.4%) (31). Xiong YQ., et al. also demonstrated reduced recurrence rate of BC at 3 and 12 months in favor of NBI compared to WLC (0.43% vs 0.81%) (30). Whereas, a large, international, multicenter, randomized trial managed by the Clinical Research Office of the Endourological Society (CROES) showed that NBI and WLC achieve similar overall recur-

rence rates 12 months after TURBT, but NBI significantly reduces disease recurrence in low-risk patients (32).

NBI is most likely beneficial for the detection of CIS as suggested by Herr (33) who demonstrated superior detection rates for NBI compared with WLC (100 vs. 83% sensitivity) in 427 patients (34). NBI reduces residual tumor, as demonstrated by several studies (35). A meta-analysis of 8 studies and 1022 patients demonstrated that the sensitivity and specificity of NBI and WLC were 94% versus 85% and 85% versus 87%, respectively (29). False-positive findings occur in approximately one-third of patients (ranging from 32% to 36%) and are common after BCG intravesical instillations and inflammation (34).

Optical Coherence Tomography

Optical Coherence Tomography (OCT) is an optical, real-time biopsy technology that enables high-resolution, subsurface tissue examination, without the exogenous use of a contrast agent. OCT is analogous to ultrasound, with the exception of the generation of cross-sectional images using near-infrared light, instead of sound waves. Image resolutions of 10–20 µm and depths of penetration of 2 mm are achievable, thus enabling real-time bladder cancer diagnosis and tumor staging. Another advantage is the relatively short learning curve for the OCT examination of the bladder, as it resembles that of B-mode ultrasound (36).

Karl et al. reported 100% sensitivity detecting a malignant lesion (specificity 65%) and 100% sensitivity in the detection of tumor invasion beyond the lamina propria of the analyzed regions. In particular, the high resolution of OCT can be used to identify anatomical structures and predict malignancy, as well as tumor invasion (37).

Nevertheless, despite promising results, technical challenges arise concerning the use of OCT in the bladder. Complete scanning of the bladder is laborious and time-consuming. The aim should be the identification of regions of interest within the bladder before targeted application of OCT (38). False-positive results are produced in case of granuloma formation, scarring, erosion of the mucosa and nephrogenic adenoma (36).

The combination of two novel techniques may improve tumor detection and staging. Schmidbauer et al. combined the use of OCT with PDD-supported cystoscopy and found a relevant increase in detection specificity and positive predictive value of combined PDD and OCT compared with WLC and PDD alone (39).

Confocal Laser Endomicroscopy

Confocal Laser Endomicroscopy (CLE) was designed to evaluate lesions of the upper gastrointestinal tract and has been under investigational use in the urinary tract since 2009. It enables real-time imaging of the in-situ, microscopic, surface architecture, using an intravesically or intravenously inserted dye (fluorescein). Based on the well-established principle of fluorescence confocal microscopy, CLE is an optical biopsy technology that enables in vivo high resolution and subsurface imaging. Compared to the other imaging techniques, CLE has the highest resolution, but does not evaluate in sufficient depth the muscularis propria.

Fluorescein, a known FDA-approved drug with an established clinical safety profile, is used as an exogenous contrast agent. Reusable miniaturized imaging probes ranging from 0.85-mm to 2.6-mm diameter are compatible with working channels of standard cystoscopes. Detail of tissue microarchitecture down to the cellular level, making it well suited for real-time evaluation of epithelial lesions in most hollow organs. The technique can differentiate between benign (inflammation) and malignant lesions, as well as between low-grade and high-grade urothelial carcinomas, with images comparable to conventional histopathology (40). A recent study demonstrated moderate inter-observer agreement in image interpretation between novice and experienced CLE urologists with respect to cancer diagnosis (41). Limitations of CLE include its narrow field of view, thus relying on another imaging modality for initial identification of suspicious bladder lesions (6).

Emerging technologies

Optical imaging and characterization of bladder cancer lesions is also possible at the molecular and cellular level using fluorescently – labeled binding agents such as antibodies, peptides, or small molecules, which bind to cancer cells (42). Fluorescent antibody CD47 has been shown to detect bladder cancer lesions ex vivo in radical cystectomy specimens (43).

Coherent anti-Stokes Raman scattering (CARS) microscopy is a new, high-resolution (0.07-0.1 μ m), real-time, imaging modality that is based on the scattering of photons following interaction with the molecular bonds. Its advantage is its microscopic imaging without needing dye, with a presented sensitivity of 85% and specificity of 79% for the detection of bladder cancer (44).

Virtual cystoscopy is currently gaining popularity, as it is a non-invasive imaging technique, aided by CT. The procedure includes drainage of the bladder of urine and insufflation with 200-600cc of room air, followed by a helical CT scan (45). Abrol S. et al. reported in their study 92% sensitivity and specificity (46). Its drawbacks include the inability of flat lesions detection and radiation exposure in cross-sectional imaging (36).

Ultraviolet (UV) auto-fluorescence is based on UV laser excitement of the endogenous fluorescence (e.g. Tryptophan) of the bladder cells, thus differentiating cancer and inflammatory and normal cells. Tissue of interest is investigated with a UV probe via the working element of a standard cystoscope (47). Future studies will shed light on safety of UV use, reproducibility and signal density between low and high grade bladder cancers (48).

Multiphoton microscopy (MPM) is a laser scanning microscopy technique based on localized nonlinear excitation produced by the simultaneous absorption of two or three near-infrared photons (700–800 nm). MPM also uses endogenous fluorophores. It enables imaging of suspicious tissue and differentiates between benign and malignant flat lesions, especially CIS. Limitations of MPM include limited depth of penetration, setting it unsuitable for staging and lack of nuclear morphology on the acquired images (48).

Scanning fiber endoscopy (SFE) is a 1.2mm tip, flexible endoscope, which provides wide-angle, full-color, high-resolution images (49). SFE has not been used yet in vivo. Its advantage is the panoramic view of the bladder, aiding at systematically surveying of the bladder and tumor mapping (48).

Photoacoustic imaging (PAI) is an experimental hybrid technology, which associates a short-pulsed laser and an ultrasound transducer. The laser illuminates the tissue, whereas the ultrasound detects an acoustic pressure, generated by the heat-induced tissue expansion. Kamaya et al demonstrated a scanning depth of 4-5 cm, thus providing a future evaluation of tumor invasion (50).

High-frequency endoluminal ultrasound (ELUS) assists in staging of larger and more invasive bladder tumors, based on its greater depth of penetration (up to 20 mm) (51).

Future perspectives


None of the reviewed methods is cancer specific, given the overlapping morphological characteristics

between benign lesions and bladder tumors and the lack of molecular specificity in image recovery. Both photodynamic diagnosis and narrow band imaging can improve diagnosis of bladder cancer tumors and reduce recurrence rates, yet there are few trials comparing the two. Naya et al., compared the two techniques on patients with flat urothelial lesions suspicious of CIS and demonstrated similar sensitivity and specificity of them (91.6% vs 62.5% and 82.7% vs 87.0%) (52).

The combination of imaging modalities potentially increases the diagnostic accuracy of TURBT. For example, macroscopic imaging (PDD, NBI) could be utilized to identify suspicious lesions, whereas microscopic imaging (CLE, OCT) could provide grading or staging information via high-resolution tissue characterization.

Last but not least, current diagnostics for the work up of the upper urinary tract (UUT) appear insufficient to properly select patients for renal sparing surgery. Introduction of NBI and digital Retrograde Intrarenal Surgery (RIRS) await to be proven indispensable in the diagnosis of UUT tumors (53).

Conclusions

There are a lot of new promising technologies that will eventually allow us to simultaneously visualize and stage NMIBC. 

Περίληψη

ΣΤΟΧΟΙ: Το μεταβατικό κυτταρικό καρκίνωμα (TCC) της ουροδόχου κύστης είναι ο δεύτερος πιο συχνός ουρολογικός καρκίνος. Οι ασθενείς συνήθως διαγιγνώσκονται στο μη μυο-διηθητικό στάδιο της νόσου κατά τη διάρκεια της κυστεοσκόπησης της ουροδόχου κύστης υπό λευκό φως (WLC, gold-standard). Ο Σκοπός αυτού του άρθρου είναι να δει αν υπάρχουν νεότερα δεδομένα σχετικά με τις νεότερες τεχνικές κυστεοσκοπικής ανίχνευσης του TCC, καθώς κι αν υπάρχουν τεχνικές που να επιτρέπουν την ταυτόχρονη σταδιοποίηση του καρκίνου της ουροδόχου κύστης.

ΜΕΘΟΔΟΙ: Διεξήχθη βιβλιογραφική έρευνα των δημοσιευμένων ιατρικών άρθρων στην Αγγλική γλώσσα για τα τελευταία 5 έτη στο Pubmed. Το θέμα της έρευνας ήταν οι νέες τεχνολογίες στη διάγνωση και ταυτόχρονη σταδιοποίηση του μη μυο-διηθητικού καρκίνου της ουροδόχου κύστης. 36 άρθρα εμφανίστηκαν.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Η WLC είναι το gold-standard στη διάγνωση του καρκίνου της ουροδόχου κύστης, παρά τους σημαντικούς περιορισμούς, όπως τα ψευδώς θετικά ευρήματα, και η υπο-

Λέξεις

ευρητηριασμού

Τεχνολογίες απεικόνισης, μη μυο-διηθητικός καρκίνος της ουροδόχου κύστης, Photodynamic Diagnosis, Narrow Band Imaging, Confocal Laser Endomicroscopy, Optical Coherence Tomography

λειμματική νόσος, ιδίως του καρκίνου in situ η οποία μπορεί να φτάσει σε ποσοστό μέχρι 20%. Οι πρόσφατες εξελίξεις στην τεχνολογία οδήγησαν σε ανάπτυξη νεότερων τεχνικών που επιτρέπουν την καλύτερη μακροσκοπική αναγνώριση του καρκίνου της ουροδόχου κύστης. Αναπτύχθηκαν ακόμα τεχνικές που επιτρέπουν την εκτίμηση του βαθμού διήθησης του κυστικού τοιχώματος. Η φωτοδυναμική απεικόνιση (photodynamic imaging) και η απεικόνι-

ση στενής ζώνης (narrow band imaging) παρέχουν πρόσθετη μακροσκοπική ενίσχυση της συμβατικής κυστεοσκόπησης και ανιχνεύουν ύποπτες αλλοιώσεις. Οι μικροσκοπικές μορφές απεικόνισης επιτρέπουν τον υψηλής ευκρίνειας υπο-επιφανειακό χαρακτηρισμό αλλοιώσεων, καθορίζοντας τη μικροαρχιτεκτονική ιστών και την κυτταρική μορφολογία, οι οποίες είναι τεχνικά αδύνατες με τη χρήση μακροσκοπικής τεχνολογίας απεικόνισης. **ΣΥΜΠΕΡΑΣΜΑΤΑ:** Υπάρχουν πολλές νέες υποσχόμενες τεχνολογίες που μας επιτρέπουν να απεικονίσουμε και ταυτόχρονα να σταδιοποιήσουμε το μη-μυοδιηθητικό καρκίνο της κύστης.

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Case Report

Supine Percutaneous Nephrolithotomy in a HIV patient with horseshoe kidney. Case report and review of the literature

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Abstract

BACKGROUND: Horseshoe kidney is one of the most common congenital renal abnormalities with increased incidence of stone formation. We present a case of an HIV seropositive patient with a both-ends encrusted 3 year forgotten DJ stent and a staghorn stone in the left moiety of a horseshoe kidney. He was treated with percutaneous nephrolithotomy in the Galdakao-modified supine Valdivia (GSMV) position and simultaneous cystolitholapaxy.

CASE PRESENTATION: A 50-year-old Caucasian man presented on a regular basis with lower urinary tract symptoms due to a forgotten D-J ureteral stent that was inserted 3 years ago for

the management of a left renal colic. The CT-KUB scan revealed a horseshoe kidney with a 3.9cm stone at the left renal pelvis with a both ends heavily encrusted D-J stent and two smaller fragments at the left lower calyces. He was HIV seropositive under retroviral medication with an undetectable viral load and diabetic. He was treated with percutaneous nephrolithotomy (PCNL) in GSMV position and simultaneous cystolitholapaxy.

CONCLUSION: Supine percutaneous nephrolithotomy is safe and feasible in horseshoe kidney and facilitates simultaneous transurethral access for cystolitholapaxy.



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Introduction and Background

Horseshoe kidney is found to be one of the most common congenital renal abnormalities. It has a prevalence of 1 in 400 persons and a male-to-female ratio of 2:1. As the lower poles of kidneys are fused during embryogenesis, the inferior mesenteric artery interferes with the ascent of the kidney to its normal position. Therefore, the horseshoe kidney remains located in a position more inferior and medial to its normal position, resulting in an anterior location of the renal collecting system. Due to renal malrotation, PCNL in prone position is considered the procedure of choice for treating large renal stones in horseshoe kidneys (1).

In 1998, Valdivia Uribe et al., reported on the first series of patients who were undergoing PCNL in the supine position (2). A further development has been the Galdakao variant developed in 2006, which introduces some medial rotation to the supine position by positioning the contralateral leg in flexion and the ipsilateral leg in extension favoring an easier subcostal access to the posteriorly located upper pole calyces of the horseshoe kidney (3).

We present a case of an HIV seropositive patient with a both-ends encrusted 3 year forgotten D-J stent and a staghorn stone in the left moiety of a horseshoe kidney that was treated successfully with PCNL in the GSMV position with simultaneous cystolitholapaxy.

Case presentation

A 50-year-old Caucasian man presented to the outpatient department with a 1-year history of increased frequency and mild dysuria. He reported a left renal colic 3 years ago that was treated with a D-J ureteral stent placement. Physical examination and laboratory profile were unremarkable. Urine culture was positive for *Escherichia Coli* sensitive to all antibiotics. He had a history of hypertension, diabetes mellitus treated with metformin, hypercholesterolemia and HIV seropositivity treated with abacavir, darunavir and ritonavir. His viral load was undetectable at the time of presentation and CD4 count was normal.

The CT KUB with intravenous contrast revealed a horseshoe kidney, left pelvicalyceal dilatation with a left staghorn renal calculus (3.9cm in maximal diameter) and 2 lower pole calculi (0.9cm and 0.7cm). He had a both ends encrusted D-J stent (figure 1, 2, 3).

Key words

horseshoe kidney,
supine percutaneous
nephrolithotomy

The patient was placed in the Galdakao Supine Modified Valdivia position. An encrusted distal end of the D-J stent was noticed during cystoscopy. A 6F ureteral catheter was introduced and retrograde ureter pyelography was performed. After thorough ultrasound examination of the

left kidney, an upper and a middle calyceal puncture was performed under fluoroscopy. Renal access was carried out through the upper calyx, with serial dilatation up to 24Fr by using single use Amplatz dilators. Nephroscopy was performed with a 18Fr nephroscope (Karl Storz) and stones were disintegrated by using Holmium laser (Sphinx Lisa Laser 30Watt). A 550µm laser fiber was used at 1,2-1.5J energy and 10-15Hz frequency. Stone fragments were washed out by using the "vacuum cleaner" effect or retrieved with the 3-prong grasping forceps. The flexible nephroscope (16Fr Karl Storz) was used for

Figure 1. C.T.KUB with coronal reconstruction showing a large left renal pelvic stone in a horseshoe kidney

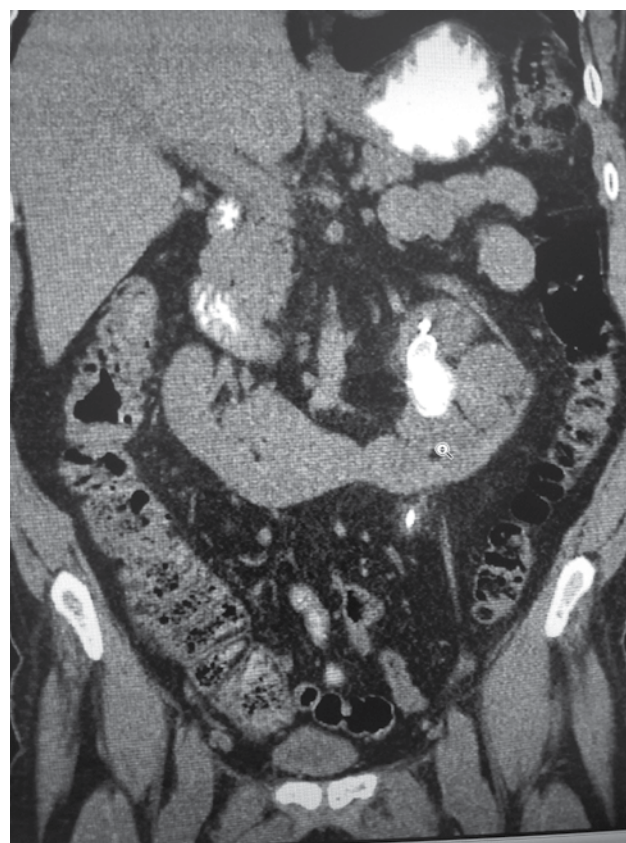


Figure 2. Plain KUB film showing a left renal pelvic stone with a heavily encrusted D-J stent in the left kidney



laser disintegration of the lower calyceal stones and to look for any residual fragments.

Cystolitholapaxy was performed at the time of renal stone disintegration. The old DJ stent was removed from the percutaneous tract under fluoroscopy. At the end of the procedure a 6Fr ureteral catheter and a 16F nephrostomy tube were inserted. The total operating time was 116min and fluoroscopy time was 88 seconds

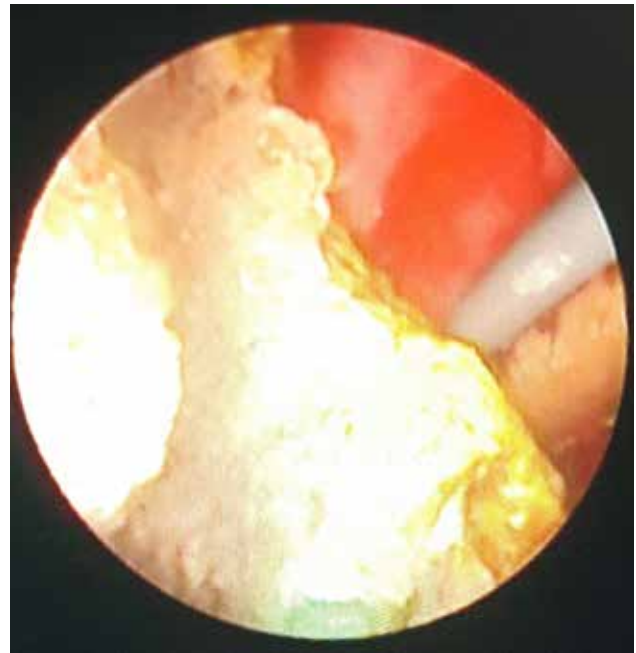
The patient had an unremarkable recovery. The ureteral catheter and the nephrostomy tube were removed on the 2nd postoperative day and the patient was discharged the 3rd postoperative day.

A new CT scan was performed one month post-operatively, confirming the patient was stone free. The stone analysis reported calcium oxalate dihydrate.

Discussion

In horseshoe kidneys, due to the lower position of renal units, upper pole access of the collecting system can be obtained easily through a subcostal approach

Figure 3. Endoscopic view of the left renal stone and the encrusted D-J stent



resulting in a lower risk of pleural injury. In supine position, upper pole access can be easily obtained and allows an easy approach to all of the collecting system resulting in complete stone clearance.

Unlike in prone position, where the patient has to be kept initially in lithotomy for insertion of ureteric catheter, in supine PCNL patients remain in same position throughout the procedure. This facilitates simultaneous transurethral access permitting same time procedures, thus less operating time and increases safety given the choice of ECIRS or operations on the lower urinary tract if needed (4). In our case, flexible ureteroscopy could be necessary if the DJ removal had not been smooth. The GSMV position facilitated cystolitholapaxy at the completion of renal stone disintegration and uncomplicated old stent removal through the percutaneous tract. In our opinion, GSMV position offers broader access to the flank of the patient compared to the standard supine position, thus facilitating more medial punctures if needed, like in a horseshoe kidney.

To the best of our knowledge, this is the first report in the literature for performing supine PCNL for the removal of an encrusted DJ stent in a horseshoe kidney with simultaneous cystolitholapaxy.

HIV seropositive patients, especially those with low CD4 count, are at higher risk for postoperative compli-

Διαδερμική νεφρολιθοτομή σε ύπτια θέση σε ασθενή με HIV και πεταλοειδή νεφρό.
Περιγραφή περιστατικού και ανασκόπηση βιβλιογραφίας, p. 50-53

cations after PCNL, such as bleeding and infections. A detailed preoperative evaluation and a careful selection of patients who are candidates for surgical stone removal are mandatory (5).

Despite the complexity of the case demanding longer operating times and the comorbidities of the patient, plus his immunosuppression, his postoperative course was uneventful.

Conclusion

Galdakao Modified Supine Valdivia position is feasible in horseshoe kidneys and can play a decisive role in the aggregate approach of complex stone cases, given the flexibility it provides.

Abbreviations

CT: Computed Tomograph.

CRP: C-Reactive Protein.

PCNL: Percutaneous Nephrolithotomy.


ECIRS: Endoscopically Combined IntraRenal Surgery.

DJ: Double-J.

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Author Disclosure Statement

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Περίληψη

Η διαδερμική νεφρολιθοτρυψία είναι η μέθοδος επιλογής για την αντιμετώπιση ευμεγέθων νεφρικών λίθων σε πεταλοειδή νεφρό. Παρουσιάζουμε την επιτυχή εκτέλεση διαδερμικής νεφρολιθοτρυψίας σε ύπτια θέση τροποποιημένη κατά Galdakao-Valdivia (GSMV) σε ασθενή με HIV υπό αντιρετροϊκή

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Ύπτια διαδερμική
νεφρολιθοτομή,
πεταλοειδής νεφρός

αγωγή και κοραλλιοειδή λίθο στον αριστερό νεφρό. Έφερε επίσης ξεχασμένο από 3 ετίας D-J stent στο σύστοιχο νεφρό. Στον ασθενή επίσης, εκτελέστηκε ταυτόχρονη κυστεολιθοτρυψία επί του επασβεστωμένου κυστικού άκρου του stent.

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Case Report

Management of a ureterocele in an adult with stone formation complicated by urinary retention due to urethral calculus. A case report

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Abstract

INTRODUCTION: Ureterocele is a cystic dilatation of the lower part of the ureter with incidence 1 in 4000 individuals. Due to its numerous types and manifestations sometimes it becomes a difficult entity to diagnose and treat especially in adults. One of its clinical presentation in the adult population is the presence of flank pain and stone formation inside the ureterocele.

CASE PRESENTATION: We herein report on a case of a ureterocele in an adult with stone formation complicated by urinary retention due to urethral calculus; managed endoscopically with transurethral deroofing of the ureterocele and cystolithotripsy with the use of laser both urethral and ureterocele stones.

DISCUSSION: A ureterocele in an adult is an entity usually without symptoms but it may co-exist with other conditions such as a ureteral calculus that can cause hydronephrosis and unmask the condition. Certain goals of treatment should apply to all cases but the type of the ureterocele and age of the patient will help in taking the right treatment decision.

CONCLUSION: Ureteroceles in adults complicated by stones can be safely treated endoscopically with simultaneously removal of the stone burden, however follow up of the patient is always needed to monitor for hydronephrosis and iatrogenic vesicoureteric reflux.



Lazaros Lazarou, Marinos Berdempes, Lazaros Tzelves, Nikolaos Chatzikraktis, Alexandros Pinitas, Kimon Tsirkas, Maria Zerva, Aggeliki Peninta, Andreas Skolarikos
Management of a ureterocele in an adult with stone formation complicated by urinary retention due to urethral calculus. A case report
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1. Introduction

Ureterocele is a congenital abnormality with a cystic dilatation of the lower part of the ureter which occurs in 1 of 4000 individuals and it is 4 times more common in females. It remains a challenge in terms of diagnosis and treatment due to its variable types and clinical presentations (1). They could lead to different results with regard to obstruction, reflux, continence and renal function. We herein report on a case of a right intravesical ureterocele and a calculus within the ureterocele in an adult male patient presenting with urinary retention due to an urethral calculus. He was managed endoscopically with transurethral deroofing of the ureterocele followed by cystolithotripsy of both the ureteral and urethral calculi and stone removal.

2. Case report

A 40-year-old male patient with no previous medical or surgical history who presented to the emergency department of our hospital complaining of urine retention and a mild right flank pain for two week. A Foley catheter was placed with 550 ml of urine. Urinalysis and laboratory investigation was unremarkable. An x-ray showed semi radiopaque in the area of the bladder and another semi radiopaque stone in the right kidney (Fig. 1). Urinary tract ultrasound showed the ureterocele and the stone within (Fig. 2). Urinary tract computerized tomography (CT) with contrast enhancement showed a large stone at the right vesicoureteric junction measured 1.8 x 1.3 cm in cross section with moderate right hydroureteronephrosis. It also showed 2 smaller calculi around 1cm next to the Foley catheter in the urethra (Figs. 3-4).

On the next day the patient underwent endoscopic operation under general anesthesia. The patient was put in lithotomy position, a 22F cystoscope was introduced into the bladder pushing back the two smaller calculi of the urethra. The left ureteric orifice was identified normal and a large right intravesical ureterocele was seen. Then a fiber laser 365μ was inserted through the cystoscope, deroofing of the ureterocele at 12 o'clock was performed. Cystolithotripsy was performed at the same session and stone fragments were removed. No need for a JJ stent since the right orifice was clearly visible and dilated after deroofing. The operation was concluded with insertion of a 3 way 20F Foley catheter

Key words

ureterocele,
urolithiasis,
stones

and irrigation was started. The Foley catheter was removed the next day and postoperative KUB x-ray showed no residual fragments in the bladder (Fig. 5).

At the 3 months follow up, renal and bladder ultrasound was performed with no right hydronephrosis and the clinical examination was unremarkable.

3. Discussion

Ureterocele is a cystic dilatation of the distal aspect of the ureter that is located either within the bladder or spanning the bladder neck and urethra (2). Several theories have been proposed through the years, however the most accepted mechanism is failure in regression of the Chwalla membrane which is a membrane between the urogenital sinus and the developing ureteral bud (3).

Figure 1. Right vesicoureteral junction stone, presence of a 20F Follev catheter



Figure 2. Bladder ultrasound showing the ureterocele and the stone inside



Figure 3. Halo sign of the wall of the right ureter

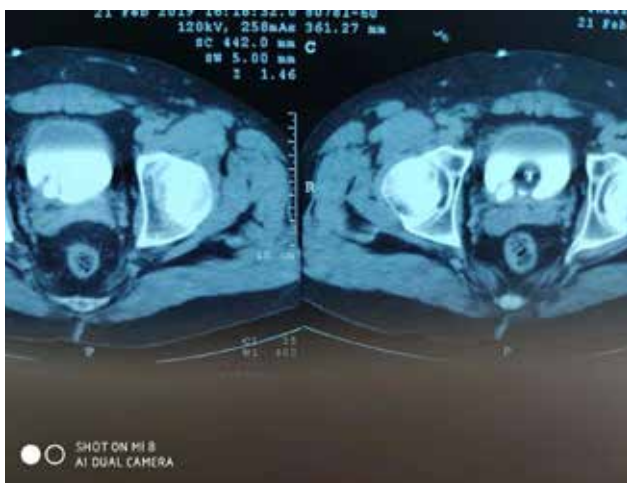


Figure 4. Right-sided moderate hydroureteronephrosis



Figure 5. Postoperative day 1 KUB x-ray



Ureteroceles have diverse presentations ranging from life-threatening sepsis, renal failure, recurrent urinary tract infections (UTIs), to no symptoms

at all being detected incidentally or by antenatal ultrasonography (4). Due to their complexity most of the systems have gained less popularity and more simplified



system was established by the American Academy of Pediatrics is more frequently used which classifies ureteroceles to intravesical (orthotopic) or ectopic (if part of the ureterocele extends to the bladder neck or urethra permanently) (5).

The clinical presentations will vary with age; in pediatric age group the presenting condition is usually recurrent UTIs or urosepsis, incontinence, failure to thrive, urinary tract calculus, abdominal mass, bladder outlet obstruction and vaginal or urethral prolapse, while in the adult population the diagnosis is usually made incidentally, sometimes it presents with intermittent flank pain, recurrent UTIs or calculus (6).


The diagnostic imaging should begin with ultrasound due to its availability and non invasive nature. It is also a great modality as it can show the cystic dilatation inside the bladder and sometimes it can provide useful information regarding system duplicity. Other diagnostic tools could be an intravenous urography, although less commonly performed nowadays, a CT with or without contrast enhancement, a voiding cystourethrogram for evaluation of the presence of vesicoureteral reflux and a renal nuclear imaging which shows the function of the renal tissue.

The large number of clinical presentations, the type of the ureterocele and the age of the patient will guide the appropriate choice of management and treatment as there is no single method for all cases and thus the management should be individualized. However the goals of each treatment should be the same including maximal preservation of renal function, prevention of

vesicoureteral reflux, unobstructed drainage, prevention of bladder outflow obstruction, maintaining continence and the removal of any potential source of infection.

With regards to our case, the ureterocele was complicated with a ureteral calculus which is not so uncommon as the incidence varies from 4% to 39% and most stones are solitary and are formed due to stasis and/or infection (7). According to Chtourou et al. who performed a study about stones in ureteroceles in 20 adult patients who were all treated by endoscopic horizontal meatotomy with stone fragmentation and extraction, concluded that endoscopic meatotomy is easy to perform and gives good results and the associated stones constitute an additional argument in favor of endoscopic treatment (8). Endoscopic treatment includes transurethral puncture and transurethral incision and may be curative in up to 90% of cases, however these patients need long term follow up to monitor renal function, symptoms and occurrence of vesicoureteric reflux (9).

4. Conclusion

Our case illustrates that ureteroceles remain a challenging entity in the field of urology in terms of diagnosis and management due to their variability in types and clinical presentations. Ureteroceles which are complicated by stones can be safely and effectively treated with endoscopic resection without the need for a JJ stent but require long term follow up. 

Περίληψη

Η ουρητηροκήλη είναι μια κυστική διάταση του κατώτερου τμήματος του ουρητήρα που πορβάλει μέσα στην ουροδόχο κύστη με συχνότητα 1 στις 4000 γεννήσεις. Λόγω των διάφορων τύπων ουρητηροκήλης καθώς και των κλινικών εκδηλώσεων αυτής, μερικές φορές καθίσταται πολύ δύσκολη η διάγνωση και η θεραπεία της ειδικά στους ενήλικες. Μία από τις κλινικές της εκδηλώσεις είναι η παρουσία κωλικοειδούς

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οσφυϊκού άλγους από σχηματισμό λίθου εντός αυτής. Το περιστατικό που περιγράφουμε αφορά έναν άνδρα ασθενή 40 ετών που προσήλθε με επίσχεση ούρων και ήπιο κωλικοειδές άλγος δεξιά λόγω λίθου ουρηθρας και λίθου εντός ουρητηροκήλης δεξιά και αντιμετωπίστηκε με διουρηθρική σχάση της ουρητηροκήλης και λιθοτριψία και αφαίρεση των λίθων στον ίδιο χρόνο.

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Η Astellas είναι αφοσιωμένη στο να μετατρέπει την επιστημονική καινοτομία σε ιατρικές λύσεις που αποφέρουν αξία και ελπίδα στους ασθενείς παγκοσμίως.

Κάθε μέρα εργαζόμαστε ώστε να καλύψουμε ανικανοποίητες ιατρικές ανάγκες εστιάζοντας πρωτίστως στις θεραπευτικές κατηγορίες της ογκολογίας, της ουρολογίας, των λοιμώξεων και της μεταμόσχευσης εξελίσσοντας παράλληλα νέες θεραπευτικές κατηγορίες και αξιοποιώντας νέες τεχνολογίες έρευνας. Παραμένουμε αφιερωμένοι στο να ικανοποιούμε τις ανάγκες των ασθενών και η υποστήριξή μας προς αυτούς δεν θα πάψει ποτέ να υφίσταται.

Μέσω της αφοσίωσής μας να προσφέρουμε στους ασθενείς ελπίδα για ένα λαμπρότερο μέλλον, επιδιώκουμε να ηγηθούμε στις θεραπευτικές κατηγορίες που εξειδικεύμαστε, εστιάζοντάς τις στις κατηγορίες όπου υπάρχουν ιατρικές ανάγκες που παραμένουν ανικανοποίητες. Μέσω της καινοτομίας, θα συνεχίσουμε να αναγνωρίζουμε και να αναπτύσσουμε νέους τρόπους για να καλυτερεύσουμε την υγεία των ασθενών.

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