Founded in 1924

ISSN 1124-3562

ARCHIVIO ITALIANO DI UROLOGIA E ANDROLOGIA

ARCH ITAL UROL ANDROL

ARCHIVES OF ITALIAN UROLOGY AND ANDROLOGY

Vol. 84; n. 2, June 2012

Indexed in: Medline/Index Medicus, EMBASE/Excerpta Medica, Medbase/Current Opinion, SIIC Data Base, SCOPUS

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I vari relatori delle più svariate discipline scientifiche hanno presentato, nei tre giorni del congresso, le più aggiornate novità nel campo dell'imaging in urologia, andrologia e nefrologia. La mattina di giovedì 17 maggio si è tenuto, presso l'Auditorium della Casa di Cura Multimedica di Castellanza (VA), un corso pratico, molto seguito, di ecografia interventistica, in diretta dalla sala operatoria, dove vari colleghi si sono alternati e hanno mostrato come l'ecografia ha indubbiamente un ruolo fondamentale non soltanto nella diagnosi ma anche come guida privilegiata nelle tecniche chirurgiche mini invasive che oramai rappresentano il futuro della chirurgia urologica.

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Durante la seduta amministrativa della Società, l'assemblea dei soci a votato in maniera unitaria la città di **Fermo nel 2014** come sede del **19° Congresso della SIEUN**. Il presidente del Congresso sarà il dott. Andrea Galosi.

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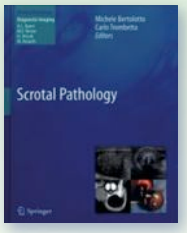

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ARCH ITAL UROL ANDROL
Archives of Italian Urology and Andrology

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Via Bassini 41 - 20133 Milano, Italy
Tel. +39 0270608091 - Fax +39 0270606917
Registrazione: Tribunale di Milano n. 289 del 21/05/2001
e-mail: scriman@tin.it - architurol@gmail.com
web: www.urologyplanet.it - www.architurol.it

SCRIPTA MANENT EDIZIONI

Direttore Responsabile: Pietro Cazzola
Direzione Generale: Armando Mazzù
Direzione Marketing: Antonio Di Maio
Consulenza grafica: Piero Merlini
Impaginazione: Stefania Cacciaglia
Stampa: Lalitotipo Settimo Milanese

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REVIEW

Hot topics in urological health economics. A mini review

Marco Racioppi, Giuseppe Palermo, Alessandro D'Addessi, Francesco Pinto, Emilio Sacco, Daniele D'Agostino, Matteo Vittori, Pier Francesco Bassi

Clinica Urologica, Università Cattolica del Sacro Cuore, Roma, Italy.

Summary

Urological diseases are becoming a major public health problem. In fact, they increasingly weigh on the economy of a country due to the high direct costs and the consequent significant loss of productivity. Prostate cancer represents 11% of the costs for the treatment of all cancers in the United States with $ 8 billion and a cost per-patient from diagnosis to death of $ 81658. Instead bladder cancer has the higher costs per-patient in terms of medical care, from diagnosis until death (U.S. $ 96,553). In Italy, in a reference hospital, the average costs of non muscle-invasive forms treated with endoscopic resection (TURB) and infiltrating forms treated with radical cystectomy are approximately € 2,242.20 and € 6,860 respectively, but they increase due to the follow-up and the ancillary treatments. In the field of functional disease, in the U.S. the average annual expenditure per capita for incontinence, including inpatient and outpatient services is $ 1,382. While for patients who had undergone surgery the average total spending rose to $ 3,620. For overactive bladder the total cost in the United States is estimated at 12.02 billion U.S. dollars, with $ 9.17 billion allocated to the community costs and $ 2.85 billion for institutional costs. However, further pharmacoeconomic studies are required to better understand the net economic impact of any alternative strategies to those actually present. Stone disease is a highly prevalent and costly condition for which United States total health care expenditures, in the year 2000, were estimated to be almost $ 2.1 billion. Treatment of nephrolithiasis depends on stone size and location, but typically involves a surgical procedure such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopic laser lithotripsy, percutaneous nephrostolithotomy (PCNL) or open stone surgery with an average expenditure per procedure of $ 2,295, $ 1,425, $ 3,624, $ 2,916 respectively.

KEY WORDS: Health economics; Urology; Urologic cancer costs; Economic burden.

Submitted 29 November 2011; Accepted 31 December 2011

INTRODUCTION

Urogenital diseases represent a major public health problem in our country and abroad. Because of the high direct costs, especially for follow up and treatment of urologic cancers, early deaths, mainly caused by genital cancers, and the consequent significant loss of productivity these diseases heavily weigh on the economy of a country.

Prostate and bladder cancers account for 85% of all genitourinary tumors. In 2004, deaths due to urogenital cancers in men have caused 0.6 million years of potential life lost (YPLL), 13.3% of the estimated 4.5 million YPLL for all cancer deaths (1).

There are specific indicators. The economic burden of disease (Economic burden) represents the value of all resources used or spent by the society as a result of the disease (2). The cost of illness (COI) is the most frequently used descriptive method to estimate the economic burden, and consider 3 types of costs: 1) direct, 2) indirect, 3) intangible (3).

Direct medical and non medical costs include the costs for diagnostic tests (eg PSA assay, spontaneous urine cytology, TRUS, CT, etc.), medical examinations, medications and medical and /or surgical treatments, check-up visits and travel expenses related to treatment (4). Indirect costs can be substantial, including the salaries

of health workers, loss of productivity resulting from disability or sick leave, loss of time (due to doctor visits, diagnostic procedures, treatment sessions and follow-up visits) and, finally, the costs arising from the consequences of the disease (the so-called "*costs of consequences*") such as falls, fractures, urinary tract infections and psychological consequences such isolation and depression (4-8, 9). Finally, the intangible costs include the impact of disease on quality of life (QoL) and the consequent psychological burden, which are difficult to evaluate and usually excluded in the cost of illness analysis.
This mini review rapidly focuses on the most important chapters in the field of urology spending.

Prostate cancer

Prostate cancer (Pca) is the most commonly diagnosed cancer in adult men and the second leading cause of cancer death in industrialized countries.
Gleason score and stage at diagnosis remain today the most important predictors of prognosis (10). With the introduction of PSA as a tumor marker, most of the Pca are now recognized years before the onset of clinically apparent disease, usually represented by locally advanced or metastatic cancer. However, screening with PSA has been controversial because many of Pca detected are of low-grade and slow growing. Due to its long natural history and the median survival in the absence of treatment that approaches even at 15-20 years, many clinicians and researchers have wondered whether screening and treatment of Pca actually improves survival, since many patients will die with prostate cancer, rather than for prostate cancer (11) at the expense of a huge deployment of resources engaged in screening and treatment of this malignancy.
With 8 billion dollars prostate cancer represents 11% of the costs for the treatment of all cancers in the United States at a cost per-patient with Pca from diagnosis to death calculated to be $ 81,658 (12, 13). There are few studies of Pca health economics and most are based on U.S. case studies. Closer to us, in Spain, *Bachino et al.* compared the direct costs of 3 most frequently used treatments in localized Pca, namely the radical retropubic prostatectomy (RRP), brachytherapy and 3D conformal external beam radiation, documenting a statistically significant difference between the costs of various treatment options evaluated in € 3,229.10, € 5,369.00 and € 6,265.60 respectively for the groups treated with 3D conformal external beam radiation, brachytherapy and RRP, therefore substaining that, in the immediate, radical prostatectomy is much more expensive than other treatment options (14). *Jayadevappa et al.* evaluated the "*out of pocket*", ie costs not reimbursed by health system and substained by patients, incorporating in the indirect costs (OPI), of patients with Pca treated with radical prostatectomy or radiation therapy (EBRT) stating that OPI total average varied among the groups EBRT and RRP at 3 months ($ 5,576 vs $ 2,010), 6 months ($ 1,776 vs $ 2,133), 12 months ($ 757 vs. $ 774) and 24 months ($ 458 vs. $ 871) of follow-up. The RRP was associated with lower total costs for medical care and OPI. OPI costs were inversely related to the data recorded on generic and prostate-specific questionnaires on quality of life given to patients before, showing that greater part of economic resources expenses are due to indirect costs (costs for urinary incontinence care, erectile dysfunction, impairment of bowel function and other effects of treatment of Pca and for follow-up) and intangible (15). *Snyder et al.* investigated how the choice of initial treatment of localized Pca impacts on spending in the short and long term. 13,769 cases of prostate cancer were analyzed and, according to the treatment received during the first 9 months after diagnosis, patients were assigned to groups watchful waiting (WW), radiotherapy, hormone therapy, hormone+radiotherapy and surgery. The WW group patients had the initial cost for 1 year ($ 4,270) and the cost of 5 years ($ 9,130) lower; higher initial costs have been shown to those in the group treated with radio + hormone therapy ($ 17,474) and surgery ($ 15,197). With U.S. $ 26,896, 5 years after the initiation of therapy, highest total costs were registered in the group treated with hormone therapy, followed by the radio + hormone therapy group ($ 25,097) and surgery ($ 19,214). Finally, excluding the last 12 months of life, highest total costs were for radiation + hormone therapy group ($ 23,488) and hormone therapy group ($ 23,199) (16).
This demonstrated that the economic and social costs of disease also widely vary according to the initial adopted treatment and hence the importance of even greater sensitivity of clinicians in the concepts of health economics.

Bladder cancer

Bladder cancer is the fourth leading cause of cancer death in men and the tenth in women. There are 2 totally different clinical-economic entities the not muscle-invasive and the muscle invasive forms. It is difficult to analyze the costs for this type of disease characterized, even in non-muscle-invasive (NMI) by numerous relapses, such to make it to be considered a real chronic illness. The direct costs of bladder cancer, namely those related to expenses related to diagnosis, treatment and follow-up amounted to 3.4 billion dollars per year and represent about 7% of the cost for all types of cancer in the U.S. Indirect costs related to lost of productivity range between U.S. $ 184,000 and $ 461,000 (currency of 1986) (27). In Italy, a country in which the epidemiological pattern of disease appears to be high, the annual cost of only NMI is about 35 million Euros. Because of the long survival and the intensive and expensive treatments, bladder cancer has the highest costs per-patient in the U.S., from diagnosis until death (U.S. $ 96,553), followed by colorectal cancer (U.S. $ 86,894), breast (U.S. $ 84,525), prostate (U.S. $ 81,658) and lung cancers (U.S. $ 49,907) (12, 28). Differing from other kinds of cancer further costs come after diagnosis; only by development of strategies aiming to inhibit the progression of the disease, the rate of recurrence and severity of complications it is possible to reduce the cost of the treatment of bladder cancer.
On the other hand, often it is a strict monitoring regime to weigh more on costs.

Diagnosis and follow-up

An universal screening for bladder cancer can not be applied in clinical practice for the inadequacy of the tools and also for disease course. Screening should only be for a specific population at high risk, which means men between 55 and 75 years, smokers of both sexes, patients with chronic inflammation of the bladder. Indeed, in the screening of population of men in the United States the cost for diagnosed cancer was $ 783,913, $ 269,028, $ 139,305, respectively, for a population of 50-59, 60-69 and 70-79 years. The use of a marker (NMP22) is only useful in the screening of a population at high risk (annual incidence rate of bladder cancer at least 6%) and the cost per cancer detected would be equal to $ 3,310 (29). The higher expectation is placed in the availability of new tumor markers that may play a role in the algorithm of screening, especially for the diagnosis and follow-up. The rationale is a close monitoring in order to prevent progression of stage and grade of the tumor, which can vary between 30 and 70% (30, 31). However, currently the markers under study are not yet widely used in clinical practice and are not able to replace cystoscopy in the surveillance system. It is widely now accepted that the surveillance system for non-muscle-infiltrating bladder cancer provides cystoscopy with urine cytology every 3 months for 2 years, then every 6 months for 2 years and annually thereafter. The FDA has recently approved the use of tumor markers such as *Bladdercheck* (NMP22) and *UroVysion* in bladder cancer screening. According to the health system reimbursement in 2005 in U.S.A. the cost of the NMP22 was $ 24, cheaper than FISH ($ 300-400 cost per assay), than outpatient cystoscopy ($ 206) and urinary cytology ($ 56). We must remember, however, that if the incidence of cancer is low, the marker needs to have a very high specificity (29). *Zippe et al.* demonstrated a cost saving ranging from $ 35,160 to $ 138,000 when the NMP22 was used to indicate the need to perform a cystoscopy. NMP22 with a cut-off of 10 U/ml had a sensitivity of 100% and a specificity of 85%. It was thus shown to be more sensitive but less specific than urinary cytology and cystoscopy (32).

Other authors have pointed out that tumor markers used in a modified regimen of surveillance, lengthening the interval between cystoscopy, may significantly lower the cost of bladder cancer (33). However, the "*ideal*" marker, unfortunately at the time has not been identified yet.

Treatment

Despite the high cost of monitoring and follow-up, the cost of hospital stay affect between 51% and 69% of the total cost of bladder cancer and have an entity variable depending on the stage of the disease. Twenty to 35% of the cost depends on the medical service, outpatient services and various costs account for 4-12% and 2-6% of all costs, respectively (12). *Racioppi et al.* analyzed the individual costs in a regional reference hospital (*Policlinico Universitario A. Gemelli*) calculating that hospital admission for NMI forms treated with endoscopic resection (TURB) costs about € 2,242.20, while for infiltrating cancers treated with radical cystectomy costs rose to € 6,860. NMI disease paradoxically becomes potentially more costly than the invasive one due to the increased number of cases, the use of topical chemo or immunotherapy, the overall follow-up, the treatment of relapses and, above all, longer survival. In invasive forms, even if need a surgical procedure such as cystectomy, which is more expensive than endoscopic resection, however, it was shown a reduction in overhead costs at a later date (34).

Considering NMI forms of bladder cancer, treatment of these patients after initial resection becomes more complex and articulated. Therefore we must add, in most cases, the cost of topical intravesical therapy cycles. The difference in cost is given by the different costs of drugs. It follows that for a single course of 8 weekly instillations of MMC, the cost is equal to € 1,420, while € 1,037 is the amount spent for a course of 6 intravesical instillation of epirubicin. Finally, a weekly cycle of BCG (lasting 6 weeks) costs € 975.

Kilbridge et al. comparing the cost of patients treated with BCG and, considering costs, benefits of treatment and the complication rates, obtained that a patient aged 65 suffering from non-muscle high-grade invasive bladder cancer treated with BCG gains 6 months of life but with a cost increase of $ 1,660, ie $ 3,320 per year life saved (35). If we also consider the device-assisted therapies that enhance the chemotherapy (such as thermochemotherapy and electromotive Drug Administration - EMDA -) costs per treatment increases.

Radical cystectomy is the gold standard for the treatment of muscle invasive cancer. As for radical cystectomy, the costs resulting from the diagnostic phase, treatment and intervention amounted to € 2,803.70. The operation costs include the costs of personnel and equipment necessary and amounted to € 633.30. In order to estimate the total amounts, costs resulting from hospitalization, which amounted to € 270.40 per day, must be added. For a period of about 15 days total expenditure turns out to be, in the above mentioned hospital, amounting to € 6,860. The total cost for the first year in the case of invasive disease is approximately € 7,790 (34).

Some therapeutic strategies have been developed trying to combine therapeutic efficacy and expenditure control.

Early instillation. Single instillation of MMC after TURB would save € 148 per patient compared with TURB alone. In clinical terms the procedure is still under discussion: single instillation would prove to be effective within 24 h after resection, especially in patients at low risk, particularly at onset, and only marginally in tumors of intermediate and/or high risk (36, 37).

Early radical cystectomy e bladder sparing. According to some authors in patients younger than 60 years with a diagnosis of T1G3 immediate radical cystectomy improve survival and quality of life at lower cost. However, for patients older than 70 years, conservative treatment seems to be the best choice (38).

The "*bladder sparing*" strategy combines chemotherapy, radiotherapy and transurethral bladder resection (TURB) with the intent to offer an effective treatment improving quality of life in invasive disease.

However, we can observe that the cost of the combined mode (including CHT, RT and TURB) is higher especially for those patients who will then undergo cystectomy (38). The introduction of new technologies and robotic surgery opens new possibilities of which is necessary to establish the benefits that justify their use in the face of much higher costs at the time (39).

Functional urology

Urinary incontinence (UI) is a condition that affects about 20% of adult women with significant individual impact on the quality of life and economy (119 million/year spent on pads in the Netherlands). The pelvic floor muscles training is considered a first line treatment, but only 15-25% of women is completely healed. About 65% reported that their condition has improved, but adherence to long-term treatment is problematic. In addition, on long-term follow-up (2-15 years) 30-50% of patients will eventually undergo surgery. In particular the *Tension-free Vaginal Tape* (TVT) has quickly become the gold standard in surgical treatment of stress urinary incontinence (17).

Subak et al. prospectively calculated the personal costs incurred by women for "*routine care*" (diapers, sanitary napkins, etc.) for stress incontinence or urge incontinence with more than 3 episodes of losses at week. The average annual cost (currency in 2005) in "*routine care*" was U.S. $ 492. The costs for urge incontinence and mixed urinary incontinence were higher than those for stress incontinence (18).

In a retrospective study on the costs of conservative treatment and surgical therapy *Kinchen et al.* have calculated that the average annual expenditure per capita for incontinence, including inpatient and outpatient services (with pharmaceutical expenditure) is U.S. $ 1,382. For patients who undergone surgery, the average total spending rose to U.S. $ 3,620, about ten times higher than that of patients who received a non-surgical treatment ($ 350) (19).

Overactive bladder (OAB) is a common disabling condition with significant negative impact on quality of life, sleep quality and mental health (20, 21) and is associated with high economic costs (22). It is defined as "*urgency, with or without urge incontinence, usually with frequency and nocturia*", in the absence of proven infection or other diseases (20).

In general, OAB symptoms can affect social, psychological, occupational, domestic, physical and sexual aspects of life (23). The OAB can lead to depression and low self-esteem, the latter partly due to embarrassment or loss and/or smell of urine, with limitation of social activity outside the home even only because of frequent need to use a toilet. In the workplace people with OAB may have decreased productivity or can avoid to go to work. The same concerns may also prevent women from having intimate relationships. Finally, for those who use disposable tampons in the bed during the night or an undergarments for incontinence, the cost of using these elements can be high and, in many countries, are not covered by medical insurance (23, 24). The total cost of OAB is based on the direct costs (routine care, treatment costs, the costs of consequence) and indirect costs (eg lost productivity). The costs of routine care include incontinence supplies and cost of laundry and dry cleaning. Treatment costs include the costs of drug therapy, outpatient visits, surgery and behavioral therapy. The costs of consequence attributable to OAB are skin conditions, falls, urinary tract infections, longer hospital stays and nursing home admissions. The cost of lost productivity include the value of wages lost due to the OAB and the cost of time spent on doctor visits. The total cost of OAB in the United States was estimated at 12.02 billion dollars, with 9.17 billion dollars allocated to the community costs and $ 2.85 billion for institutional costs. Within the community, the cost of OAB for women was 3 times higher than for men, for a total of $ 7.37 and $ 1,79 billion respectively. These estimates indicate that the cost of OAB is comparable to that of osteoporosis (13.8 billion dollars) and gynecologic cancers and breast cancer (11.1 billion dollars). Data from the *National Institutes of Health* indicate that the direct annual cost of urinary incontinence can be high, amounting to 17.5 billion dollars, making the cost of OAB compared to that of pneumonia and influenza (15.8 billion dollars) and arthritis (17.6 billion dollars) (25).

Wu et al. studied the economic burden of the loss of working days for employees (women) with overactive bladder in 9 major U.S. companies. The number of days of absence was 15% higher among the 3,077 employees with OAB compared with 6,154 controls. Female patients with OAB were 4.4 days off from work more than non-OAB, producing an annual spending exceeding $ 1,220 per employee OAB (26).

Urinary stone disease

Stone disease is a highly prevalent and costly condition for which United States total health care expenditures, in the year 2000, were estimated to be almost $2.1 billion, of which almost half was accounted for inpatient services (40-42). The incidence of nephrolithiasis peaks between the ages of 20 and 60 so that primarily affects working-age adults (43). Fifty per cent of stone formers will have a recurrence within 5 years (44). *Saigal et al.* calculated the direct and indirect costs of nephrolithiasis in an employed population assessing substantial costs among working-age adults (45). More than 1% of working-age adults were treated for nephrolithiasis in 2000. Given an incremental cost of $ 3,494 per person, total health care spending in the United States for evaluation, hospitalization, and treatment of nephrolithiasis was approximately $ 4.5 billion annually in the employed population. In addition, they estimated that treatment of nephrolithiasis is associated with 3.1 million lost workdays per year (among the privately insured patients). If each day of work of an employer costs $ 250, in a conservative estimate, the indirect costs of nephrolithiaisis are approximately $ 775 million per year (45).

Treatment of nephrolithiasis depends on stone size and location, but typically involves a surgical procedure such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopic laser lithotripsy, percutaneous nephrostolithotomy (PCNL) or open stone surgery with an aver-

age expenditure per procedure of $ 2.295, $ 1.425, $ 3.624, $ 2,916 respectively (45).
Hyams et al. compared clinical outcomes and the estimated cost of percutaneous nephrostolithotomy vs ureteroscopy for 2 to 3 cm renal stones. The estimated cost of percutaneous nephrostolithotomy was significantly greater than that of ureteroscopy ($ 19,845 vs $ 6,675, p < 0.0001).There were significantly more second stage procedures among percutaneous nephrostolithotomy cases (11 vs 1, p = 0.003) but stone clearance (0 to 2 mm) was superior for percutaneous nephrostolithotomy vs ureteroscopy (89% vs 47%, p = 0.01). Using a less than 4 mm threshold stone clearance improved to 100% vs 95% (p not significant) (46).

Conclusions

The economic burden of urologic diseases appears on rise due to the high prevalence of the disease but also for treatment options available. Further specific pharmacoeconomics studies are needed, less empirical, to better understand the net economic impact of loading possible alternative strategies at present.

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Correspondence

Giuseppe Palermo, MD
Clinica Urologica Università Cattolica del Sacro Cuore
Largo F. Vito 1 - 00168 Roma, Italy
gpalerm@libero.it

Marco Racioppi, MD
Alessandro D'Addessi, MD
Francesco Pinto,MD
Emilio Sacco, MD
Daniele D'Agostino, MD
Matteo Vittori, MD
PierFrancesco Bassi, MD
Clinica Urologica Università Cattolica del Sacro Cuore
Largo F. Vito 1 - 00168 Roma, Italy

ORIGINAL PAPER

Comparison of tumor grade and stage with nuclear factor kappa b and p38 mitogene activated protein kinase expressions in renal cell cancer

Emin Ozbek [1], Tamer Aliskan [1], Alper Otunctemur [1], Gokhan Calik [1], Suleyman Cakir [1], Murat Dursun [1], Adnan Somay [2]

[1] Okmeydani Training and Research Hospital, 1st Urology Clinic, Istanbul, Turkey;
[2] Fatih Sultan Mehmet Training and Research Hospital, Pathology Clinic, Istanbul, Turkey.

Summary

Objectives: *Renal cancer is common among urinary system cancers. Most common one is clear cell carcinoma and it makes up 60-70% of renal cell carcinomas. Invasion pathophysiology and molecular mechanisms that take part are crucial for the diagnosis, treatment and prognosis of this disease. In this study, nuclear factor kappa B(NFKB/p65) and p38 mitogene activated protein kinase, which play an important role in signal transduction system of clear cell renal carcinoma, are assessed.*

Materials and methods: *We considered 40 patients who had radical nephrectomy or partial nephrectomy for renal tumor in Okmeydani Training and Research Hospital 1st Urology Clinic. Normal tissue samples of these patients were used as control group. Paraffin embedded samples of renal cancer were studied with immunohistochemistry using spesific monoclonal and polyclonal antibodies of NFKB and MAPK. Expression density was compared with tumor grade and diameter, semiquantitively. Results were assessed with Spearman correlation and Pearson chi-square tests.*

Results: *There were 28 (70%) males and 12 (30%) females in our study. Age range of patients was between 19 and 80 years, and mean age was 59,3 ± 13,4. NFKB and p38MAPK expressions were higher in cancer specimens compared with control group ($p < 0,05$). Tumor diameter and grade increase were directly correlated with p65(NFKB) and p38MAPK expression ($p < 0.05$).*

Conclusions: *MAPK and NFKB expression is related to tumor grade and stage. Also more studies are needed to define the relationship with lymph node metastasis, organ metastasis and survival rates.*

KEY WORDS: *Renal cell carcinoma; NFKB; p38MAPK; Signal transduction; Immunohistochemistry.*

Submitted 23 September 2011; Accepted 30 September 2011

INTRODUCTION

The evolution and progression of cancer is a multi-step process, during which malignant cells develop pathophysiological transformations affecting major aspects of cellular function, such as adhesion, proliferation, differentiation and apoptosis (1). The characteristics of malignant cells, which are the synthesis of metastasis-associated molecules (e.g., proteolytic enzymes, angiogenic factors), refractoriness to apoptotic signals and immortality originate from a variety of extracellular signals, including stress, growth factors, transforming factors, cytokines and mitogens. These are mediated via membrane receptors and in turn relay their messages to the nucleus using a complex network of intracellular signaling pathways (2). Nuclear factor kappa b(NFKB) notably p65 protein functions during deoxyribonucleic acid (DNA) transcription and takes action against cytokines, oxidative stress, free radicals, ultraviolet (UV) radiation, low density lipoprotein (LDL) oxidation and bacterial/viral antigens in the cell (3-7). Nuclear p65 initiates the transcription of a wide variety of genes that code for angiogenic factors, cell adhesion molecules, anti-apoptotic factors and cytokines, which are involved in cell survival, tumour invasion and metastasis. Extensive studies performed on cancer cell lines and preclinical models support a role of NFKB in cancer development and pro-

gression (8). Mitogen-activated protein kinase (MAPK) pathways are key regulatory pathways for the control of growth and the induction of stress responses in cells (9). Thus inhibitors of stress activated p38MAPK reduce in vitro invasion of malignant melanoma cells (10).
In this study we tried to describe and compare the relationship of p38MAPK and p65NFKB expressions in renal cell carcinomas (RCC).

Materials-Methods

Forty patients who had undergone radical or partial nephrectomy for renal cell carcinoma in the *1st Urology Clinic of Okmeydani Training and Research Hospital* from October 2007 to April 2010 were included in this study after local ethics committee permission. Patients' records were analysed retrospectively. Paraffin embedded blocks, Hematoxylin-Eosin stained and formalin fixed preparates were retrieved from the archive. Two new preparates (cancer, control) for each patient were made. For the immunohistochemical staining, blocks which contained the most tumor load were selected and normal renal tissue samples of the same patients were stained also with the same antibodies. These normal tissue samples were designated as the control group.
Antibodies used in the study are as follows; NFκB p65 (F-6): sc-8008 (*SantaCruz Biotechnology Inc., CA, USA*): Mouse monoclonal antibody. p38α/β (H-147): sc-7149 (*SantaCruz Biotechnology Inc., CA, USA*): Rabbit polyclonal antibody. To identify the p65NFKB and p38MAPK expressions we performed immunohistochemical staining in all groups, 3-4 μ sections from 10% formaline fixated and paraffin embedded blocks were prepared. These sections were put on Poly-L-Lysine coated stages. Sections were taken to incubator at 58°C for 80 minutes, put into the xylene three times for 5 minutes. 100% ethanol was applied twice for 3 minutes, then 95% and 80% ethanol were applied twice for 3 minutes each. Deparaffinization procedure ended with distilled water washing. Sections were dipped into the Citrate Buffer solution and heated in the microwave oven 4 times for 5 minutes. Sections cooled down under the room temperature for 20 minutes. Ten minutes of incubation with trypsine were made according to p38 data sheet. After that stages were taken to the phosphate buffered solution (PBS). After the stages dried, lines were drawned around the sections with hydrophobic pen. These stages were put into the PBS. To decrease the nonspecific stage staining, hydrogen peroxide was applied for 10 minutes. Stages were washed with PBS three times. Under room temperature Ultra V Block procedure was performed for 10 minutes. Only spilling the excess Ultra V Block from the stages without washing, p65 NFKB and p38 MAPK, both diluted to 1/100, were dripped to cover the entire tissue sections and then incubated for 45 minutes. Sections were washed with PBS three times. Primary antibody enhancer was applied and the sections were incubated for 20 minutes under the room temperature. Again sections were washed with PBS three times. After a HRP (horse radish peroxidise) polymer incubation period of 30 minutes, sections were washed with PBS three times. AEC (3-amino-9-ethylcarbazole) chromogen was dripped then incubated for 15 minutes. Chromogen had been prepared 1 minute before the procedure. Stages were washed with distilled water. Counterstaining with Mayer's Hematoxylin was performed for 1 minute. Then stages were washed with tap water. Finally all of the stages were closed with aqueous closing materials.
Immunohistochemical scoring of the stages was done according to the membranous and cytoplasmic staining. The following scoring system was used in agreement to the literature (11): ≤ 5% positive cells-score 0, 6%-25% positive cells-score 1, 26%-50% positive cells-score 2, > 51% positive cells were designated as score 3.
All data were statistically analyzed with SPSS (Statistical Packages for Social Sciences) program using Spearman Correlation and Pearson Chi-Square tests. Probability of < 0.05 was considered significant.

Table 1.

p38 positivity and distribution over male and female patients.

			p38 marker score			Total
			1	2	3	
Gender	Male	n	10	8	10	28
		Gender %	35.7%	28.6%	35.7%	100.0%
		p38 %	66.7%	72.7%	71.4%	70.0%
	Female	n	5	3	4	12
		Gender %	41.7%	25.0%	33.3%	100.0%
		p38 %	33.3 %	27.3%	28.6%	30.0%
Total		n	15	11	14	40
		Gender %	37.5%	27.5 %	35.0%	100.0%
		p38 %	100.0%	100.0%	100.0%	100.0%

Table 2.

p38 and gender relationship analysis.

	Value	df	p
Pearson Chi-Square	1.398(a)	2	**.497**
Likelihood Ratio	1.424	2	.491
Linear-by-Linear Association	.446	1	.504
N	40		

Table 3.

p65 positivity and distribution over male and female patients.

			p65 marker score				Total
			0	1	2	3	
Gender	Male	n	1	9	7	11	28
		Gender %	3.5%	32.1%	25%	39.6%	100.0%
		p65 %	100.0%	64.2%	63,6%	78.5%	70.0%
	Female	n	0	5	4	3	12
		Gender %	.0%	35.7 %	36.6%	21.4%	100.0%
		p65 %	.0%	35.8%	36.4%	22.5%	30.0%
Total		n	1	14	11	14	40
		Gender %	2.5%	35.0%	27.5%	35.0%	100.0%
		p65 %	100.0%	100.0%	100.0%	100.0%	100.0%

Table 4.

p65 and gender relationship analysis.

	Value	df	p
Pearson Chi-Square	4.524(a)	2	**.104**
Likelihood Ratio	4.788	2	.091
Linear-by-Linear Association	2.701	1	.100
N	40		

Results

There were 28 males (70%) and 12 females (30%) in our study. Male to female ratio was 2.33:1. Age range was between 19 and 80 years, mean age was 59.3 ± 13.4 years. Mean age of male patients was 60 ± 13.2 and mean age of female patients was 57.6 ± 14.4 years. There was no correlation between age and antibody expression ($p > 0.05$). Also there was not any relationship between gender and marker expressions ($p > 0.05$) (Tables 1-6).

Tumor diameter range was 1 to 14 cm and mean tumor diameter was 5.7 ± 3.4 cm. There were 31 (77.5%) patients with pT1 stage (tumor diameter ≤ 7 cm) and 9 (22.5%) patients with pT2 stage (tumor diameter > 7 cm). p65 and p38 expressions in the cancer group were higher significantly than the control group ($p < 0.05$). As the tumor size increased p65 and p38 positivity increased in the cancer group compared to the controls ($p < 0.05$). We detected higher antibody expressions in patients with pT2 tumors than the pT1 patients ($p < 0.05$) (Tables 7, 8).

Grading of renal cell carcinoma was done according to Fuhrman grading system. There were 4 patients (10%) with Fuhrman Grade 1, 26 patients (65%) with Fuhrman

Table 5.

Age and p38 positivity comparison.

	value	df	p	p	p
Pearson Chi-Square	4.215(b)	1	.040		
Continuity Correction(a)	2.762	1	.097		
Likelihood Ratio	4.117	1	.042		
Fisher's Exact Test				**.057**	.050
Linear-by-Linear Association	4.110	1	.043		
N	40				

Table 6.

Age and p65 positivity comparison.

	value	df	p	p	p
Pearson Chi-Square	1.290(b)	1	.256		
Continuity Correction(a)	.255	1	.614		
Likelihood Ratio	2.165	1	.141		
Fisher's Exact Test				**.557**	.344
Linear-by-Linear					
Association	1.258	1	.262		
N	40				

Table 7.

Distribution of tumor diameter and p38 positivity.

			p38 marker score			Total
			1	2	3	
Tumor diameter	0-7 cm	n	15	14	2	31
		Tumor diameter %	48.4%	45.2%	6.5%	100.0%
		p38 %	100.0%	100.0%	18.2%	77.5%
	> 7 cm	n	0	0	9	9
		Tumor diameter %	.0%	.0%	100.0%	100.0%
		p38 %	.0%	.0%	81.8%	22.5%
Total		n	15	14	11	40
		Tumor diameter %	37.5%	35.0%	27.5%	100.0%
		p38 %	100.0%	100.0%	100.0%	100.0%

Table 8.

p65 positivity and tumor diameter distribution.

			p65 marker score				Total
			0	1	2	3	
Tumor diameter	0-7 cm	n	1	14	10	6	31
		Tumor diameter %	3.2%	45.2%	32.3%	19.4%	100.0%
		p65 %	100.0%	100.0%	90.9%	42.9%	77.5%
	> 7 cm	n	0	0	1	8	9
		Tumor diameter %	.0%	.0%	11.1%	88.9%	100.0%
		p65 %	.0%	.0%	9.1%	57.1%	22.5%
Total		n	1	14	11	14	40
		Tumor diameter %	2.5%	35.0%	27.5%	35.0%	100.0%
		p65 %	100.0%	100.0%	100.0%	100.0%	100.0%

Table 9.

p38 positivity among Fuhrman grades.

			p65 marker positivity			Total
			1	2	3	
Fuhrman	1	n	4	0	0	4
		Fuhrman %	100.0%	.0%	.0%	100.0%
		p38 %	26.7%	.0%	.0%	10.0%
	2	n	10	9	7	26
		Fuhrman %	38.5%	34.6%	26.9%	100.0%
		p38 %	66.7%	64.3%	63.6%	65.0%
	3	n	1	3	2	6
		Fuhrman %	16.7%	50.0%	33.3%	100.0%
		p38 %	6.7%	21.4%	18.2%	15.0%
	4	n	0	2	2	4
		Fuhrman %	.0%	50.0%	50.0%	100.0%
		p38 %	.0%	14.3%	18.2%	10.0%
Total		n	15	14	11	40
		Fuhrman %	37.5%	35.0%	27.5%	100.0%
		p38 %	100.0%	100.0%	100.0%	100.0%

Table 10.

p65 positivity among Fuhrman grades.

			p65 marker score				Total
			0	1	2	3	
Fuhrman	1	n	1	3	0	0	4
		Fuhrman %	25.0%	75.0%	.0%	.0%	100.0%
		p65 %	100.0%	21.4%	.0%	.0%	10.0%
	2	n	0	9	8	9	26
		Fuhrman %	.0%	34.6%	30.8%	34.6%	100.0%
		p65 %	.0%	64.3%	72.7%	64.3%	65.0%
	3	n	0	1	2	3	6
		Fuhrman %	.0%	16.7%	33.3%	50.0%	100.0%
		p65 %	.0%	7.1%	18.2%	21.4%	15.0%
	4	n	0	1	1	2	4
		Fuhrman %	.0%	25.0%	25.0%	50.0%	100.0%
		p65 %	.0%	7.1%	9.1%	14.3%	10.0%
Total		n	1	14	11	14	40
		Fuhrman %	2.5%	35.0%	27.5%	35.0%	100.0%
		p65 %	100.0%	100.0%	100.0%	100.0%	100.0%

Grade 2, 6 patients (15%) with Fuhrman Grade 3 and 4 patients (10%) with Fuhrman Grade 4 RCCs. Antibody expression increased as the tumor grade increased ($p < 0.05$) (Tables 9-11) . Tumor samples with Fuhrman grade 2,3 and 4 had higher marker positivity than Fuhrman grade 1 samples ($p < 0.05$). But antibody expression dif-

Table 11.

Comparison of p38 and p65 with tumor diameter and Fuhrman grade.

			Tumor			
			Fuhrman	**Diameter**	**p38**	**p65**
Spearman's rho	Fuhrman	r	1.000	**.341(*)**	**.424(**)**	**.371(*)**
		p	.	**.031**	**.006**	**.019**
		N	40	40	40	40
	Tumor diameter	r	.341(*)	1.000	**.730(**)**	**.781(**)**
		p	.031	.	**.000**	**.000**
		N	40	40	40	40
	p38	r	.424(**)	.730(**)	1.000	.727(**)
		p	.006	.000	.	.000
		N	40	40	40	40
	p65	r	.371(*)	.781(**)	.727(**)	1.000
		p	.019	.000	.000	.
		N	40	40	40	40

Figure 1.

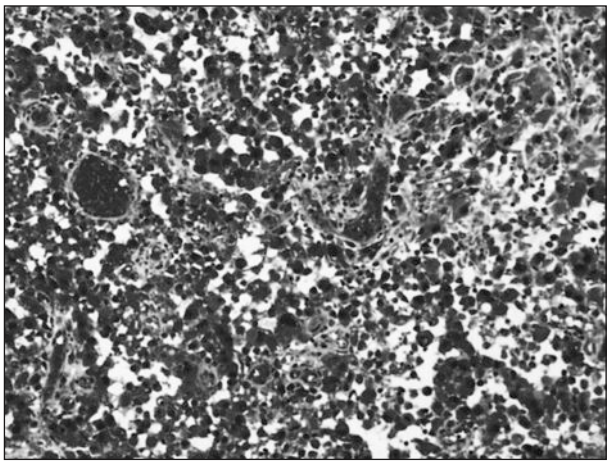
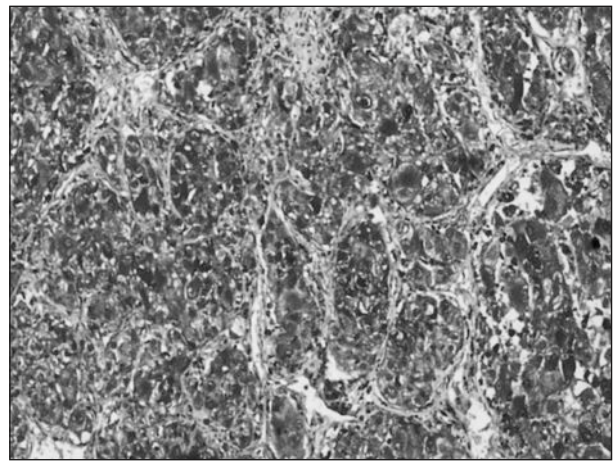


Figure 2.



ference was not significant between Fuhrman grade 2, 3 and 4 tumors ($p > 0.05$). The following pictures are examples of RCC tissues stained with immunohistochemical study (Figures 1, 2).

Discussion

p38 MAPKs were shown to take part in cell adhesion, evolution, proliferation, differentiation and apoptosis (12-14). p38MAPK expression was higher in cancer cells compared to the normal tissue in our study. We think that this situation is due to the increased cell response against oxidative stress, inflammatory cytokines, mitogens and growth factors. In a study about human colorectal carcinoma, p38 expression was increased in the tumor tissue when compared to the normal mucosa (15). There was a relationship between age and p38 expression in serous ovarian carcinoma (16). However in a study about mammarian cancer, MAPK expression was not related with the age of patient (17). We didn't find any correlation between age and antibody expression.

In non small cell pulmonary and gastric cancer, p38 expression was related with tumor stage (18, 19). In our study pT2 renal tumors had higher levels of p38 MAPK expression than pT1 renal tumors. We propose that p38 positivity is correlated with tumor stage in RCC.

As the Fuhrman grade increased, p38 expression increased also in our study. Antibody expression was not different among Fuhrman grades of 2, 3 and 4 but they were significantly higher than antibody expression of Fuhrman grade 1 RCC. High grade colorectal carcinoma had higher levels of p38 expression than low grade carcinoma (15). High grade tumor means poor differentiation and more invasive cancer. Daphnetin may lead to maturation via MAPK pathway and may be used in poor differentiated human RCC (20).

RCC is a highly vascularised and chemoresistant tumor. RKTG (Raf Kinase Trapping to Golgi) negatively regulates MAPK pathway and stop angiogenesis in clear cell RCC by inhibiting VEGF (Vascular endothelial growth factor) (21). Tumor angiogenesis in RCC was inhibited through MAPK pathway by injecting lethal dose anthrax toxin (22). Angiogenesis in RCC by VPF/VEGF (vascular permeability factor/vascular endothelial growth factor) was suppressed with the MAPK inhibition by von Hippel-Lindau (VHL) tumor suppressor gene products (23).

Sorafenib is a tyrosine and serine/threonin kinase inhibitor which is used as a chemotherapeutic agent in tumor progression and angiogenesis. Inhibition of VEGF and PDGF (platelet derived growth factor) mediated angiogenesis and tumor progression is achieved in RCC with this drug (24). New drugs will emerge about the close relationship of MAPK pathway and angiogenesis in the future.

MAPK pathway may be used to direct the cell to apoptosis. Oubain leads to ion influx to the cell by p38 phosphorylation in renal epithelial cells without using Na K ATPase pump. This influx leads to apoptosis (25). Inhibition of one of the MAPK pathways namely JNK, may direct the renal cancer cells to apoptosis (26). In our study MAPK expressed tumor cells show progression and invasion.

Ochratoxin A (OTA) is a carcinogenic substance and renal tumor incidence increased via MAPK activation in male rats that ate food mixed with OTA (27).

Defects in cell motility lead to local invasion and distant metastasis in cancer cells. Motility disregulation through activation of MAPK by hepatocyte growth factor increases invasion of renal cancer cells (28).

NFKB has a role in DNA (deoxyribonucleic acid) transcription and takes part in cellular response against oxidative stress, free radicals, cytokines, ultraviolet radiation, low density lipoprotein oxidation, bacterial or viral antigens (29-33). NFKB also takes part in immune response against infection. Disregulation of NFKB may lead to cancer, inflammatory and autoimmune diseases, septic shock, viral infections and low immune response. p65 expression was significantly higher in transitional cell carcinoma of bladder when compared to normal bladder mucosa (34). Also high expression of p65 was detected in pancreatic ductal adenocarcinoma cells which was adjacent to normal tissue having lower levels of p65 (35). In a study about RCC, p65 expression is increased in cancer cells which was also true in our study (36). We think that p65 positivity in our study is because of increased intracellular signal pathways in renal tumor cells.

NFKB expression is not correlated with the age or gender of our patients. p65 expression is correlated with tumor stage in gall bladder cancer (37). There is increased expression of NFKB in invasive lahrynx cancer (38). p65 nuclear expression is correlated with tumor stage in superficial and invasive bladder urothelial carcinoma (39). In an article about 45 patients with RCC, ratio of p65 positivity in ≥ pT3 patients is higher than the ratio in ≤ pT2 patients (36). In our study we observed that renal tumors greater than 7 cm had significantly higher levels of p65 compared to the levels of renal tumors smaller than 7 cm. p65 increase was parallel to tumor stage increase because of local invasion.

Pyrrolidine dithiocarbamate (PDTC) is an inhibitor of NFKB and in animal RCC studies it is shown to have antiproliferative and anticancer effects (40, 41). Some of these effects are mediated by antiangiogenesis (42).

Bcl-2 and Bcl-(XL) are two proteins responsible for antiapoptosis in renal cancer cells and accused for chemoresistance. Inhibition of transcription function of NFKB reduces the synthesis of these proteins in renal cancer cells (43). Inhibition of NFKB independent from VHL gene leads the cell to apoptosis (44). This inhibition may create new chemotherapeutic agents against RCC in the future.

NFKB and VEGF are shown to coexpress and later tumor angiogenesis, progression and invasion occurs (45).

Epithelial mesenchymal transition (EMT) is an important issue in carcinogenesis. Loss of VHL gene in RCC causes the loss of control over the NFKB pathway and increases the epithelial mesenchymal transition. This leads to increased invasion of renal cell carcinoma (46). We can say that increased expression of NFKB in RCC speeds up EMT and tumor progression p53 inactivation due to NFKB activity may be reversed in renal tumors by a small molecule – 9-aminoacridine (9AA) – and by the antimalarial drug – quinacrine –. This p53 reactivation may kill the cancer cells (47). So the small molecules may be active in renal tumor progression and invasion.

VHL gene disfunction is often seen in renal cancer. VHL tumor suppressor protein inhibits the NFKB dependent antiapoptosis by causing cytotoxicity with TNF-alpha (tumor necrosis factor) (48). Also biallelic loss of VHL gene induces tumor progression by NFKB pathway activation (49). As a result HIF alpha (hypoxia-inducible factor) accumulation occurs and this increases cancer invasion with the help of TGF alpha (transforming growth factor) and EGF (epidermal growth factor). Susceptibility of renal tumor cells to tyrosin kinase inhibitor bortezomib is closely related to NFKB inactivation by VHL gene (50). NFKB pathway activation is an important step in renal cancer chemoresistance and determination of VHL marker may point out which patient the drug will help.

The article about 116 bladder urothelial cancer patients mentions that NFKB expression is correlated to tumor grade (39). In our study we found NFKB levels got higher from Fuhrman grade 1 to 2. Fuhrman grade 2, 3 and 4 had indifferent antibody expressions but they were significantly higher than grade 1. Poorly differentiated tumors had more active NFKB pathways. It must be kept in mind that p65 expression in poorly differentiated renal tumors may lead to progression and invasion.

Coexpression of p38 and p65 had been studied in some articles in the literature. Both antibodies were expressed in colorectal carcinoma cells (15). There is not any study about p38-p65 coexpression in RCC in the literature and our study is the first one.

Finally we think that p38 MAPK and p65 NFKB are important intracellular signal transduction pathways which take part in tumor progression and invasion of RCC. In future chemotherapeutic research and development about renal cancer may focus on these pathways.

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Correspondence

Emin Ozbek, MD
Associate Professor
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
ozbekemin@hotmail.com

Tamer Aliskan, MD
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
av_myazici@hotmail.com

Alper Otunctemur, MD
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
alperotunctemur@yahoo.com

Gokhan Calik, MD
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
drgokhan80@hotmail.com

Suleyman Cakir, MD
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
ssamicakir@hotmail.com

Murat Dursun, MD
Okmeydani Training and Research Hospital, 1st Urology Clinic
Darulaceze cad. No: 25 Sisli, Istanbul, Turkey
mrt_drsn@hotmail.com

Adnan Somay, MD
Fatih Sultan Mehmet Training and Research Hospital
Pathology Clinic, Istanbul, Turkey
adnansomay@hotmail.com

ORIGINAL PAPER

Effects of the association of potassium citrate and Agropyrum repens in renal stone treatment: Results of a prospective randomized comparison with potassium citrate

Simone Brardi [1], Patrizio Imperiali [1], Gabriele Cevenini [2], Tiziano Verdacchi [3], Roberto Ponchietti [4]

[1] Hemodialysis Unit, Ospedale S. Donato, Arezzo, Italy;
[2] Department of Surgery and Bioengineering, University of Siena, Italy;
[3] Extracorporeal shock wave lithotripsy Unit, Ospedale S. Donato, Arezzo, Italy;
[4] Postgraduate Nephrology School, University of Siena, Italy.

Summary

Objectives: *To evaluate by a prospective randomized controlled study the efficacy of the association of potassium citrate and dry extract of couch grass (Agropyrum repens) (CalcoMEV®) in renal stone treatment.*

Materials and Methods: *50 patients with nephrolithiasis associated with one or more active metabolic alterations that constitute an indication to the use of potassium citrate were randomly divided in two equal unblinded treatment groups. A group of patients was assigned to treatment with the association of potassium citrate and couch grass (at the dose of 24 mEq of potassium citrate and 100 mg of dry extract of Agropyrum repens bis in die) and the other group to potassium citrate (at a dose of 20 mEq ter in die). Each form of main treatment was associated, depending on the results of metabolic basal assessment, to allopurinol and/or an association of amiloride and hydrochlorothiazide and/or pyridoxine. Patients of both groups were advised the same diet based on a reduced intake of sodium, foods rich in oxalate and protein of animal origin, a normalized intake of calcium and an increase in fluid intake (> 2 liters every day).*

Results: *At the end of the 5-month follow-up period, the group treated with the association of potassium citrate and couch grass showed a significant reduction in the total number of stones (-1.0 ± 0.2 vs 0.0 ± 0.2 stones) and in the larger diameter of the stones (-3.6 ± 0.9 mm vs 0.0 ± 0.8 mm), as well as a statistically significant reduction of uric acid urinary excretion (-164.7 ± 45.3 vs -38 ± 42 mg/24 h). No significant differences in the two groups were observed with respect to urinary citrate, oxalate and calcium urinary excretions and urinary pH.*

Conclusions: *This prospective randomized study demonstrates the superiority of the association of potassium citrate and dry extract of couch grass, in combination with standard pharmacological and dietary treatment, in reducing the number and size of urinary stones with respect to potassium citrate in association with the same pharmacological and dietary regimen.*

KEY WORDS: *Nephrolithiasis; Potassium citrate; Dry extract of couch grass; Prospective randomized study.*

Submitted 21 December 2011; Accepted 31 March 2012

INTRODUCTION

The goal of the medical therapy of nephrolithiasis is to prevent the formation of new stones in the urinary tract through the identification of the metabolic alterations predisposing to nephrolithiasis and the subsequent prescription of specific pharmacological agents, along with proper dietary recommendations, in order to restore a normal urinary pattern. Among the various pharmacological preparations currently in use for the medical therapy of nephrolithiasis a primary role is played by potassium citrate (1-6) that provides an alkali load in order to increase urinary pH and urinary citrate excretion and to decrease urinary calcium excretion and urinary saturation with

respect to calcium oxalate and uric acid (1). A prospective randomized study was planned to evaluate the therapeutic effects on renal stone formation of the dry extract of couch grass (*Agropyrum repens*) in association to potassium citrate (at the dose of 24 mEq of potassium citrate and 100 mg of dry extract of Agropyrum repens) in comparison with potassium citrate alone.
The efficacy of the association of potassium citrate and dry extract of couch grass was evaluated not only in patients with hypocitraturia but also in the case of absorptive or renal hypercalciuria, hyperoxaluria associated with chronic diarrheal diseases, increased uric acid excretion or abnormally low urinary pH (1). Depending on the metabolic alterations present, the two pharmaceutical regimens under evaluation were associated with other drugs currently used for specific stone prevention (thiazide diuretics, allopurinol, pyridoxine).
Furthermore to all the patients was prescribed the same diet and water intake in order to rule out possible confounding factors related to food and fluid intake.
The prospective randomized comparison was designed to administer both therapeutic regimens at a dosage of maximum effectiveness, that was equal to 24 mEq of potassium citrate plus 100 mg of dry extract of Agropyrum repens in a day and 20 mEq of potassium citrate ter in die, respectively (5, 7).

Materials and Methods

Study Design

From June 2009 to January 2011, patients with nephrolithiasis were recruited from patients attending the outpatient nephrologic clinic in order to evaluate the therapeutic effects of the association of potassium citrate and dry extract of couch grass.

Inclusion and exclusion criteria

Patients were considered eligible for the study if they had an active documented renal stone disease (2 or more stones formed during the previous two years) and at least one of the standard indications for the use of potassium citrate as hypocitraturia, hyperoxaluria associated to chronic diarrhea, hyperuricosuria, abnormally low urinary pH, renal or absorptive hypercalciuria.
Instead, they were excluded in the case of controindication for use of potassium citrate (renal failure, hypoadrenocorticism) (1), infection stones (struvite), bladder stones, cystinuria or stone disease associated with hyperparathyroidism. A total of 50 patients were enrolled, 39 males (mean age 56.4 ± 13.8 yrs, mean height 171.6 ± 6.5 cm, mean weight 81.5 ± 12.6 kg, mean body mass index 27.7 ± 3,8 kg/m^2) and 11 females (mean age 53.6 ± 19.1 yrs, mean height 160.5 ± 5 cm, mean weight: 65.4 ± 11 kg, mean body mass index: 25.5 ± 5 kg/m^2).
None had diabetes mellitus, renal failure, hyperkalemia, active forms of urinary tract infection or gastrointestinal disease.
None was already being treated with specific drugs for nephrolithiasis. Pregnant women and children were also exluded.

Study Protocol

At the time of enrollment a written informed consent was obtained by all the patients. At baseline all the patients, consuming their abitual diets, underwent an extensive assessment for factors predisposing to nephrolithiasis including blood determination of urea nitrogen, creatinine, sodium, potassium, calcium, magnesium, phosphorus, uric acid, parathyroid hormone and 24 hour urine collection for determination of daily urinary excretion of citrate, urate, oxalate, calcium, magnesium and total volume. An early morning urinary sample was obtained for urinalysis and fast urinary pH measurement. Urine culture and Brandt test were performed for the exclusion of urinary infection and cystinuria, respectively. Renal ultrasound examination was carried out for determination of the number of eventual present stones and their larger diameter and to rule out hydronephrosis. Each patient was also subjected to physical examination with determination of weight, height and blood pressure.
At the end of the scheduled follow-up period of 5 months, urine and blood determinations were repeated (except for the Brandt test) as well as ultrasound examination of the urinary tract. Patients were again subjected to further medical examination with recording of weight and blood pressure, and collection of data about the therapeutic and dietary compliance and any adverse reaction to treatment.
Patients were randomly divided in two unblinded main therapeutic groups.
A group (19 males and 6 females, mean age 55.9 ± 15.2 yrs, mean height 169.1 ± 7.6 cm, mean weight 75.8 ± 12.9 kg, mean body mass index 26.5 ± 3.7 kg/m^2) was assigned to treatment with potassium citrate and couch grass dry extract a sachet b.i.d in combination, depending on the results of the metabolic assessment study (1, 5), with allopurinol at a dose of 300 mg q.d and/or amiloride+hydrochlorothiazide at a dose of 5 + 50 mg q.d (*Moduretic®*, hereinafter referred to as thiazide) and/or pyridoxine at a dose of 300 mg q.d.
The first subgroup included 11 patients (8 males e 3 females, mean age 60 ± 15.4 yrs) treated with allopurinol and the association of potassium citrate and couch grass, the second 6 patients (5 males and 1 female, mean age 54.2 ± 15.2 yrs) treated with allopurinol and thiazide plus potassium citrate and couch grass, the third 4 patients (3 males and 1 female, mean age: 53.5 ± 18.7 yrs) assigned to treatment with allopurinol, thiazides and pyridoxine plus potassium citrate and couch grass and the fourth 4 patients (3 males and 1 female, mean age 49.8 ± 13.9 years) treated with pyridoxine and allopurinol plus potassium citrate and couch grass (Table 1).
The second group (20 males and 5 females, mean age 55.7 ± 15.1 yrs, mean height 169.2 ± 8 cm, mean weight 80.1 ± 14.9 kg, mean body mass index 28 ± 4.5 kg/m^2) was assigned to treatment with potassium citrate at a dosage of 20 mEq t.i.d in combination, depending on the results of the metabolic assessment study (1, 5), with allopurinol at a dose of 300 mg q.d and/or to the pharmacological association amiloride + hydrochlorothiazide at a dose of 5 + 50 mg q.d (hereinafter referred to as thiazide) and/or to pyridoxine at a dose of 300 mg q.d. The

Table 1.

Main therapeutic groups and related subgroups.

Main therapeutic group	Theraputic group assigned to potassium citrate plus wheatgrass dry extract (CalcoMEV®)	Theraputic group assigned to potassium citrate
Therapeutic subgroup and number of assigned patients	CalcoMEV® plus allopurinol (11 patients: 8 males and 3 females, mean age: 60 ± 15.4 years)	Potassium citrate plus allopurinol (11 patients: 7 males and 4 females, mean age: 60.5 ± 17.7 years)
	CalcoMEV® plus allopurinol and thiazide (6 patients: 5 males and 1 female mean age: 54.2 ± 15.2 years)	Potassium citrate plus allopurinol and thiazide (6 patients: 5 males and 1 female, mean age: 52.7 ± 14 years)
	CalcoMEV® plus allopurinol, thiazide and pyridoxine (4 patients: 3 males and 1 female, mean age: 53.5 ± 18.7 years)	Potassium citrate plus allopurinol, thiazide and pyridoxine 4 patients: 4 males, mean age: 47.3 ± 11.2 years)
	CalcoMEV® plus allopurinol and pyridoxine (4 patients: 3 males and 1 female, mean age: 49.8 ± 13.9 years)	Potassium citrate plus allopurinol and pyridoxine (4 patients: 4 males, mean age: 55.5 ± 11 years)

resulting four therapeutic subgroups assigned to primary treatment with potassium citrate alone were equal by number and secondary pharmacological regimen to the four subgroups of the other main pharmacological group assigned to the primary treatment with the association of potassium citrate and couch grass.

A first subgroup included 11 patients (7 males and 4 females, mean age 60.5 +/- 17.7 years) assigned to treatment with potassium citrate and allopurinol, a second subgroup of 6 patients (5 males and 1 female mean 52.7 +/- 14 years) was treated with potassium citrate, allopurinol and thiazide, a third subgroup of 4 patients (4 males, mean age: 47.3+/-11.2 years) was placed to treatment with potassium citrate, allopurinol, thiazide and pyridoxine and a final subgroup of 4 patients (4 males, mean age: 55.5 +/- 11 years) to treatment with potassium citrate and pyridoxine (Table 1).

For homogeneous comparison, the total number of patients was equally divided in the two main therapeutic groups and the number of participants in each subgroup was kept equal to the corresponding subgroup of the other main treatment group.

The distribution by age and sex in the two main therapeutic groups and their subgroups was randomly obtained with an high prevalence of male gender in all groups of treatment.

The anthropometric parameters (weight, height, age and body mass index) resulted quite similar in the two main therapeutic groups and their subgroups (Table 2).

All the patients at the time of the first basal visit were

Table 2.

Descriptive anthropometric data by gender and main therapeutic group.

Descriptive anthropometric data by gender.

Descriptive data				
	GENDER	N	Mean	Std deviation
Height	Maschi	39	171.6	6.5
	Femmine	11	160.5	5.0
	Totale	50	169.1	7.7
Age IFUP	Maschi	39	56.4	13.8
	Femmine	11	53.6	19.1
	Totale	50	55.8	15.0
Weight	Maschi	39	81.5	12.6
	Femmine	11	65.4	11.4
	Totale	50	78.0	13.9
BMI	Maschi	39	27.7	3.8
	Femmine	11	25.5	5.0
	Totale	50	27.2	4.2

Descriptive anthropometric data by main therapeutic group (MTG).

Descriptive data				
	GENDER	N	Mean	Std deviation
Height	0	25	169.1	7.6
	1	25	169.2	8.0
	Totale	50	169.1	7.7
Age IFUP	0	25	55.9	15.2
	1	25	55.7	15.1
	Totale	50	55.8	15.0
Weigh	0	25	75.8	12.9
	1	25	80.1	14.9
	Totale	50	78.0	13.9
BMI	0	25	26.5	3.7
	1	25	28.0	4.5
	Totale	50	27.2	4.2

Legenda

Abbreviation	Coded data	Abbreviation	Coded data
MTG	Main therapeutic group	H	Height (cm)
0	CalcoMEV®	W	Weight (at initial follow up) (kg)
1	Potassium citrate	BMI	Body mass index (at initial follow up) kg/m^2
AGE IFUP	Age at initial follow up		

advised the same dietary regimen based on a restriction of the Intake of sodium, foods rich in oxalate and protein of animal origin, a normalized intake of calcium and an increase intake of fluids (> 2 liters every day) with preferential use of low mineral waters to moderate the intake of calcium (1).

The parameters used to evaluate the efficacy of each treatment were identified in the variations of citrate, urate, oxalate and calcium urinary excretions and of urinary pH and in the variations of the total number of urinary calculi and their greater diameters.

In order to better evaluate the formation of new stones, spontaneous stone passages and extracorporeal or surgical treatments for stone removal were also recorded, both in the case of absence of stones at the time of initial evaluation and in the case of absence of variation in the total number of stones at final sonography with respect to initial evaluation.

Statistical analysis

All chemical measurements were performed at chemistry laboratory of S. Donato Hospital in Arezzo using enzymatic methods (Siemens) for citrate, urate and oxalate and colorimetric methods (Siemens) for calcium, magnesium and phosphate.

Statistical analysis was performed by multivariate analysis of variance (MANOVA), evaluating the variation of parameters for both main treatment groups and subgroups after correction for gender. Statistical significance was considered for p values < 0.05.

A descriptive analysis for each variable was also made and expressed in terms of marginal means as estimated by the statistical model determined by MANOVA.

Data were analyzed using the statistical software SPSS, version 10.

Results

All patients completed the planned 5 months period of therapy, none was excluded because of intolerance or lack of compliance.

All parameters under investigation in the study (citrate, urate, oxalate and calcium outputs; total number of stones, mean greater diameter of stone), were not different in the two treatment groups at baseline with the exception of the total number of stones that was higher in the group treated with the association of potassium citrate and couch grass with respect to potassium citrate group (2.5 ± 0.4 *vs* 1.3 ± 0.4 stones).

Effect of treatment on stone formation

During the period of follow-up in both the primary therapeutic groups no spontaneous stone passage was registered nor any lithotripsy or surgical treatment was requested for removal of uri-

Table 3.

Results (marginal means) by main therapeutic groups.

				Confidence interval 95%	
Dependent variable	**MTG**	**Mean**	**Error std.**	**Lower limit**	**Upper limit**
CTR0	0	620.9	84.6	449.4	792.5
	1	713.5	78.5	554.4	872.6
CTR1	0	755.9	78.3	597.2	914.6
	1	766.4	72.6	619.2	913.6
UR0	0	560.9	49.4	460.8	661.1
	1	434.6	45.8	341.7	527.5
UR1	0	396.2	34.3	326.7	465.7
	1	396.6	31.8	332.1	461.1
OX0	0	31.8	2.6	26.5	37.1
	1	26.1	2.4	21.2	31.0
OX1	0	30.3	3.0	24.1	36.5
	1	26.4	2.8	20.6	32.1
CA0	0	224.9	36.2	151.5	298.3
	1	153.7	33.6	85.6	221.8
CA1	0	172.1	19.5	132.5	211.7
	1	176.8	18.1	140.1	213.5
NOS0	0	2.5	0.4	1.7	3.2
	1	1.3	0.4	0.6	2.0
NOS1	0	1.4	0.4	0.7	2.2
	1	1.4	0.3	0.7	2.0
LOS0	0	8.7	1.3	6.0	11.3
	1	6.3	1.2	3.8	8.8
LOS1	0	5.0	1.1	2.7	7.3
	1	6.3	1.0	4.2	8.4
CTRD	0	135.0	69.7	-6.4	276.3
	1	52.9	64.6	-78.1	184.0
URD	0	-164.7	45.3	-256.6	-72.8
	1	-38.0	42.0	-123.2	47.3
OXD	0	-1.5	3.6	-8.9	5.8
	1	0.3	3.4	-6.5	7.1
CAD	0	-52.8	27.0	-107.6	2.0
	1	23.1	25.1	-27.7	73.9
NOSD	0	-1.0	0.2	-1.4	-0.7
	1	0.0	0.2	-0.3	0.4
LOSD	0	-3.6	0.9	-5.4	-1.9
	1	0.0	0.8	-1.6	1.6

Legenda

Abbreviation	**Coded data**
MTG	Main therapeutic group
0	CalcoMEV©
1	Potassium citrate
CTR0	Urinary Citrate (basal) mg/24 h
CTR1	Urinary Citrate (final follow-up) mg/24 h
UR0	Urinary Urate (basal) mg/24 h
UR1	Urinary Urate (final follow-up) mg/24 h
OX0	Urinary Oxalate (basal) mg/24 h
OX1	Urinary Oxalate (final follow-up) mg/24 h
CA0	Urinary Calcium (basal) mg/24 h
CA1	Urinary Calcium (final follow-up) mg/24 h
NOS0	Number of stones (basal)
NOS1	Number of stones (final follow-up)
LOS0	Larger stone diameter (basal) mm
LOS1	Larger stone diameter (final follow-up) mm
CTRD	Differential variation of Urinary Citrate
URD	Differential variation of Urinary Urate
OXD	Differential variation of Urinary Oxalate
CAD	Differential variation of Urinary Calcium
NOSD	Differential variation of stone number
LOSD	Differential variation of stone larger diameter

nary calculi. At the end of the period of follow-up in the main therapeutic group treated with the association of potassium citrate and couch grass, a significant reduction in the total number of stones was observed (-1.0 ± 0.2 *vs* 0.0 ± 0.2 stones) (Table 3).
Similarly, in the group treated with the association of potassium citrate and couch grass a significant reduction in the mean diameter of stones was recorded (3.6 ± 0.9 mm *vs* 0.0 ± 0.8 mm) (Table 3).

Effect of treatment on urinary stone risk factors
At the end of follow-up, in the therapeutic group treated with the association of potassium citrate and couch grass (*CalcoMEV®*), we observed a significant decrease of daily uric acid urinary output (-164.7 ± 45.3 *vs* -38 ± 42 mg/24 h) while there were no significant differences between the two main therapeutic groups in relation to daily urinary citrate (135 ± 69.7 mg/24 h *vs* 52.9 ± 64.6 mg/24 h), oxalate (-1.5 ± 3.6 mg/24 h *vs* 0.3 ± 3.4 mg/24 h) and calcium output (-52.8 ± 277 mg/24 h *vs* 23.1 ± 25.17 mg/24h) and urinary pH.
A significant reduction of daily urinary calcium output was observed in the comparison between the subgroup treated with the combination therapy of potassium citrate+couch grass and allopurinol and the subgroup treated with the combination of potassium citrate+ couch grass, allopurinol and thiazide (5.3 ± 35.2 mg/24 h *vs*. -227.1 ± 56.9 mg/24 h) although this reduction was not found in the comparison of the therapeutic subgroup treated with the combination of potassium citrate and allopurinol and the subgroup treated with the combination of potassium citrate, allopurinol and thiazide (Table 3).

Other statistical results
There were no significant changes in the comparison between the two main therapeutic groups, for blood parameters such as BUN, creatinine, sodium, potassium, calcium, magnesium, phosphorus, uric acid, parathyroid hormone and for total urinary volume.

Adverse reactions to treatment
There were only complaints for poor palatability of the potassium citrate and wheatgrass preparation but no problems related to adverse reactions or intolerance in any of the two main therapeutic groups were reported.

Discussion
This study proves the superiority of the association of potassium citrate and couch grass compared to potassium citrate alone, in reducing the number and size of renal stones, when administered in combination with standard therapy and dietary recommendations for nephrolithiasis.
In fact, at the end of the follow-up, in the main therapeutic group treated with the association of potassium citrate and couch grass, it was recorded a significant reduction in the total number of stones as well as in the mean larger diameter of stones.
These parameters remained completely unchanged, although not incresed, in the therapeutic main group treated with potassium citrate alone. The clinical response to the association of potassium citrate and couch grass was associated with a greater reduction in the daily urinary excretion of uric acid whereas a statistically significant decrease of the daily urinary excretion of calcium was observed only in the comparison between the subgroup treated with the combination therapy of potassium citrate and couch grass and allopurinol and the subgroup treated with the combination of potassium citrate and couch grass, allopurinol and thiazides although this decrease was not observed in the comparison of the therapeutic subgroup treated with the combination of potassium citrate and allopurinol and the subgroup treated with the combination of potassium citrate, allopurinol and thiazide.
However no significant variations between the two main therapeutic groups were found for daily citrate urinary excretion nor for the urinary pH, probably due to the absence of a significant difference in the amount of potassium citrate administered with the two therapeutic regimens at the dose used in the study.
The potassium citrate and couch grass preparation contains in fact for each sachet 24 mEq (2612 mg) of potassium citrate for a total, at the dosage used in the study, of 48 mEq/day, while the formulation of potassium citrate used in the study contains 18 mEq (2000 mg) of potassium citrate for a total, at the dose used in the study, of 54 mEq/day.
It is likely, therefore, that the above reported findings can be explained by the effect of the dry extract of couch grass (*Agropyrum repens*) that was present in the citrate and couch grass preparation at a dose of 100 mg for each sachet (Table 4).
The dry extract of couch grass, despite the lack of conclusive clinical data, has traditionally been known since ancient times for its mild diuretic, soothing and anti-inflammatory property. Dioscorides already stated that the root of couch grass, taken in the form of decoction was an useful remedy for bladder stones (8-14). More particularly the effect of *Gramigna*, according to its traditional use, is attributed to its ability to mildly increase urine output and to provide relief from infections and stones of the urinary tract (12-14).
The main constituents of the dry extract of couch grass (3-8% of total) are triticin, an inulin like fruttosan polysaccharide which releases by hydrolysis inositol and mannitol (2-3% of total), as well as mucilage (10% of total), saponins and vanillin.
The dry extract of couch grass also contains other components such as a constituent agropirene volatile oil (8-11, 14). In the specific literature (8-11, 14) the above

Table 4.

Concise description of dry extract of couch grass used in CalcoMEV®.

Product: dry extract of couch grass (Agropyrum repens P. B.) 1:4
Botanical Part: Rhizome
Origin: ITALY
Carrier: Maltodextrin
Extraction Solvent: Aqueous

reported diuretic properties are attributed, although not supported by formal clinical data, to the presence of non-absorbable sugars such as mannitol, saponins and vanillin while anti-inflammatory property is related to the presence of mucilage polysaccharides (8-11, 14). An alcoholic extract of couch grass has demonstrated anti-inflammatory properties being able to induce a weak inhibition of inflammation induced by carrageenan in the paws of rodents (9).

Although the specific pharmacological properties of wheatgrass are mainly desumed from the common, though widespread, traditional herbal medicine (12-14) and there are no clinical data to formally support them, the mild diuretic properties of the dry extract could explain the finding of a statistically significant reduction of uric acid urinary excretion in the main therapeutic group treated with the association of potassium citrate and couch grass. It is known that diuretics reduce the urinary excretion of urate through a net increase of its resorption (15, 16), induced by the reduction of the state of hydration, since the retention of urate does not occur when the water losses induced by diuretic treatment are replaced (17); the degree of retention of urate is dose-dependent (18).

Furthermore, it is well known that thiazide diuretics, through the reduction of the state of hydration, lead to a compensatory increase in proximal reabsorption of sodium and to a secondary increase of the passive proximal reabsorption of calcium that can reduce the urinary calcium output up to 50% (19, 20); also in this case the mechanism is related with the dose of diuretic (21). Although the study did not show significant changes between the two main therapeutic groups for the total urinary volume (though fluid intakes were not controlled), it is theoretically possible, although unproven, that the mild diuretic properties traditionally attributed to the dry extract of couch grass may have induced, through the aforementioned mechanism linked to the reduction of the state of hydration, the statistically significant reduction of uric acid excretion in the group treated with the association of potassium citrate and couch grass.

The same mild diuretic property of couch grass could enhance the effect of the thiazide diuretic resulting in a statistically significant reduction of urinary calcium output, when the subgroup treated with the combination therapy of potassium citrate and couch grass and allopurinol was compared to the subgroup treated with the combination of potassium citrate and couch grass, allopurinol and thiazide.

Conclusions

This prospective randomized study demonstrates the superiority of the association of potassium citrate and dry extract of couch grass, administered together with standard pharmacotherapy and dietary recommendations for nephrolithiasis, in reducing the number and size of urinary stones when compared to treatment with potassium citrate alone in association to standard pharmacological treatment and dietary recommandations for nephrolithiasis.

There is therefore an indication to use the association of potassium citrate and dry extract of couch grass, together with standard pharmacotherapy and dietary recommendations for nephrolithiasis not only in the case of hypocitraturia but also in the presence of absorptive or renal hypercalciuria, hyperoxaluria associated to chronic diarrhea, increased uric acid excretion and abnormally low urinary pH, or alterations of urinary saturation with respect to calcium oxalate and uric acid.

However, further studies are needed to clarify the actual mechanism of action of the dry extract of couch grass.

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Correspondence

Simone Brardi, MD
Hemodialysis Unit, Hospital S. Donato
Via P. Nenni - Arezzo, Italy
sibrardi@tin.it

Patrizio Imperiali, MD
Hemodialysis Unit, Hospital S. Donato
Via P. Nenni - Arezzo. Italy

Gabriele Cevenini, MD
Department of Surgery and Bioengineering
University of Siena, Siena, Italy

Tiziano Verdacchi, MD
Extracorporeal Shock Wave Lithotripsy Unit
Hospital S. Donato
Via P. Nenni - Arezzo, Italy

Roberto Ponchietti, MD
Postgraduate Nephrology School,
University of Siena, Italy

ORIGINAL PAPER

Has the cost of anti-muscarinic a key role in the success rate of patients diagnosed with overactive bladder syndrome?

Carlo Vecchioli Scaldazza [1], Carolina Morosetti [2], Gianna Pace [1], Berouz Azizi [1], Willy Giannubilo [1], Vincenzo Ferrara [1]

[1] Department of Urology, [2] Department of Clinical Laboratory, Hospital of Jesi, Jesi, Italy.

Summary

Introduction: *Overactive Bladder Syndrome (OAB) is a chronic disease, the prevalence in the general population is reported to be 14-16%. Anti-muscarinic agents are considered the first-line pharmacological treatment for the management of OAB; although a long lasting therapy is indicated to reach a better control of OAB symptoms an high percentage of patients discontinue the cure after a brief period. Our attempt is to investigate whether the cost of solifenacin succinate may influence the long lasting regimen and patients' drug efficacy.*

Materials and Methods: *70 consecutive women, with symptoms of OAB were enrolled in this randomized controlled study. In group A, all patients received solifenacin 5 mg by the urologist, without any cost; they were instructed to get the drug once daily for 4 months, differently, in group B, patients need to buy the drug which was administered as in the group A. Frequency, nocturia, incontinence, voided volume, were evaluated by a 3-day micturition diary. Overactive Bladder Questionnaire Short Form (OAB-qSF) was used to assess the impact of OAB symptoms on patients' quality of life (QoL). Urgency was assessed by patient's perception of intensity of urgency scale (PPIUS). Micturition-diary, OAB-qSF, PPIUS, were completed at baseline and after four months.*

Results: *A greater number of patients discontinued solifenacin in the group B who need to buy the drug. We observed significant differences in groups A and B in relation to frequency, nocturia, urge incontinence and voided volume comparing the pre and post treatment symptoms. The patients' perceptions of intensity of urgency and the PGI-I scale showed a significant improvement greater in group A in respect with group B.*

Conclusions: *The cost of anticholinergic may be responsible for both early discontinuation of treatment and incomplete adherence to therapy with unsatisfactory results on symptoms and an incorrect assessment of the effectiveness of the drug by the urologist.*

KEY WORDS: *Anti-muscarinic; Overactive bladder syndrome; Drug cost/efficacy.*

Submitted 21 November 2011; Accepted 31 March 2012

INTRODUCTION

Overactive Bladder Syndrome (OAB) is a chronic disease characterized by urinary urgency with or without urge incontinence, frequency and nocturia (1-4). The prevalence of OAB in the general population is reported to be 14-16% (5, 6). The total cost for diagnosis and treatment of OAB in USA, during 2000, was estimated to be about 12.6 billion dollars, comparable to the charge for osteoporosis, gynaecologic and breast cancers (6). *Irwin et al.* reported the economic impact of OAB in six Western countries Canada, UK, Germany, Italy, Spain and Sweden: the total annual cost amounted to about 3.9 billion, with nursing home costs of 4.7 billion and work absenteeism costs of 1.1 billion (5). Anti-muscarinic agents are considered the first-line pharmacological treatment for the management of OAB; although a long lasting therapy is indicated to reach a better control of OAB symptoms an high

percentage of patients discontinue the cure after few months (7-14). Focusing on the costs associated to the OAB, the direct costs are represented by diagnosis, treatment, routine care and conditions related to the disease, and indirect costs like the productivity loss, emerges how the great amount may be accounted to the OAB-induced comorbidities (15-17). Previous studies have been carried out in the attempt to elucidate the economic impact of anti-muscarinic agents both at the beginning of the treatment and in the long-lasting regimen (18-27). Despite this, several aspects relating to the impact of the costs of anti-muscarinic agents on the patient's adherence to the requested prolonged treatments still need to be clarified.
In this study, our attempt is to investigate whether the cost of solifenacin succinate may influence the long lasting regimen and patients' drug efficacy.

Materials and Methods

70 consecutive women, mean age 57 years old (range 35-81 years) with symptoms of OAB were enrolled in this randomized controlled study. All women underwent a detailed clinical evaluation, including a complete history and physical examination. Patients with urinary tract infection, neurological disease, bladder lithiasis, bladder cancer, or a previous anti-muscarinic treatment or radiation therapy, were excluded. Patients were randomized in a 1:1 ratio. In group A (35 patients), all patients received solifenacin 5 mg by the urologist, without any cost; they were instructed to get the drug once daily for 4 months. Differently, in group B (35 patients), patients need to buy the drug which was administered once a day for 4 months as in the group A. All women were informed of the need of a prolonged therapy to reach better results related to OAB symptoms control. Frequency, nocturia, incontinence, voided volume, were evaluated by a 3-day micturition diary. Overactive Bladder Questionnaire Short Form (OAB-qSF) was used to assess the impact of OAB symptoms on patients' quality of life (QoL). The questionnaire consists of 6 items related to symptoms with 6 possible options ranging from "*not at all*" (score = 1) to "*a very great deal*" (score = 6), and a health related quality of life (HRQL) scale with 13 items, with 6 response options ranging from "*none of the time*" (score = 1) to "*all of the time*" (score = 6). Urgency was assessed by patient's perception of intensity of urgency scale (PPIUS) represented by a 5 point scale from 0 (no urgency) to 4 (Urge incontinence). Improvement has been evaluated with the Patient Global Impression of Improvement questionnaire (PGI-I). The PGI-I is a validated generic tool for assessment of the overall improvement or deterioration that patients experience following the treatment. It is a 7-point scale from very much improved (score = 1), to very much worse (score = 7). Micturition-diary, OAB-qSF, PPIUS were completed before treatment (at baseline) and after four months of treatment. The follow-up was performed by physicians not involved in the study protocol. The version SPSS 18.0 was used for statistical analysis. Wilcoxon test for paired samples, Mann Whitney test for independent samples and the Chi square test ($\chi 2$ test) were applied. Statistical significance was accepted if $p < 0.05$.

Results

In Table 1, we reported the percentage and the causes of drug discontinuation. We had a greater number of patients who discontinued solifenacin in the group B (who bought the drug). Among all causes just poor efficacy showed a significant difference (P = 0.0328) between groups A and B.
Thus, of the 70 patients (35 vs 35) initially enrolled, 58 were eligible and completed the study, 34 in the group A and 24 in the group B.
In both groups A and B we observed a significant improvement of all symptoms: frequency, nocturia, urge incontinence and voided volume, after 4 months of treatment (Table 2). Furthermore, in the comparison of post treatment results we noticed a significant difference between the 2 groups for all items except for urge

Table 1.

Reason for discontinuing therapy with solifenacin succinate in the two groups of patients.

	Group A	Group B	P value *
Patients enrolled	35	35	
Age (range)	57.6 (35-79)	56.4 (38-81)	
Reason for discontinuing therapy			
side effects	1	3	P = 0,6066
poor efficacy	0	6	P = 0,0328
cost of the drug	–	2	
Patients evaluated	34	24	

* $\chi 2$ test

Table 2.

Difference in daily micturitions, nocturia, urge incontinence, voided volume in groups A and B, before and after treatment.

	Group A - before Mean/median	Group A - after Mean/median	P value	Group B - before Mean/median	Group B - after Mean/median	P value
Daily micturitions	12.12-12	8.5 -8	< 0.0001*	12.46-12	9.92-10	0.0001*
Nocturia	3.09-3	1.06-1	< 0.0001*	2.92-3	2.17-2	0.0461*
Urge Incontinence	3.53-4	1.21-0.5	0.0004*	3.29-4	1.96-2	0.0453*
Voided Volume (ml)	178.53-190	295.88-322.50	< 0.0001**	184.17-187.50	261.88-270	< 0.0001**

* $\chi 2$ test; ** Wilcoxon test for paired samples.

Table 3.

Difference in daily micturitions, nocturia , urge incontinence, voided volume in group A versus group B, before and after treatment.

	Group A - before Mean/median	Group B - before Mean/median	P value	Group A - after Mean/median	Group B - after Mean/median	P value
Daily micturitions	12.12-12	12.46-12	0.2639*	8.5-8	9.92-10	0.0112*
Nocturia	3.09-3	2.92-3	0.4203*	1.06-1	2.17-2	0.0446*
Urge Incontinence	3.53-4	3.29-4	0.4831*	1.21-0.5	1.96-2	0.2604*
Voided Volume (ml)	178.53-190	184.17-187.50	0.8189**	295.88-322.5	261.88-270	0.0331**

* $\chi 2$ test; ** Mann Whitney test for independent samples.

Table 4.

Patients' perception of intensity of urgency scale (PPIUS): distribution of frequencies in the two groups before and after treatment.

PPIUS	Group A before	Group A after	P value *	Group B before	Group B after	P value *
0	0	13		0	3	
1	2	14		1	6	
2	9	3	< 0.0001	5	7	0.0291
3	9	2		6	3	
4	14	2		12	5	

* $\chi 2$ test.

Table 5.

Patients' perception of intensity of urgency scale (PPIUS): distribution of frequencies in group A versus group B before and after treatment.

PPIUS	Group A before	Group B before	P value *	Group A after	Group B after	P value *
0	0	0		13	3	
1	2	1		14	6	
2	9	5	0.8189	3	7	0.0331
3	9	6		2	3	
4	14	12		2	5	

* $\chi 2$ test.

Table 6.

Overactive bladder questionnaire short form (OAB-qSF: 6- item symptom bother scale): groups A and B before and after treatment and group A versus group B before and after treatment.

Group A - before Mean/median	Group A - after Mean/median	P value	Group B - before Mean/median	Group B - after Mean/median	P value
29.03-29	14.76-15.50	< 0.0001*	29.50-30	21.21-20	< 0.0001*
Group A - before Mean/median	**Group B - before** Mean/median	**P value**	**Group A - after** Mean/median	**Group B - after** Mean/median	**P value**
29.03-29	29.50-30	0,4873 **	14.76-15.50	21.21-20	0.0018 **

* Wilcoxon test for paired samples; ** Mann Whitney test for independent samples.

incontinence (Table 3). In Table 4 are reported results, showing a significant difference in both groups relating to pre and post treatment results, greater in group A ($p < 0.0001$) respect to group B ($p < 0.0291$). No differences were observed in the patients' perceptions of intensity of urgency between the two groups before treatment while after 4 months, group A showed a significant improvement in the perception of urgency respect to group B ($p = 0.0331$) (Table 5). Table 6 and Table 7 show the results of the Overactive Bladder Questionnaire Short Form (OAB-qSF) concerning the 6 items symptom bother scale and the 13 items HRQL scale, respectively; there was a significant difference in both groups in the comparison of the pre and post

Table 7.

Overactive bladder questionnaire short form (OAB-qSF: 13- item HRQL scale): groups A and B before and after treatment and group A versus group B before and after treatment.

Group A - before	**Group A - after**	**P value**	**Group B - before**	**Group B - after**	**P value**
Mean/median	Mean/median		Mean/median	Mean/median	
60.79-63	29.68-28	< 0.0001 *	61.17-63	43.42-40.50	< 0.0001 *
Group A - before	**Group B - before**	**P value**	**Group A - after**	**Group B - after**	**P value**
Mean/median	Mean/median		Mean/median	Mean/median	
60.79-63	61.17-63	0.6584**	29.68-28	43.42-40.50	0.0024**

* Wilcoxon test for paired samples; ** Mann Whitney test for independent samples.

Table 8.

Patient global impression of improvement (PGI- I) scale: distribution of frequencies in groups A and B after treatment.

PGI-I	**Group A**	**Group B**	**P value ***
0	0	0	
1	13	2	
2	18	11	
3	2	6	
4	1	5	0.0045
5	0	0	
6	0	0	
7	0	0	

* χ^2 test

treatment data as well as between those relating to the post treatment results (p = 0.0024).
Table 8 shows the results of the patient's global impression of improvement (PGI-I): we observed a significant difference in the distribution of frequencies with a significant improvement in group A respect to group B (p = 0.0045).

Discussion

Previous studies have evaluated the adherence to OAB pharmacotherapy and the high percentage of patients discontinuing therapy. *Yu* et al. investigating on patients' persistence patterns for OAB/urinary incontinence medication treatment found that 88.2% of them discontinued the treatment within the following year (28). *Shaya* et al. pointed out that only 32% of patients treated by oxybutynin IR and 44% of patients assuming either tolterodine ER or oxybutynin ER remained persistent after 30 days; after 1-year the persistence rates were 9%, 6% and 5% for tolterodine ER, oxybutynin ER and oxybutynin IR, respectively (11). *Lawrence* et al. in a retrospective analysis, evaluated adherence to IR oxybutynin and tolterodine: only 32% of patients taking tolterodine and 22% oxybutynin continued therapy for 6 months (29).
Focusing on the reasons for discontinuing OAB medication, the low level of education, cultural and socio-economic factors, poor efficacy, side effects (dry mouth, constipation, dry eyes, blurred vision, cognitive impairment), smoking, alcohol consumption, beliefs about illness and treatment, costs were the most important causes (30-33). Moreover, in an interesting study by Berner at al. on patients' reported reasons for discontinuing therapy, the authors found that 46% of patients discontinued therapy because "*it didn't work as expected*"; 23.3% because they learned to get by without medication, 21.1% because of side effects and only 17.2% because the cost of medication (34). *Ulka* et al. reported a percentage of patients who discontinued therapy of about 45%: 41.3% of them discontinued therapy because of the poor efficacy, 22.4% for side effects and 18.7% due to the cost (35). Significant predictors of higher persistence include age and race: patients aged 40 to 64 years are significantly less likely to discontinue therapy than the younger adults and African Americans were more likely than Caucasians to discontinue or switch (11). Of particular importance is the type of anti-muscarinic agent and its action. It has been shown that an extended-release formulation of anti-muscarinic agents improves tolerability and patient's adherence. *Juzba* et al. found that nearly half of the patients evaluated in their study failed to refill the first prescription and that continuation was more likely for patients taking tolterodine ER than oxybutynin IR (36). Moreover, an extended-release oxybutynin formulation has a lowered frequency of adverse effects compared with immediate-release oxybutynin. The cost of the drugs, although reported as cause of the low persistence and adherence to OAB pharmacotherapy, is not considered among the main cause of discontinuation. In our mind the impact of the cost of the anti-muscarinic on patients' drug efficacy should not be underestimated. In Italy drugs for treatment of OAB are not included in the reimbursement list and the cost of a 30 days treatment is about 60 euros. A significant percentage of patients affected by OAB are more than 60 years old with limited economic possibilities. Moreover, 55% of retired patients get monthly less than 1000 euros and 24% less than 500 euros, therefore buy an anti-muscarinic deeply impact on their economic resources. In our study both groups were homogeneous before treatment and randomized to buy or to get freely the drug for a period of four months. No differences were observed comparing bladder diary results, OAB-qSF, patients' perceptions of intensity of urgency, in group A vs group B before treatment. A significant improvement of symptoms and of questionnaires results was observed after treatment in the group A who had freely the drug respect to group B. The only significant difference among the causes of discontinuation between the two groups has

been represented by poor efficacy. It is of importance to underline that frequently patients are reluctant to reveal their personal economic difficulties to buy an expensive drug. This should be a cause of the lack of the cost among the real reasons of discontinuation therapy which may negatively impact on a long lasting regimen causing a reduced efficacy. Oral anti-muscarinic represent the first-line pharmacologic therapy for the treatment of OAB and it should be assumed only without discontinuation to get good therapeutic results. Unsatisfactory therapeutic results can be due to either interruption of the therapy or incorrect and not continued taking the drug. While patients are not afraid to reveal the discontinuation of therapy, frequently it is not referred an intermittent drug assumption. This last is mainly a consequence of the belief to still achieve satisfactory therapeutic results reducing the cost of the drug.

Conclusions

Our results seem to support the hypothesis that the cost of the anti-muscarinic should be partly involved in an incomplete adhesion to the treatment protocol of several patients thus reducing the efficacy. Therefore the cost of anticholinergic may be responsible for both early discontinuation of treatment and incomplete adherence to therapy with unsatisfactory results on symptoms and an incorrect assessment of the effectiveness of the drug by the urologist.

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Correspondence

Carlo Vecchioli-Scaldazza, MD
Corso Cavour 66 - 62100 Macerata, Italy
cascave@alice.it

Carolina Morosetti, MD
Gianna Pacea, MD
Berouz Azizi, MD
Willy Giannubilo, MD
Vincenzo Ferrara, MD
Department of Clinical Laboratory-Hospital of Jesi
Jesi, Italy

ORIGINAL PAPER

Awareness of the role of the pelvic floor muscles in controlling the ejaculatory reflex: Preliminary results

Giuseppe La Pera

Dept. of Urology, San Camillo - Forlanini Hospital, Rome, Italy.

Summary

The difficulty in correctly identifying the etiologic factors of premature ejaculation (PE) could be due to the fact that the role of the pelvic floor muscles (PFMs) in the voluntary control of ejaculatory reflex has not been elucidated.

The aim of the present investigation was to measure the prevalence of awareness of the role and use of PFM contraction in controlling the ejaculatory reflex among PE and non-PE participants.

A total of 44 men with PE and 73 men without PE were recruited. In the first part of the study, we validated a test that rendered the participants aware of the PFMs through digital rectal examination and the PFM contraction. In the second part, we posed this multiple-choice question: "Which muscles do you use to delay ejaculation?". Men not answering correctly were considered not to be using the PFMs and also to be unaware that it is necessary to contract the PFMs to control the ejaculatory reflex. Only 3 of 44 subjects (6.8%) with PE and 60 of 73 subjects (82%) without PE answered correctly and used PFMs to control the ejaculatory reflex (Fisher test p < 0.0001). This test has a sensibility of 93%, a specificity of 82%, and an accuracy of 86%. The vast majority of PE subjects were unaware that to inhibit or delay ejaculation it is necessary to contract the PFMs. This association also raises the question whether the difficulties in defining PE and finding effective PE therapies could be due to a nonhomogeneous population of PE patients with different etiopathogenetic factors. More studies are required to confirm these data and to answer this question.

KEY WORDS: Premature ejaculation; Pelvic floor; Awareness; Etiology.

Submitted 10 December 2011; Accepted 31 March 2012

INTRODUCTION

Although both biologic and psychological factors are considered important in the etiology, the exact etiopathogenesis of premature ejaculation (PE) (1-15) remains to be clarified. The difficulty in achieving the correct identification of etiologic factors could be due to the fact that the role of the pelvic floor muscles (PFMs) in the voluntary control of ejaculatory reflex has not been clearly elucidated (16, 17).

The role of the PFMs has often been reported as necessary to inhibit the ejaculatory reflex as in the mechanism of urinary and faecal incontinence (16, 18-22). Various papers have appeared recently related to investigations in which the inhibitory effects of the contraction of the pelvic floor in the micturition reflex have been observed and evaluated, especially in relation to symptoms from bladder hyperactivity (23, 24). Pelvic floor exercises and biofeedback rehabilitation were reported to be useful in strengthening this inhibitory method and improving the quality of life of patients (25). The inhibitory impulses activated with pelvic floor contraction could exert this effect even on the ejaculatory reflex because it occurs in the inhibition of the micturition reflex, and the two have pathways and centres in common (Onuf's nucleus) (26). An indirect sign of such a role could also reside in the effect of the rehabilitation of the pelvic floor in PE patients (19), although the intimate mechanisms at the base of these results remain to be elu-

cidated. If we assume these muscles are necessary to achieve inhibition of the ejaculatory reflex, it is mandatory before using them correctly that men be aware of the need to activate these muscles. Thus it is reasonable to say that in some cases PE occurs not only because there is a precocity of the arrival of the ejaculation reflex but also because some men do not use these muscles correctly. Should this be the case, it indirectly supports the hypothesis that PFM contraction plays one of the decisive factors in the control of ejaculatory reflex. The aim of the present study was to measure the prevalence among PE and non-PE subjects of the awareness of the role and use of PFM contraction in the control of the ejaculatory reflex.

Materials and methods

During a campaign for andrologic prevention, various men who had come in for a checkup were recruited for this non interventional observational study. The study design and the recruitment of patients followed local ethical committee rules for non pharmacologic, non interventional observational studies. The procedures performed, such as digital rectal examination, were included in the clinical routine practice for those who required andrologic or urologic consultation. All of the patients gave their written consent to participate in the study. All of the patients were given the International Index of Erectile Function (IIEF)-5 questionnaire (27), the Premature Ejaculation Diagnostic Tool (PEDT) (28), and various questionnaires regarding their state of health. The patients were considered to have long-time PE based on two criteria. The first was a clinical criterion where the diagnosis was derived from the medical history and the definition of PE from the ISSM (29), in which PE is defined as "*a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy*".
The second criterion was derived from the PEDT test (28), a five-item tool developed to diagnose the presence or absence of PE. Subjects with a score = 8 were considered to be without PE; those with a score of 9 and 10 were considered as having a probable diagnosis of PE. Those with a score = 11 were considered as having PE.

Definition of a patient with erectile dysfunction

All of the subjects with a score < 21 on the IIEF-5 were defined as affected by erectile dysfunction (ED). Criteria for inclusion included age between 18 and 69 yr and normal erectile function with a score > 21 on the IIEF-5 test. Criteria for exclusion included men with ED, men who had undergone surgery for the prostate or penis, men who use antidepressants, men previously treated with rehabilitation of the pelvic floor, men with a history of neuromuscular disorders, and those whose native language was not Italian.

Description of the Awareness Test

The first problem we encountered when constructing this test was that most people do not know of the existence of the muscles of the pelvic floor even if they utilize them to block their urinary flow and their ejaculatory reflex. Thus the goal of the first stage of the test was to raise each participant's awareness of the existence of the muscles of the pelvic floor through digital rectal examination and when asking to contract these muscles. To avoid influencing participants in their answer following the questionnaire, they were also asked to contract other groups of muscles. On completing the checkup, the participant was asked if he was aware that the muscles of the pelvic floor must be contracted to inhibit the ejaculatory reflex. The test was carried out as follows. The patient was asked to lie down and focus his attention on various muscles. The examining physician indicated and touched various groups of muscles and then asked the patient to contract them. In sequence the physician touched and asked the patient to contract the abdominal, thigh and gluteus muscles, and the muscles of the pelvic floor. At the time of the digital rectal examination the physician placed one hand on the patient's abdomen to verify if an abdominal contraction occurred and asked the patient to contract selectively the muscles of the pelvic floor. At the end of the examination the physician distributed a questionnaire with this question: "*What are the muscles that you utilize to delay ejaculation?*" with the following choices of answers:
1. Abdominal muscles 2. Thigh muscles 3. The muscles within the anus or the muscles of the so-called pelvic floor 4. The gluteus muscles 5. Other (specify) 6. Do not know.
The subjects that chose the wrong answer and did not indicate response number 3 were considered to be unaware that to control the ejaculatory reflex it is necessary to contract the muscles of the pelvic floor.

Validation of the Awareness Test

Content validation

To validate the content and the comprehensibility of the questionnaire, three focus groups were organized according to the Morgan technique (30) with subjects without PE (10 subjects), with PE (10 subjects), and with and without PE. Twenty "*one-on-one*" in-depth interviews were carried out with 10 patients with PE and 10 without PE. During the interviews and the focus groups, it clearly emerged that only after the checkup with the digital rectal examination and the request to contract the muscles was the question and the test understood by all the subjects. This was obvious because the question could not be understood if the men are not aware of the existence of the contraction of the pelvic floor. During the interviews and the focus groups, the moderators used interview guides that included open-ended questions on the following topics: general comments or concerns regarding PE, development and experience of PE for the male partner, emotional distress and the impact of PE, partner communication about PE, PE effect on physical and emotional intimacy with their partners, impact of PE on the overall partner relationship, and characteristics of a successful treatment for PE and coping strategies and awareness of the role of the pelvic floor in the control of the ejaculation reflex. The participants (all with Italian as their native language) were asked to discuss their understanding of each question and what they thought about when choosing a response. The questionnaire was then validated for the comprehensive-

ness of the questions according to the techniques of Converse and Presser (31). Thus, in the discussion of the focus groups, all participants were in agreement concerning the meaning of the questions, and there were no misunderstandings regarding possible answers. All participants then received an evaluation scale from 0 to 100 in which they expressed their degree of comprehension and univocal interpretation of the questions listed in the questionnaire (32). A value of 0 meant the question was absolutely incomprehensible or could be interpreted in more than one way, whereas 100 meant the question was clearly comprehensible and could be interpreted in only one way. All questions on the questionnaire that had not been assigned a minimum score > 90 were eliminated or rewritten on the basis of the agreement reached by the participants of the focus groups.

Formulation of the question

During the interview various open questions were formulated: What do you do to delay ejaculation? And these two questions were posed after the checkup:

A. Which muscles do you use in order to delay ejaculation? (1) abdominal muscles, (2) thigh muscles, (3) the muscles within the anus or so-called elevator muscle of the anus, (4) gluteus muscles, (5) other (specify), (6) do not know.

B. Which muscles should be utilized to delay ejaculation? (1) abdominal muscles, (2) thigh muscles, (3) the muscles within the anus or so-called pelvic floor, (4) gluteus muscles, (5) other (specify), (6) do not know.

In practice, before the checkup, none of the participants answered indicating the contraction of the muscles of the pelvic floor, and the answers to the two questions were inconclusive. Therefore, we decided to simplify by only asking question A.

Results

A total of 117 subjects were recruited. Utilizing the clinical criteria of PE, 44 subjects had PE and 73 did not. According to the PEDT test, 31 subjects had PE, 8 subjects had a probable PE score, and 68 subjects did not have PE. The age of the subjects in the three groups was not statistically different, and the three groups were distributed as follows: group with PE, average age 46 yr (range: 18-69); group with probable PE, average age 44 yr (range: 21-67); and group without PE, average age 46 yr (range: 18-69). Using the clinical diagnosis of PE, only 3 of 44 (6.8%) of men with PE who responded correctly to question A were aware that to control the ejaculatory reflex it is necessary to contract the pelvic floor. In contrast, among non-PE men, 60 of 73 (82%) were aware (Fisher exact test $p < 0.00001$). The test has an 86% accuracy, 95% sensibility, and 82% specificity, and > 95% negative predictive value in discriminating PE from non-PE patients (Table 1). Utilizing the PEDT test for the diagnosis of PE, among the subjects with PE only 2 of 31 (9.6%) gave the correct response, whereas of those who had a probable PE score, only 1 of 8 (12.5%) gave the correct response. In the group of subjects without PE and with a score < 8 for the PEDT test, 61 of 78 (78%) gave the correct response (Table 2). Using the

Table 1.

Distribution of subjects with PE ad without PE according to the Awareness test.
Subjects aware are those subjects that know that in order to inhibit or delay ejaculation it is necessary to contract the PFM.
Test Fisher exact's test p < 0.00001.

		P.E.	Non P.E.	
Awareness Test	Not Aware	41 (93.1)	13 (17.8%)	
	Aware	3 (6.8%)	60 (82.1)	
				117
Accuracy	86%	95% C.L.	0.8%	0.93%
Sensibility	93%	95% C.L.	0.89%	0.98%
Specificity	82%	95% C:L.	0.75%	0.89%
Positive predictive value	76%	95% C.L.	0.64%	0.84%
Negative predictive value	95%	95% C.L.	0.91%	0,99

Table 2.

Awareness Test agreement with Premature Ejaculation Diagnostic Tool (PEDT).
Subjects aware are those subjects that know that in order to inhibit or delay ejaculation it is necessary to contract the PFM.
In this table subjects with Premature Ejaculation (PE) and subjects with probable PE are grouped together.
The agreement rate is 81% with Cohen's K 62% p < 0.00001.

		P.E.	Probable P.E.	Non P.E.	
	Not Aware	29	7	17	53
PEDT	Aware	2	1	61	64
		31	8	78	117

Cohen test and uniting both patients with PE and with a dubious score, a $p < 0.00001$ was obtained that was statistically significant.

Discussion

Most PE subjects do not use PFM contraction to control ejaculation, and the lack of awareness necessary to contract the muscles of the pelvic floor to control the ejaculatory reflex is significantly associated with PE patients. Although this observation is addressed to clarify the etiologic factors of PE, this association also raises the question whether it is extremely difficult to define PE as such or to find effective treatment (1, 29, 33-36) purely because we could only include in our sample three different kinds of patients.
In fact, according to this hypothetical etiological factor, we could have these types of patients:

1. Patients in whom there is a precocious ejaculatory stimulus.
2. Patients in whom ejaculation occurs before it is necessary, just because patients are not aware of what to do at the right moment.
3. Patients who are not able to perform the correct movement to delay the ejaculation reflex.

Should this be the case, the concept of PE definition, healing, or improvement would be different in this non homogeneous population. This can change the routine clinical practice because only patients in group 1 and 3 are suitable for pharmacologic treatment, whereas those in group 2 only need to be informed and trained to use the PFMs. More data and more observation are required. Nevertheless, it is important to have found a difference between PE and non-PE subjects because this observation supports our hypothesis and does not
contradict it. If the relationship between unawareness and nonuse of PFMs in PE subjects is found to have a cause-and-effect relationship, the animal model for the study of PE in some cases could limit some of the research applied to PE because it is not possible to investigate those variables linked to the awareness and use of the pelvic floor. Naturally, it can be argued whether we are in the presence of a fact that is simply associative or if the nonuse and non awareness is a causal fact. Although it is to early to draw such conclusions, it can be helpful to remind us in this regard that in one study (19) on the rehabilitation of the pelvic floor on PE subjects, it was observed that approximately 60% of subjects were cured with such therapy, but this observation has not been replicated.
Finally, there is yet another aspect that could be significantly influenced by this observation because it could decrease the prevalence of PE: Educational programs on sexual health for adolescents should include learning to contract the pelvic floor in the control of the ejaculatory reflex (37, 38).
This study has various limits. First, patients were not differentiated on a temporal basis but solely on the basis of clinical and PEDT tests that discriminate patients with PE from those without it. Therefore, if affected by a so-called lifelong PE or an acquired ejaculation, this could result in a potential bias. Nevertheless this potential bias should be minimal in this study because from a clinical viewpoint, historically only 4 of 44 patients present with an acquired PE.
The second aspect, which in our opinion deserves a further in-depth study, is the fact that the tone of the contraction of the pelvic floor was not measured. Hence it is not possible to identify patients with hypotone, hypertone, or an inversion of command that we already know from urinary and faecal incontinence does exist in the population.
A future study could give us a better understanding of which patients are truly unaware from those that are unaware because they are unable to contract the pelvic floor adequately.
Finally, this observation on the awareness of the role of pelvic floor has a temporal limit because it has value only at this time when this type of information is not available to all men. In fact, it is possible to assume that within a few decades when sexual health education is taught in schools, this unawareness will no longer be an issue because all boys will be taught to contract the muscles of the pelvic floor. At the moment it is not possible to evaluate the duration of this temporal limit; in any case, we believe it is reasonable to predict that the diffusion of an andrologic culture will require at least a few decades before it becomes common knowledge.

Conclusions

The prevalence of the use and awareness of the role of the contraction of PFMs in the control of ejaculatory reflex in non-PE subjects is significantly higher than in PE subjects in agreement with the assumption that PFM contraction plays a decisive role in the delay of ejaculation. This observation can elucidate the possible etiologic factors of PE, raising the question of whether the difficulties in PE definition and in finding effective PE therapies could be due to a non homogeneous population of PE patients with different etiopathogenetic factors. Further studies are required to confirm this observation and answer this question.

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Correspondence

Giuseppe La Pera, MD
Dept. of Urology
San Camillo - Forlanini Hospital
Circonvallazione Gianicolense 87 - 00152 Rome, Italy
lapera@libero.it

ORIGINAL PAPER

(Micro)surgical and percutaneous procedures in the management of varicocele: 25 years of experience

Gianni Ughi, Lucio Dell'Atti, Consuelo Ricci, Giovanni Pietro Daniele

Urology Unit, Arcispedale "S. Anna", Ferrara, Italy.

Summary

Background: *The effectiveness of different procedures for varicocele varies in terms of recurrence, sperm-count improvement, pregnancies and deliveries.*
Objectives: *To determine if microsurgical varicocelectomy plus antegrade sclerotherapy under local anaesthesia is the first choice surgical modality to treat this disease.*
Methods: *Since 1983 out of more than 1000 patients treated for primitive varicocele, we considered 800 patients with a follow-up of two years. Out of them 195 underwent a "standard" surgical procedure, 280 received a percutaneous sclerotherapy and 325 were managed microsurgically. Out of the last group, the first 90 cases were operated by microsurgical technique alone, while the remaining were offered microsurgery plus antegrade sclerotherapy.*
Results: *Traditional surgery had the higher incidence of relapse whereas percutaneous sclerotherapy needed use of Gianturco's coil to minimize relapses. Microsurgical technique plus antegrade sclerotherapy had the lower incidence of failures.*
Conclusions: *An extensive experience through the years led us to consider microsurgery plus sclerotherapy as the first choice treatment for varicocele.*

KEY WORDS: *Varicocele; Microsurgery; Infertility.*

Submitted 21 November 2011; Accepted 31 March 2012

INTRODUCTION

Varicocele is defined as the varicosity of the veins in the pampiniform plexus. This results from retrograde blood flow into the spermatic veins and is a common cause of male infertility (1). Sperm count; sperm mobility and normal cells can improve after correction of varicocele (2, 3).

MATERIALS AND METHODS

Since 1983 out of more than 1000 patients treated for primitive varicocele, we considered 800 patients with a follow-up of two years (4). Age ranged between 11 and 46 years (median 24). We performed the procedure on patient's demand but we recommended it in presence of symptoms (pain, hypotrophy of the testicle), in cases of couple infertility when FSH was less than double the normal value or in couples undergoing intrauterine insemination and – in case of persistence – if any pain persisted or sperm count did not improve.
All the patients underwent physical examination, color Doppler sonography of the spermatic cord and scrotal ultrasound (in order to disclose possible associated diseases and determine testicular diameters) (Table 1).
Hormonal assessment and sperm culture were performed if necessary.
All patients underwent sperm count and Doppler examination 3, 6, 12 and 24 months postoperatively (Table 2).
We treated 195 patients with conventional open surgery, initially by the surgical technique proposed by Ivanissevich (5) and subsequently by the inguinal ligature. Such procedures required the patient under general or spinal anaesthesia, with a mean hospital stay of 2 days.
Afterwards we treated 280 patients by percutaneous sclerotherapy (6-7). According to the Seldinger's technique, a catheter was placed into the involved spermatic vein: a 3% solution of Polidocanol (about 4 ml.) was injected and sometimes a Gianturco's coil was inserted (dramatically improving recurrence rate) (Figure 1). This procedure requires a local anaesthesia and a few hours hospi-

Table 1.

Clinical classification.

Subclinic	G I	G II	G III
1.6%	8.3%	66.5%	23.5%

Table 2.

Side localization of varicocele.

Left side	Bilateral	Right side
80.25%	19%	0.75%

tal stay. Using such a radiological technique, in 3.22% of the cases – for anatomical reasons – the catheter could not be advanced in the spermatic vein (8) and the patients had to be operated. The transfemoral approach is a very demanding manoeuvre on the right side and for this reason this approach was avoided for bilateral primitive varicocele, usually best managed by microsurgery. On the other hand, sclerotherapy (in our opinion plus Gianturco's coil insertion) is mandatory to treat recurrences in that it allows either to diagnose the refluxing vein (which gives rise to the recurrence itself) and to correct the reflux at the same time.

Figure 1.

Percutaneous sclerotherapy is performed and Gianturco's coils are inserted.

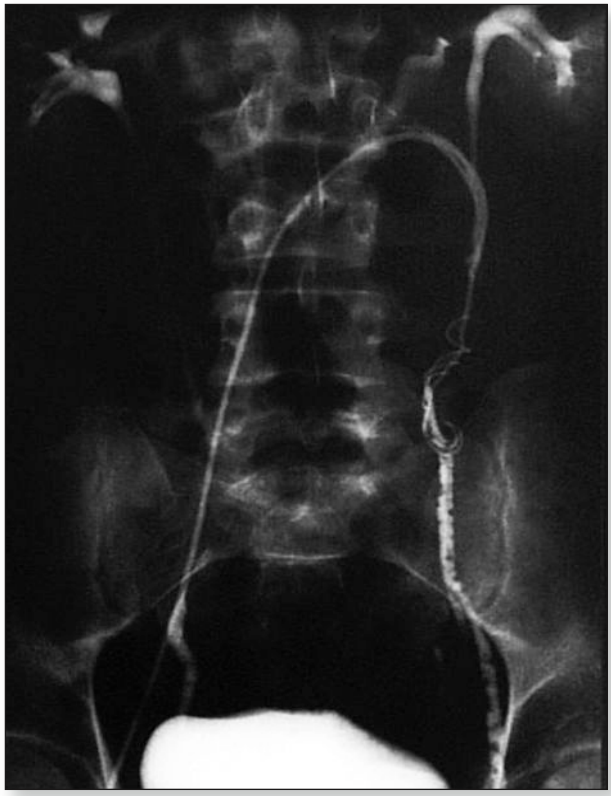


Figure 2.

Small skin incision (in this case 18 mm-long)..

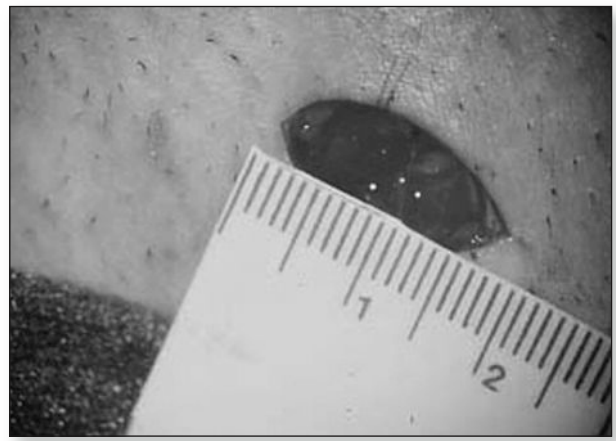
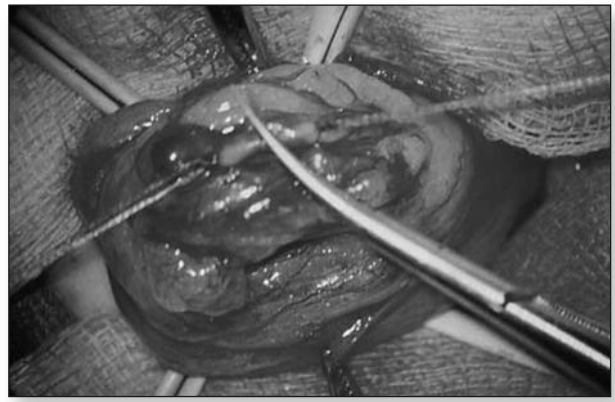


Figure 3.

Veins are ligated and divided, others structures preserved.



Since 1990, we performed the ligation and section of the spermatic vein at a lower inguinal level, using a microsurgical technique (9) in 325 cases.

Through an about 2 cm. long (Figure 2) cutaneous inguinal incision (10) the spermatic cord was isolated without opening the inguinal canal. All varicose veins were legated and divided (Figure 3) step by step after other structures (arteries, nerves, vas deferens and lymphatic vessels) have been identified. Sometimes the deferential and/or cremasteric veins (Figure 4) were coagulated, if varicose, after being dissected free from the artery. Also the periarterial plexus of thin veins were not preserved because if left intact they may dilate and cause recurrence. After the initial 90 cases, we performed in adjunct an antegrade injection of Polidocanol 3% solution (3 to 4 ml.) (Figure 5).

Length of operation was 28 to 58 minutes in relation to number of veins. The microsurgical technique was also used in cases of bilateral localization with slight lengthening of the operating time (up to 80 minutes) and same hospital stay of monolateral ones. No complications are observed.

Figure 4.

Cremasteric vein is ligated if varicose.

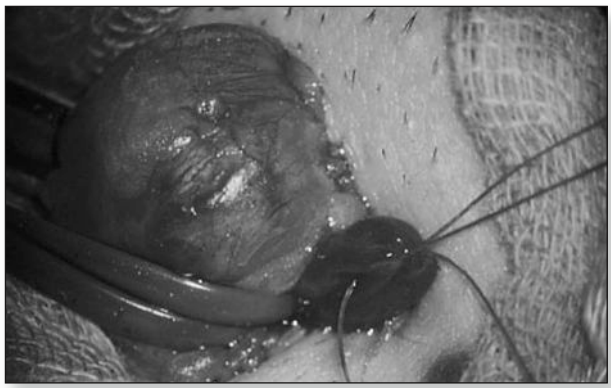
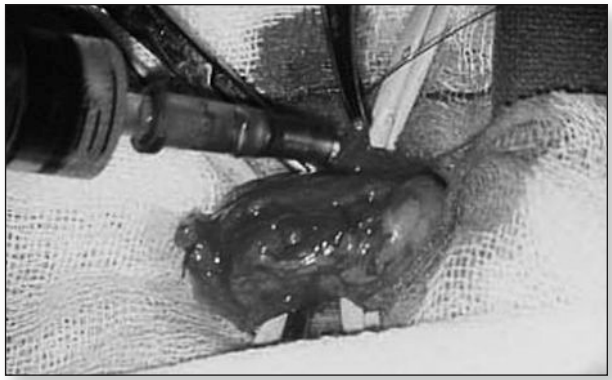


Figure 5.

Polidocanol 3% (up to 4 cc.) is injected to perform antegrade sclerotherapy.



Both local anaesthesia and microsurgical technique enable us to admit and discharge the patient from the hospital the very same day of the operation (Table 3).
We tried some anastomoses between the epigastric vein and a branch of the pampiniform plexus, but shortly we abandoned this approach due to the poor results obtained in the adult patients (16).
Despite a fair experience with laparoscopic surgery we used this approach just once, treating a varicocele during a cholecystectomy. In fact laparoscopic varicocelectomy requires general anaesthesia, several cutaneous ports, expensive equipment and an adequate training. Moreover, complications are to be considered, while other methods are safe, at least in adults (at our institution we do not have a large experience on treating paediatric patients) (17).
Recurrences could be successfully treated by microsurgery plus antegrade sclerotherapy (11) but we preferred percutaneous retrograde sclerotherapy (12-13) or Tauber's technique (14) without phlebography (15) in order to avoid any radiogenic exposure. No erroneous vascular accesses was registered. The minimum follow-up after treatment was two years.

Results

After the surgical procedure by the Ivanissevich technique we observed an high percentage of recurrences (18% or more) and after inguinal ligature up to 11% of persistence and hydrocele in 2 % of cases.
With percutaneous sclerotherapy we observed recurrences in 3.6% of the cases, hydrocele in two cases and epididymitis in one
We observed recurrences (Figure 6) in 6.6% of microsurgically treated cases, and in 3.8% of 235 patients who undergone microsurgery plus antegrade sclerotherapy.
No major complication was recorded.

Figure 6.

Collateral vessels are identified after ligation of a main vein: this is quite important to avoid relapses.

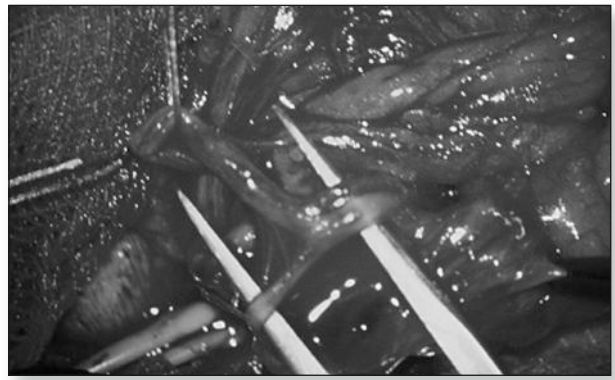


Table 3.

Techniques used in treatment of varicocele.

Type	Patients	Recurrences	Technical failure	Radiation	Sclerotization	Embolization
Surgery	195	11%	No	No	No	No
PSE	280	3.6%	3.22%	Yes	Yes	Yes
MS	90	6.61%	No	No	No	No
MS+AS	235	3.83%	No	No	Yes	No

Surgery = traditional surgery; PSE = percutaneous sclero-embolization; MS = microsurgical; MS+AS = microsurgical plus antegrade sclerotization

Table 4.

Pregnancy rates.

Pathology-Disease	Operated	Pregnancy after operation alome	Pregnancy after operation and assisted fecondation
Varicocele	64	29.6%	
Varicocele and female genital problems	36	2.7% (1 case)	30.5%

The impact of several therapeutic options on the sperm count or on pregnancy rate was similar, with no statistically significative differences. In 83% of the patients semen parameters improved, mainly in number and mobility. In infertile couples whose men received a treatment for varicocele the pregnancy rate was about 32% (18-19) although our study considered just carried-through pregnancies.

Due to a low mean age (23 years) our series can't provide a reliable cumulative pregnancy rate: in fact some patients will procreate 15-20 years after the procedure and will be lost at follow-up.

Therefore, we considered 100 consecutives patients willing a pregnancy in a short while excluding those whose partner had gynaecological problems (Table 4).

These patients operated on with the aim to procreate in a brief time frame, presented a 29.6% pregnancy rate if their partners had no gynaecological problems. On the other hand (20) female partners with gynaecological problems who undergone to artificial insemination with different methods obtained regular pregnancies in 11 out of 36 cases (30.5%). In this group, the operation alone warranted pregnancy in one case (2.7%). We did not treat our patients with hormones (FSH) after surgery.

Conclusions

Traditional surgery demonstrated the higher incidence of relapses. Percutaneous sclerotherapy required Gianturco's coil or an alternative method for embolization to minimize relapses. Laparoscopy is too invasive in comparison to either options, is very expensive and requires appropriate surgical skills. Microsurgical technique plus antegrade sclerotherapy presented the lowest incidence of failures. Therefore after an extensive experience with 800 patients treated and followed up for at least two years, we consider microsurgical varicocelectomy plus antegrade sclerotherapy under local anaesthesia (21) as the first choice surgical modality to treat this disease.

Acknowledgements

We want to thank *Roberto Galeotti MD*, Interventional Radiologist, that performed the majority of percutaneous sclerotherapy.

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Correspondence

Gianni Ughi, MD
Via Pomposa, 94 - 44123 Ferrara, Italy
gianniughi@ospfe.it

Lucio Dell'Atti, MD
U.O. Urologia - Azienda Osp.-Univ. Arcispedale "S. Anna"
Cors. Giovecca 203 - 44100 Ferrara, Italy
dellatti@hotmail.com

Consuelo Ricci, MD
U.O. Urologia - Azienda Osp.-Univ. Arcispedale "S. Anna"
Cors. Giovecca 203 - 44100 Ferrara, Italy
urologia@ospfe.it

Giovanni Pietro Daniele, MD
U.O. Urologia - Azienda Osp.-Univ. Arcispedale "S. Anna"
Cors. Giovecca 203 - 44100 Ferrara, Italy
gpdan@hotmail.com

ORIGINAL PAPER

Corporoplasty for induratio penis plastica with soft axial tutors, single relaxing albugineal incision and safenous grafting. A 3-year follow up

Mauro Silvani [1], Stefano Pecoraro [2], Alessandro Zucchi [3]

[1] Department of Urology ASLBI Hospitals Infermi Biella, Italy;
[2] Department of Urology & Andrology Clinica "Malzoni", Avellino, Italy;
[3] Urological and Andrological Clinic University of Perugia, Italy.

Summary

Objectives: *Etiological and pathogenic mechanisms of Peyronie's disease (PPI) are today better known than in the past, but till now therapeutic options are not completely satisfactory. In fact several therapeutic alternatives were suggested, but none demonstrated its superiority. Surgery is the preferred option in chronic stable disease with the following goals: penile straightening, penile lengthening and recovery of penetrative coital activity. Aim of this paper was to present a personal experience with modifications of the original surgical technique.*

Materials and Methods: *From September 2005 to December 2008, a total of 58 patients (mean age 44.7 years) underwent corrective penile surgery for PPI. All patients had a single plaque with dimensions ranging 1.2-2.6 cm in length. Simple dorsal recurvatum > 50° was observed in 38 patients, dorsolateral left recurvatum > 45° in 8, ventral recurvatum > 40° in 6, lateral left recurvatum > 45° in 4, dorsolateral right recurvatum > 45° in 2. Forty patients were implanted with a 7 F Virilis II prosthesis, 7 with a 7 F Virilis I, 8 with 10 F Virilis I and 3 with 9.5 F SSDA prosthesis. Implanted tutor length ranged between 16.6 and 20 cm, measuring from crura to corpora apex. In 46 patients we implanted a safena graft and in 12 with recurvatum > 60° we used bovine pericardial collagen patch (Veritas - Hydrix).*

Results: *At long term follow up (1-3 years) we observed a penile elongation from 1.2 to 2.3 cm with complete correction of penile recurvatum in all the patients. After 12-36 months excellent penetrative sexual activity was referred by 75% of the patients, satisfactory in 20% and disappointing in 5%. Major complaints were "cool glans" feeling, delayed ejaculation, unnatural penis appearance due to permanent hyperextension. None developed lower urinary tract symptoms.*

Conclusions: *According to such results, the described technique should be considered as a gold standard for all cases of PPI associated to recurvatum > 35-40° (lateral, ventral and dorsal) associated to a plaque with mild-moderate erectile dysfunction.*

KEY WORDS: *Recurvatum; Peyronie' s disease; Venous graft; Penile prosthesis.*

Submitted 17 February 2011; Accepted 30 September 2011

INTRODUCTION

About 0.3-2% of men are affected by Peyronie's disease (PPI), involving relevant physical and psychological problems (1). Medical therapy has the only role to try to slow down or to stop the development of fibrous plaques, from the first clinical acute inflammatory phase to the chronic fibrotic evolution of the sub albugineal fascia. PPI has an irregular but slow clinic evolution, alternating acute episodes ("*pousseè*") to apparent relief. Medical therapy is recommended in patients in the early phase of the illness characterized by unstable progressive plaque and painful erections or in patients refusing surgery or with concomitant clinical controindications.

However shared protocols for conservative therapy of PPI are completely lacking and no standardized therapy is defined.

Clinically we can recognize two separate phases of illness: active (clinical duration of about 12-18 months, accompanied with painful erections and sometimes asso-

ciated to recurvatum) and chronic (frequent erectile dysfunction, presence of recurvatum, progressive shortening of the penis length, rarely evolving to a micropenis). The main pathological characteristic of the chronic disease is the plaque. Surgery is the preferred option in chronic stable disease, by which we try to reach the following goals: penile straightening, penile lengthening, recovery of penetrative coital activity.

Several surgical options are proposed for PPI correction. Plaque surgery is preferred in case of.stabilized disease, solitary plaque non involving erectile structure and good erectile rigidity.

Techniques for recurvatum correction with albuginea shortening (Nesbit or Yachia procedure) (2, 3) are considered as "*minimal*" surgical procedures, but cosmetic results are often unsatisfactory. Reduction of penis length is proportional to the recurvatum degree and can be calculated measuring the difference between the longest and the shortest curve of the penis in complete erection. These techniques are widely used because are easy to perform and usually are reserved to patients with lateral or ventral recurvatum not over 35/40° and with sufficient length of the penis or to aged patients with co-morbidity that are not suitable for more complex surgery in order to avoid major complications (4).

A possible advantage related to such corporoplasties is related to the possible diminution of corpora cavernosa volume, as consequence of penis shortening, that sometimes is followed by improved sexual performance.

Excision techniques are abandoned by now due to well known functional sequelae (5), a relaxing incision is preferred with an autologous graft or eterologous patch (6-8). Between several techniques, Paulo Egydio's geometrical corporoplasty (9) followed by the implant of a collagen pericardial bovine patch represents a complicated procedure, because it needs accurate measurements of the erected penis to evaluate an adequate tailoring of the patch. Erection is obtained by PGE 1 intracavernous injection, as preferable alternative to the usual hydraulic maneuver. On the other hand this kind of erection can modify the linear forces of the penis sometimes causing inadequate measuring of the size of the patch.

Plaque surgery can be associated to prosthesis implant. For patients with recurvatum and severe erectile dysfunction (ED) inflatable prosthesis can be implanted after plaque incision and heterologous patch grafting or after simple plaque incision (Wilson's maneuver without cavernous grafting) (10-13).

In patients with recurvatum associated with mild-moderate erectile dysfunction the surgical positioning of small caliber soft axial penile tutors, associated to plaque incision and saphenous autologous grafting is preferable. In particular, Austoni's surgical technique was widely popularized in Italy and now is often adopted in several Italian andro-urological departments. Aim of this paper was to present our personal experience with modifications of the original Austoni's surgical technique (8).

Surgical technique

The main steps of the original surgical procedure were: mini-invasive implant of soft axial penile prosthesis (9-10 mm in caliber) 2 cm longer than corpora cavernosa to make more evident the recurvatum location; single-step corpora cavernosa calibration by 10 F Hegar dilator in order to spare as much possible of cavernous tissue; relaxing incision of tonaca albuginea on the guide of the soft prosthetic support to save the erectile tissue (inci-

Figure 1.

Inguinal incision for taking saphenous vein at cross

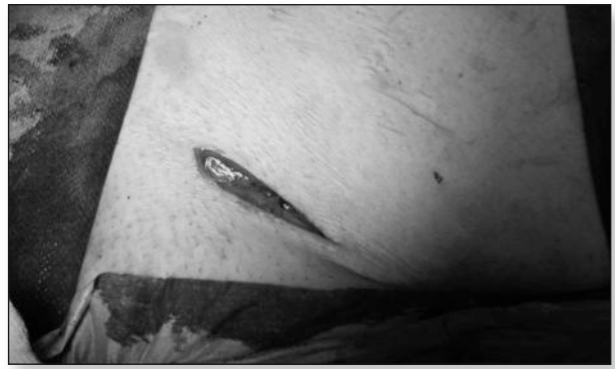


Figure 2.

Grafting of saphenous vein taken from the cross.

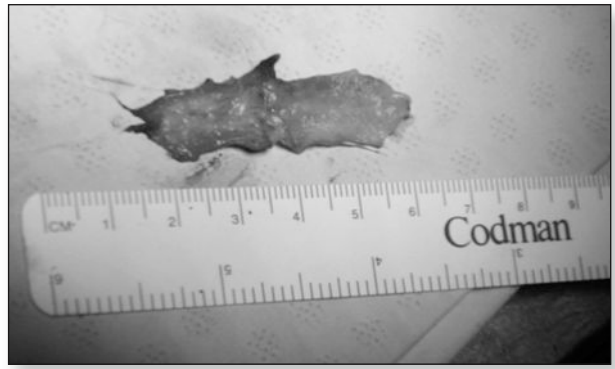


Figure 3.

Saphenous graft adapted to the tunica albuginea. Perfect consistency of the saphenous graft to the defect of substance after plaque incision.

Figure 4.

Anastomosis of the saphenous graft to the tunica albuginea.

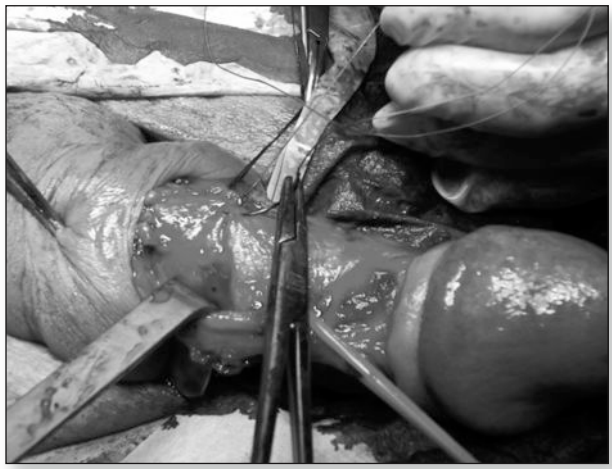
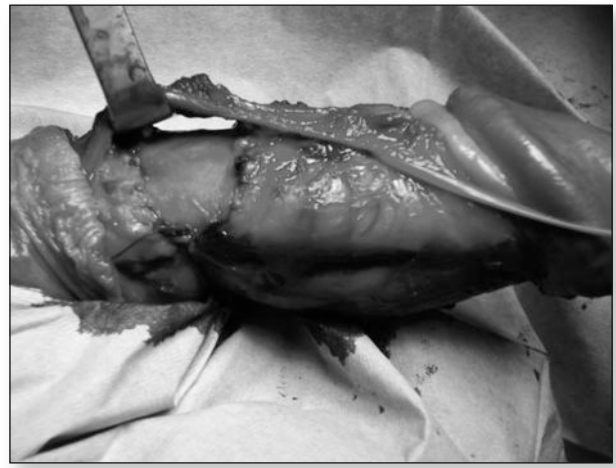


Figure 5.

Saphenous vein graft anastomosed to the tunica albuginea.



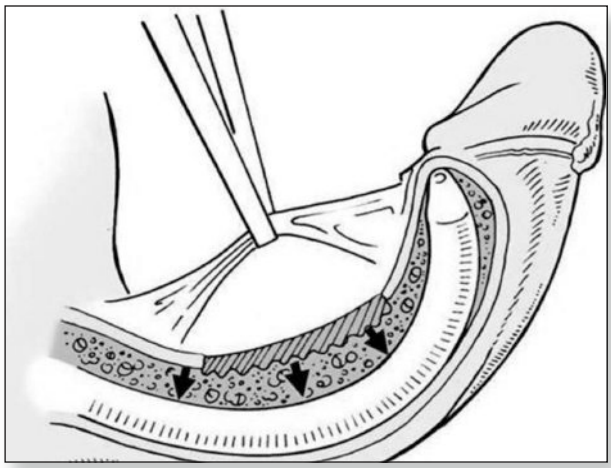
sion should create a para urethral acute angle lozenge, having the main extension on the concavity of albuginea); covering of the lozenge with saphenous graft taken at the cross (a very small graft can cover a wide albuginea defect, thanks the elastic characteristic of the vein patch); saphenous-albugineal suturing by 3/0 monothread running suture; circumcision performed at the end of surgery; positioning of a vacuum sub dartoic drainage; restraining non-compressive bandage to allow serum and blood discharge and promote nocturnal erections.

Compared with this classical surgical technique the following modifications were adopted in the present series:

1) use of smaller 7 F soft axial implant with different rigidity aiming to spare as much as possible the surrounding erectile tissue, to promote easy penetration and to hide as more as possible the presence of the prosthesis;
2) reduction of implant length limiting at no more than 1 cm over corpus cavernosum length in order to prevent tension that can cause alterations in vascular supply and the risk of necrosis especially to the glans (in consideration to the often difficult and incomplete dissection of the vascular nervous bundle that in PPI patients is often involved in albugineal fibrosis) and to avoid a permanent erection of the penis;
3) plaque excision by a 11 blade scalpel with magnification loops to optimize the sparing of erectile tissue;
4) in case of recurvatum over 60 degrees use of bovine pericardium collagen patch, instead of saphenous autologous graft (in consideration that severe curvature may need wider lozenges, not so easy to cover with a single saphenous graft.

Figure 6.

Incision of the tunica albuginea at the point of maximum curvature. Tutor of at least 1 cm longer than the cc to highlight the recurvatum.
(Kind concession Prof. E. Austoni by Atlas of reconstructive penile surgery, Pacini Editore).

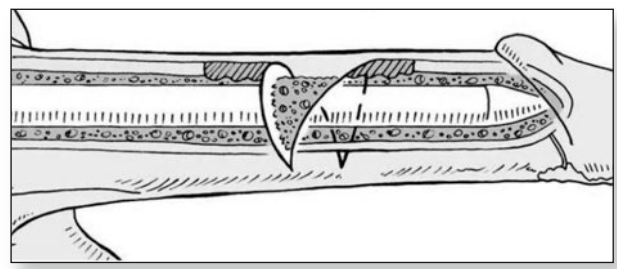


The patch in use (Hydrix) presents peculiar characteristics of handling and softness. Only 72 hours after positioning, the patch is inosculated in the host tissues and after three months it is not possible to distinguish it from the original albuginea fascia.

The described technique can be used in different types of recurvatum: dorsal, dorsolateral in right or left side, lateral and ventral. In the case of pure lateral recurvatum the length of the two tutors has to be the same for each

Figure 7.

Elongation of the shaft after relaxation incision of the plaque.
(Kind concession Prof. E. Austoni by Atlas of reconstructive penile surgery, Pacini Editore).



corpus cavernosum; dissection of the bundle must be very careful from a para-urethral incision of Buck's fascia in the curvature site to the lateral side of the opposite corpus; urethra has to be isolated from the plate in the side of recurvatum; albuginea incision must be performed involving the corpus cavernosum affected by recurvatum on both dorsal and ventral side in a semicircular shape from 12 to 6 o'clock to allow an adequate positioning of the patch or graft with complete correction of lateral recurvatum. Ventral recurvatum is the more complex condition requiring an accurate dissection of the bundle and mobilization of the urethra in the site of recurvatum. A wide bundle dissection in the opposite side of recurvatum is suggested in order to permit a mild hypercorrection of the recurvatum. A meticulous dissection of the urethra from the ventral plate of corpora cavernosa is required to avoid excessive manipulations and risk of devascularization of the glans and damage of the urethral blood supply.

Materials and Methods

From September 2005 to December 2008, a total of 58 patients (mean age 44.7 years) underwent corrective penile surgery by the previously described surgical technique.

Sexual activity was completely preserved in only 12 patients who presented several risk factors for erectile dysfunction, as hypertension in pharmacological treatment and severe hypercholesterolemia. Six of them were strong smokers. The remaining 46 patients were affected by mild or moderate erectile dysfunction. Six of them had diabetes in oral therapy, although in good metabolic control.

Pre-operative examination included: penile dynamic echo color Doppler, photographic evaluation of penile recurvatum, penile dynamic magnetic resonance (10 patients), serum free and total PSA, uroflowmetry, renal and bladder sonography, IIEF 5 questionnaire, SEP2 and SEP3. Psycosexuological evaluation was also performed to investigate possible couple problems.

All patients had a single plaque with dimensions ranging 1.2-2.6 cm in lenght.

Simple dorsal recurvatum > 50° was observed in 38 patients, dorsolateral left recurvatum > 45° in 8, ventral recurvatum > 40° in 6, lateral left recurvatum > 45° in 4, dorsolateral right recurvatum > 45° in 2.

In all patients preliminary subcoronal degloving was performed and 6 patients had scrotal peri penile incision. Forty patients were implanted with 7 F Virilis II prosthesis, 7 with a 7 F Virilis I, 8 with 10 F Virilis I and 3 with 9.5 F SSDA prosthesis. Implanted prosthesis length ranged between 16.6 and 20 cm , measuring from crura to corpora apex. In 46 patients we implanted a saphenous graft and in 12 with recurvatum > 60° we used bovine pericardial collagen patch (Veritas - Hydrix).

All patients had erectile rehabilitation with iPDE5 from postoperative 15th day with the aim of optimize distal erectile tissue vascularization.

Post operative follow up evaluation was achieved after 15, 30, 60 and 90 days and after 4, 8, 12, 16, 24 and 36 months by IIEF 5, SEP2 and SEP3 administration.

Results

At long term follow up (1-3 years) we observed a penile elongation from 1.2 to 2.3 cm with complete correction of penile recurvatum in all the patients.

Recovery of penetrative sexual activity was achieved after 60 days in 31 patients, after 90 days in 11 and after 120 days in 6. After 4 months penetrative sexual activity was considered satisfactory in 65% of the patients, but disappointing in 35% of cases; after 8 months was considered satisfactory in 75%, and rather satisfactory in 25%; after 12-36 months excellent penetrative sexual activity was referred by 75% of the patients, satisfactory in 20% and disappointing in 5%. Major complaint were "*cool glans*" feeling, delayed ejaculation, unnatural penis appearance due to permanent hyperextension. Eight patients reported use of iPDE5, 3-5 times monthly, to achieve a better erective performance. Twenty-five percent of patients reported usual sexual intercourse with more than a partner and 15% started a new steady relationship with a new partner after marriage separation after 2 years from surgery. None developed lower urinary tract symptoms.

Discussion

The reported results suggest several considerations: respect to the original operative technique the use of small caliber implants ensured a differentiated rigidity and resulted more respectful of the residual cavernous tissue; at 2 months the pseudo-capsule surrounding small caliber implants involved less scarring of the surrounding erectile tissue; use of iPDE5 is mandatory in the 2 months after surgery in order to enhance cavernous endothelial healing and stabilization during the period in which the fibrous pseudo-capsula is developing.

We suggest a measurement of the implant length in order to not exceed cavernous length itself. A difference of 1 cm can be enough to make evident the recurvatum. Longer implants did not obtain an increase of penile length because all the albuginea is often involved in illness that may cause a penile shortening. The neurovascular bundle is often involved in albuginea fibrosis and its dissection is often incomplete and troublesome: an excess of dissection and pulling of the bundle may cause alteration in gland vascularization until necrosis.

Recently Austoni et al propose to implant tutors longer than cavernous corpus, 1 cm more for every 30° of curvature. However an excessive tutor length causes steady erection or semi-erection of the penis, not respecting the original objectives of the technique, which require only an hyperextension of the penis in order to allow an acute angle positioning during erection and make easy penetration. A small percentage of patients referred a "*genital discomfort*" relative to penis hyperextension, considered difficult to hide. In severe recurvatum (more than 50°) is preferable, as alternative to saphenous autologous graft that is often insufficient to an adequate covering of a wide lozenge, to use a bovine pericardial collagen patch with good biocompatibility and flexibility that makes it easier to apply. Complete albuginea tissue absorption is usually very quick and we did not observe scarring after implantation. Furthermore surgical time is reduced and possible complications related to venous excision are avoided.

Conclusions

The surgical technique described is considered a satisfactory option for PPI with recurvatum involving difficulty for penetrative sexual activity, in association or not to mild to moderate ED; it is a technique, quite easy to learn and to perform. The implantation of a support prosthesis preserves penile extension along time, in comparison to other techniques for recurvatum correction. Small soft implants are not really a true prosthesis, because erection is spontaneously obtained by the presence of the residual spared erectile tissue. No manipulation of the prosthesis is requested to achieve an erection, as necessary after implantation of a double or tri- component prosthesis or a semi rigid one.

Surgical alternatives are represented by geometric corporoplasty (Paulo Egydio technique) or hydraulic prosthesis implant associated or not to plaque surgical management. The first technique is difficult to learn and to be reserved to very experienced surgeons and in patients with good erectile performances. On the other hand hydraulic prosthesis implant associated to plaque surgery should be reserved to patients with PII associated to severe ED. Not every patient, however, is psychologically inclined to a procedure involving a definitive modification that transforms erection to a totally artificial act. This aspect has to be carefully defined by psycho-sexual pre-operative counseling, that is mandatory for all patients committed to an andrologic surgical procedure to correct PPI.

Patient worries and expectances are usually focalized on the resolution of recurvatum, that is the most important clinical symptom of the pathology. Often patient underestimate erectile function problems, that are so frequently associated to PPI in relation to veno-occlusive dysfunction correlated to the fibrosis of albuginea.

According to such results and considerations, together with the easy learning of the technique, the described technique should be considered as a gold standard for all cases of PPI associated to recurvatum > 35-40° (lateral, ventral and dorsal) associated to a plaque with mild-moderate erectile dysfunction.

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Correspondence

Mauro Silvani, MD
Department Urology - ASL BI
Ospedale degli Infermi - Biella, Italy
dr.silvani@libero.it

Stefano Pecoraro, MD
Urology & Clinical Andrology Department
Clinica Malzoni, Avellino, Italy

Alessandro Zucchi, MD
Urological and Andrological Clinic - University of Perugia
Perugia, Italy

ORIGINAL PAPER

A prospective observational cohort study on patients with PSA levels ranging from 4 to 10 ng/ml at opportunistic screening: management and responses to ciprofloxacin 1000 mg

Paolo Verze [1], Fabio Parazzini [2], Davide Arcaniolo [1], Sonia Cipriani [2], Vincenzo Mirone [1]

[1] Department of Urology, University of Naples Federico II, Napoli, Italy;
[2] Clinica Ostetrica Ginecologica, Università di Milano, Fondazione IRCCS, Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena, Milano, Italy.

Summary

Objective: *To analyze in the real life clinical setting the effect of fluorchinolones treatment in the management of elevated (4-10 ng/ml) prostate-specific antigen level we conducted an observational prospective cohort study.*

Material and methods: *Eligible for the study were subjects aged 45-75 years with a PSA level 4-10 ng/ml, consecutively observed during their routine practice by first level outpatients urologic centres.*

Results: *A total of 740 patients, mean value of total PSA at study entry: 5.8 (SD = 1.6) entered the study. A total of 616 subjects were treated with ciprofloxacin. The mean serum t-PSA value decreased between study entry and final visit of 1.31 ng/ml (SD 4.19) ($p < 0.05$). At follow up visit the 49.4% (95% CI 44.1-55.5) of patients had PSA level < 4 ng/ml. In comparison with patients with t-PSA < = 5.0 ng/ml, the OR of having normal t-PSA value at follow up were respectively 0.61 (95% CI 0.4-0.9) and 0.23 (0.1-0.3) for patients with t-PSA 5.1-6.2 and ≥ 6.3.*

Conclusion: *The results of this large observational prospective study showed that a 2-3 week course of treatment with ciprofloxacin 1000 mg is able to significantly reduce the PSA level in about 50% of men aged 45-75 years with t-PSA levels of 4-10 ng/ml.*

KEY WORDS: *PSA level; Prospective study; Antimicrobial treatment.*

Submitted 8 February 2012; Accepted 31 March 2012

INTRODUCTION

Despite the lack of definitive evidence regarding its effect on mortality due to prostate cancer (1-3), opportunistic screening of healthy men by prostate-specific antigen (PSA) testing has become a common practice.

Although testing for high PSA levels involves only a blood test, a positive result affects patients both mentally and physically even if a patient elects not to proceed to prostate biopsy (4).

It is worth considering that the three most common prostatic diseases: prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer, can all be associated with elevated serum PSA levels. In particular, microscopic foci of prostatitis may induce a t-PSA increase. Elevated t-PSA levels have been reported in about 60% of patients with acute or chronic bacterial prostatitis (5).

In order to improve PSA specificity, various PSA derivates have been proposed and tested such as PSA velocity, PSA density and %free PSA (fPSA). The fPSA, in particular, takes advantage of the fact that PSA exists in the blood in two fractions: one bound to plasma proteins (complexed) and the other in a free state. Benign prostate tissue contains more free PSA than prostate cancer tissue. Patients with prostate cancer tend to have lower free/total ratios, whereas men with benign disease have higher free/total ratios, except in the case of prostatitis (6).

When elevated total (t) PSA levels are found, indication to

prostate needle biopsy is often given. However it has been found that a large portion of histological specimens from prostate needle biopsies taken from patients with abnormal t-PSA levels do not detect cancer (2). Although the risks of biopsy are small, they are not insignificant: bleeding and infection occur in 1% to 4% of patients (7-9). Several studies have suggested that treatment with antibiotics will decrease PSA by approximately 30% in men whose PSA elevation is due to prostatitis alone (10-11) and fluoroquinolones are considered the drug of choice for bacterial prostatitis therapy (12).

These issues raise the problem of appropriate selection of subjects with elevated t-PSA levels but without concomitant clinical suspicion of prostate cancer who are designated to undergo prostate needle biopsies.

As suggested, the first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardised conditions (i.e. no ejaculation and no manipulations and no urinary tract infections) in the same diagnostic laboratory, using the same methods (13-14).

Considering that the need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious digital rectal examination (DRE), no guidelines are currently available for treatment of patients simply presenting 4-10 ng/ml t-PSA levels at opportunistic screening. To analyse in a real life clinical setting, the the effect of fluorchinolones treatment in the management of elevated (4-10 ng/ml) prostate-specific antigen levels and no other clinical suspicion of prostate cancer, as observed during opportunistic screening, we conducted a prospective observational study.

Methods

This prospective observational study evaluated the management of patients with t-PSA values of 4-10 ng/ml but with no other indications for immediate needle prostatic biopsies in routine clinical practice.

Patients were referred to the study centres by their general practitioners who had tested patients' t-PSA levels within the framework of routinely prescribed opportunistic screening.

Subjects aged 45-75 years with PSA levels ranging from 4 to 10 ng/ml, no clinical suspicions of prostatic cancer and normal rectal examinations were included in the study. Patients were consecutively observed during routine practice in 61 outpatient urologic centres throughout Italy. All patients were affected with chronic prostatitis that had been diagnosed upon the presence of more than 10 white blood cells per high power field in expressed prostatic secretions. The mean number of patients enrolled in each centre was 12 (range 3-26). Each subject gave his written informed consent prior to enrolment and the study protocol was approved by the institutional review board of the participating centres. The study started on October 2006 and the last patients entered the study on February 2009.

Eligible patients were not currently taking antimicrobial, non-steroidal anti-inflammatory drugs (NSAIDs) nor 5-alpha reductase inhibitors. Patients with known prostate cancer or recent transurethral resection of the prostate were excluded from study. Additionally, patients with any gross abnormalities of the prostate gland identified by digital rectal examination were excluded. No other exclusion criteria was foreseen.

Subjects meeting the set criteria were invited to participate in the study.

Data concerning age, medical history and current medications being taken upon patients' enrolment was obtained. Furthermore, each referent specialist involved in the study recorded the modality of treatment prescribed to each patient.

Patients were asked to come back for a follow-up visit 10-12 weeks after entering the study.

The protocol foresaw the inclusion of 700 patients. With this sample size the 95% confidence interval of the proportion of subjects who lowered their total PSA levels at the follow-up visit were 26.6-33.5, in the case of value of this proportion equal to 30%, 36.3-43.7 in case of 40% and 46.2-53.8 in case of 50%.

Data analysis

Descriptive statistics such as the mean, standard deviation (SD) and proportion were used to describe the characteristics of study subjects. The mean difference between basal and final total PSA and PSA ratio values of each patient was computed.

Age-adjusted odds ratio (OR) and corresponding 95% confidence interval (CI) of reaching total PSA value after treatment of < 4 ng/ml were computed according to the Mantel Haenszel procedure (15). The 95% confidence interval (CI) of frequencies has been computed according the Poisson's approximation.

Results

Out of the 740 patients enrolled in the study twenty-five did not receive any antimicrobial treatment in response to the contraindication or clinical evaluation of participating urologists. These subjects' characteristics were: mean age 62.9 (SD = 7.2), mean BMI 26.5 (SD = 2.1), mean total PSA value at study entry: 5.8 (SD = 1.6).

Ninety-nine of the patients who were lost to follow-up had a mean age of 64.5 (SD = 7.3), mean BMI 26.7 (SD = 2.9) and a mean total PSA value at study entry of 6.3 (SD = 1.5). A total of 616 subjects are included in this analysis.

Table 1 shows the distribution of study subjects according to selected characteristics at study entry. Median age was 63.6 (SD = 7.2) years. In consideration of the body mass index (BMI, kg/m^2) the mean value was 26.6 (SD = 3.0).

A total of 616 subjects were treated with ciprofloxacin (1000 mg once daily for 2 or 3 weeks based on clinical judgement). A concomitant medication with alpha-adrenergic blockers was prescribed to 43 patients.

Mean interval in days between study entry and final visit was 75 (SD = 32). Mean values of total PSA and PSA ratio at study entry and at final visit is shown in Table 2.

The mean serum t-PSA value decreased between study entry and final visit by 1.31 ng/ml (SD 4.19) and the difference between the study entry and final values was statistically significant ($p < 0.05$). No marked difference

Table 1.

General characteristics of study subjects.

	No. (No. 616)	%
Age (years)		
Median (SD), (range)	63.6 (7.2)	(45-75)
45-50	44	6.9
51-55	49	7.6
56-60	114	17.8
61-65	137	21.4
66-70	184	28.7
71-75	113	17.6
Chronic diseases		
Hypertension	126	20.5
Diabetes	77	12.5
Cardiovascular diseases	43	7.0
Hypercholesterolemia	16	(2.6)
Bening Prostatic Hyperplasia	12	(1.9)
Gastritis/gastric ulcer	11	(1.8)
Asthma/COPD	11	(1.8)
Glaucoma	9	(1.5)
Other chronic diseases	49	(8.0)
Current treatment with drugs for BPH		
Yes	43	(7.0)

Table 2.

Total serum PSA (ng/ml) and PSA ratio: study entry, final visit, difference.

	Study entry	Final visit	Difference
Total serum PSA, mean (SD)	6.03 (1.52)	4.72 (4.31)	-1.31 (SD 4.19)*
PSA ratio, mean (SD)	0.23 (0.20)	0.24 (0.27)	0.02 (SD 0.21)

*p < 0.05

emerged between baseline and final PSA ratio value. At the follow-up visit 49.4% (95%CI 44.1-55.5) of patients had PSA levels < 4 ng/ml. This proportion was equal to 61.1% amongst men aged < 60 years, but 38.9% amongst those aged > 68 years (OR 0.41, 95% CI 0.3-0.6).

The OR of having PSA values of < 4 ng/ml at final visit was lower for men with higher total serum PSA values at study entry than for men with t-PSA ≤ 5.0 ng/ml while the OR of having normal t-PSA values at follow-up were respectively, 0.61 (95%CI 0.4-0.9) and 0.23 (0.1-0.3) for patients with t-PSAs ranging 5.1 to 6.2 ng/ml and ≥ 6.3, compared to those with t-PSA ≤ 5.0 ng/ml.

No statistically significant association emerged between PSA ratios at study entry and normal t PSA values at follow-up (Table 3).

Table 3.

Factors associated with total PSA value < 4 ng/ml at final visit.

	Total PSA value < 4 ng/ml at final visit					
	No* (No. 312) No. (%)		Yes (No. 304) No. (%)		OR (95% CI)	
Age (years)						
≤ 60	77	(24.7)	121	(38.8)	1**	
61-67	100	(32.1)	97	(31.9)	0.62	(0.4-0.9)
≥ 68	135	(43.3)	86	(28.3)	0.41	(0.3-0.6)
Total PSA at study entry (ng/ml)[a]						
≤ 5.0	68	(21.8)	132	(43.4)	1**[a]	
5.1-6.2	94	(30.1)	109	(35.9)	0.61	(0.4-0.9)
≥ 6.3	150	(48.1)	63	(20.7)	0.23	(0.1-0.3)
PSA ratio at study entry						
≤ 0.16	86	(27.6)	66	(21.7)	1**[a]	
0.17-0.20	56	(18.0)	56	(18.4)	1.34	(0.8-2.2)
≥ 0.21	94	(30.1)	112	(36.8)	1.53	(1.0-2.4)
Not collected	76	(24.4)	70	(23.0)	1.17	(0.7-1.9)

* In some case the sum does not add up the total due to missing values.
** Reference category.
[a] Adjusted for age.
OR: odds ratio CI confidence interval.

Discussion

PSA is currently the most useful serum marker for prostate cancer and is commonly combined with DRE in early tumour detection. Yet PSA is organ, not cancer-specific, hence its elevation can be caused by benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions as well (16).

The average man older than 50 years of age with a non-suspicious DRE has about a 17% to 32% likelihood of having biopsy-detectable prostate cancer if his serum PSA level is 4.0 to 10.0 ng/mL (17-19).

Furthermore the prostate biopsy, though well tolerated by the patient, is a procedure that can cause psychological discomfort and even morbidity as well as induce low, but not insignificant, incidences of side effects (2).

The results of our prospective observational study concur with the results of several previously published retrospective studies that show the relationship between prostatic inflammation and elevated PSA, and confirm that the treatment of chronic bacterial prostatitis with antimicrobials and antinflammatory drugs can decrease serum PSAs to within the normal range in a significant percentage (40% to 50%) of cases (20-23). Most of published studies are however based on a retrospective analysis.

In this prospective study, the results indicate that in men with t-PSA levels of 4-10 ng/ml and no clinical suspicions of prostatic cancer, treatment with daily ciprofloxacin 1000 mg lowered their t-PSA levels to circa 20%, while circa 50% of patients had a post-treatment t-PSA value of 4ng/ml or less. The 20% PSA reduction found in our study is similar to that reported in other studies (23.4% to 36.4%) (20-21; 24).

The main factors associated with reaching t-PSA value < 4 ng/ml at final visit are age and starting PSA values. In particular, a higher probability of achieving a reduced PSA level within the normal range was observed in patients aged < 60 years who presented a baseline PSA ≤ 5 ng/ml.

The difference between the baseline and final PSA ratio was not statistically significant and furthermore, a baseline PSA ratio level did not influence the possibility of achieving a final PSA within the normal range. This data contrasts with the results of previously published studies showing that free PSA (fPSA) levels decrease and %fPSA significantly increases after antibiotic treatment (6; 25).

The major strengths of the study are based on the fact that a prospective observational profile was adopted, the study sample was considerably large and designated study centers were spread out in all parts of the country ensuring an adequate representation of different socio-cultural and clinical settings. Furthermore, all patients received only an antimicrobial treatment without assuming concomitant NSAIDs, that are supposed to exert a direct inhibitory effect on prostate cancer and could induce a reduction in PSA levels notwithstanding the presence of a prostatic tumour. However, some potential limitations of the study should be taken into account. Firstly, a control group was not included to determine if the absence of fluoroquinolone treatment could result in decreased PSA. Secondly, there was no long-term PSA follow-up and data regarding the eventual indication to prostate biopsy and related histological findings are lacking.

Despite the prospective profile of the study, data were collected over the course of a 3 year period. This extended duration is due to the fact that the participating centres were recruited in different phases. However, an analysis conducted separately for each year of the study did not show any significant differences in the results (data not shown).

Although the results of our study are strongly indicative in confirming that a clear association between bacterial prostatic inflammation and increased PSA levels exists and subsequently antimicrobial treatment is able to lower PSA levels and thereby avoid an immediate prostate needle biopsy in a consistent percent of patients, a definitive indication on the correct management of patients presenting elevated PSAs and no clinical suspicion of prostate cancer is still far from being reached.

First of all, it should be kept in mind significant degrees of biological variations of PSAs can be observed in normal men (26) and that a physiological fluctuation in PSA from 10% to 20% in a screening population has been confirmed (27).

Furthermore, the reduction of PSA serum levels to less than 4 ng/ml after prolonged antibiotic therapy will not necessarily eliminate the risk of prostate cancer nor the need for prostate biopsy. In fact an interesting study showed that in men initially presenting serum PSA levels ranging 4-10 ng/ml with final PSAs of less than 4 ng/ml following a 3-week treatment with ofloxacin, in 29.5% of the cases prostate cancer was indeed detected at final biopsy (28).

Although these considerations appear to limit the use of an antibiotic therapy for asymptomatic men with a newly increased PSA, the Authors believe that an empiric course of antimicrobial treatment for patients presenting moderately elevated PSA levels (4-10ng/ml) and non-concomitant clinical suspicion of prostate cancer may be a reasonable course of therapy prior to prostate biopsy. This modality of management is particularly indicated in the case of patients with diagnosed bacterial prostatitis, under 60 years of age with a PSA range of up to 5 ng/ml.

Conclusion

The results of this large observational prospective study show that about 50% of men aged 45-75 years presenting t-PSA levels of 4-10 ng/ml, no clinical suspicions of prostatic cancer and normal rectal examinations who were treated with ciprofloxacin 1000 mg had t-PSA levels in the normal range 10-12 weeks after first evaluation. Age and basal t-PSA levels were the main determinants of treatment response.

Patients' PSA ratios did not significantly alter post-treatment and were not a determinant of t-PSA responses to ciprofloxacin 1000 mg.

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Correspondence

Paolo Verze, MD
Department of Urology, University of Naples Federico II, Napoli, Italy
verzep@hotmail.it

Fabio Parazzini, MD
First Obstetric and Gynecologic Clinic,
University of Milan and IRCCS Fondazione
Policlinico Mangiagalli Regina Elena
Via Commenda 12 - 20122 Milano, Italy
fabio.parazzini@marionegri.it

Davide Arcaniolo
Department of Urology, University of Naples Federico II, Napoli, Italy
arcaniolo@unina.it

Sonia Cipriani, MD
Clinica Ostetrica Ginecologica, Università di Milano,
Fondazione IRCCS, Ospedale Maggiore Policlinico,
Mangiagalli, Regina Elena, Milano, Italy
sonia.cipriani@marionegri.it

Vincenzo Mirone, MD
Department of Urology, University of Naples Federico II, Napoli, Italy
mirone@unina.it

ORIGINAL PAPER

Multicentre study on the efficacy and tolerability of an extract of Serenoa repens in patients with chronic benign prostate conditions associated with inflammation

Roberto Giulianelli [1], Stefano Pecoraro [2], Giuseppe Sepe [2], Rosario Leonardi [3], Barbara Cristina Gentile [1], Luca Albanesi [1], Stefano Brunori [1], Luca Mavilla [1], Francesco Pisanti [1], Renato Giannella [2], Patrizia Morello [4], Domenico Tuzzolo [5], Mario Coscione [6], Fabio Galasso [6], Tammaro D'Angelo [7], Paolo Ferravante [8], Emilio Morelli [9], Antonio Miragliuolo [10], and Cooperative Ur.O.P group

[1] Villa Tiberia Clinic, Urology Department, Rome, Italy;
[2] Malzoni Clinic, Urology Department, Avellino, Italy;
[3] Musumeci GECAS Clinic, Urology Department, Catania, Italy;
[4] ASL RM H, 4 District, Urologic Service, Rome, Italy;
[5] Casa del Sole, Urology Department, Formia, Italy;
[6] S. Rita Clinic, Urology Department, Benevento, Italy;
[7] S. Pio Clinic, Urology Department, Mondragone, Italy;
[8] Fatebenefratelli Hospital, Surgical Department, Benevento, Italy;
[9] Villa Maria Clinic, Urology Department, Mirabella Eclano, Italy;
[10] S. Maria della Pietà Hospital, Urology Department, Casoria, Italy.

Summary

Introduction: *Chronic benign prostate diseases are very common and certainly feature significantly in urological practice.The treatment of chronic benign prostate diseases is a common problem in clinical practice: few studies have been conducted in routine clinical practice to evaluate the efficacy of the treatments for this clinical condition. The objective of this study was to evaluate the efficacy of an extract of Serenoa repens (Permixon®) in the treatment of lower urinary tract symptoms (LUTS) in patients with chronic benign prostate diseases with associated inflammation, also taking into consideration the influence of treatment on sexual function and, therefore, on patients' quality of life.*

Materials and Methods: *All the 591 eligible subjects were evaluated on entering the study; after a screening visit, including medical history, physical examination, physical examination and digital rectal examination (DRE) and laboratory tests, the patients underwent uroflowmetry. The subjects under investigation were also asked to complete the IPSS, NIH-CPSI and IIEF-5 questionnaires, for the purpose of evaluating urinary symptoms and erectile function in relation to sexual activity in the previous 6 months.*

Results: *The analysis of the uroflowmetry results showed that treatment with extract of Serenoa repens distinctly improves bladder voiding and lower urinary tract symptoms, as highlighted also by the improvement in the scores for the IPSS and NIH-CPSI questionnaires which serve as a basis for evaluating the urinary symptoms of patients with prostatic hyperplasia and chronic prostatitis respectively. The results also suggest that using an extract of Serenoa repens for 6 months in patients with chronic benign prostate diseases gives rise to an improvement in erectile function, as demonstrated by the increase in the scores for the IIEF-5 questionnaire after 6 months of treatment.*

Conclusions: *The results of this study demonstrate how treatment for 6 months with an extract of Serenoa repens in routine clinical practice gives rise to a statistically significant improvement in Qmax values and in the IPSS, NHI-CPSI and IIEF-5 questionnaire scores, resulting not only in an improvement in urinary symptoms but also in an overall improvement in patients' quality of life.*

KEY WORDS: *Benign prostatic hyperplasia; Inflammation; Plant extract; Serenoa repens; Lower urinary tract symptoms.*

Submitted 13 February 2012; Accepted 31 March 2012

Introduction

Chronic benign prostate diseases are very common and certainly feature significantly in urological practice. Prostatitis is a relatively common and widespread condition which affects adults most frequently. It has been estimated that, out of 1,000 male subjects seen for an annual check-up, 76 have genito-urinary conditions, and prostatitis accounts for 25% of these cases. Furthermore, on the basis of recent studies, it would seem that almost 50% of males have at least one episode of prostate inflammation of varying severity in the course of their lives. Benign prostatic hyperplasia (BPH) begins with microscopically small stromal nodules from the age of 35, with an incidence which increases with age throughout the male population. This suggests that almost all men can develop BPH if they live long enough. More than 50% of subjects aged between 60 and 69 have clinically significant BPH. Of these, a significant percentage is at risk of developing acute urinary retention in the absence of appropriate medical and/or surgical treatment.

The treatment of chronic benign prostate diseases is a common problem in clinical practice: few studies have been conducted under routine clinical conditions to evaluate the efficacy of the treatments for this clinical condition.

An extract of *Serenoa repens* (*Permixon®*) has been available for some years for the treatment of benign prostatic diseases. This product is the n-hexane lipidosterolic extract of a dwarf palm known as *Serenoa repens* and represents a complex mixture of various compounds. A number of pharmacodynamic effects have been identified using this product, and multiple mechanisms of action have been suggested. These include in vitro inhibition of type 1 and type 2 isoenzymes of 5α-reductase and interference with the binding of dihydrotestosterone to androgen receptors in prostate cells.

The objective of this study was to evaluate the efficacy of the extract of *Serenoa repens* in the treatment of lower urinary tract symptoms (LUTS) in patients with chronic benign prostate diseases with associated inflammation, also taking into consideration the influence of treatment on sexual function and, therefore, on the patients' quality of life.

Material and methods

Patients

Patients with chronic benign prostate diseases with associated inflammation referred to UROP urology centres in 2009 were enrolled.

Study design

This was an open-label, multicentre study, the primary endpoint of which was to evaluate the efficacy and safety of the extract of *Serenoa repens* in the treatment of lower urinary tract symptoms in patients with chronic benign prostate diseases with associated inflammation. The secondary endpoints comprised:

1) evaluation of the influence of treatment on quality of life in relation to sexual function;
2) evaluation of the change in total PSA values from the start of treatment to the end of the study after six months. The inclusion and exclusion criteria are listed in Table 1.

Table 1.

Inclusion and exclusion criteria.

Inclusion criteria

- Male subjects aged between 35 and 65
- Clinical diagnosis of BPH, chronic prostatitis without infection
- Non-acute irritative dysuric symptoms
- IPSS ≥ 13 at baseline
- Chronic painful prostatitis symptoms index ≥ 2 at baseline
- Q_{max} < 12 ml/sec at baseline
- PVR < 150 ml at baseline
- DRE not suggestive of prostate cancer
- Total PSA ≤ 4 at baseline*

**If PSA > 4, a prostate biopsy had to be performed to rule out the presence of cancer in situ. In the event of a positive result, the patient had to be withdrawn from the study.*

Exclusion criteria

- Previous pelvic surgery
- Urological conditions already diagnosed: neurogenic bladder, bladder outlet obstruction, urethral stricture, bladder tumours, prostate cancer, bladder stones, diabetes mellitus, bladder diverticula, psychiatric disorders, UTI, treatment with: diuretics, androgen antagonists, antidepressants
- Patients under treatment with: finasteride, mepartricin, dutasteride, *Pigeum Africanum*, other adjuvants indicated for BPH may be enrolled in the study after a wash-out period of at least 4 weeks
- Patients diagnosed with irritable bowel disease
- Patients with documented hypersensitivity to one or more ingredients of Permixon®

All the eligible subjects were evaluated on entering the study: after a screening visit, including medical history, physical examination, physical examination and DRE, laboratory tests (total PSA, urinalysis and urine culture, semen analysis with screening for *Chlamydia* and *Mycoplasma*), the patients underwent uroflowmetry.

The subjects under investigation were also asked to complete three questionnaires:

1) the IPSS (*International Prostatic Symptoms Score*) questionnaire, which permits an objective evaluation of the urinary symptoms of the patient with prostatic hyperplasia;
2) the NIH-CPSI (*National Institute of Health - Chronic Prostatitis Symptom Index*) questionnaire for the evaluation of symptoms, divided into three different areas: pain, urinary symptoms and impact on quality of life;
3) the IIEF-5 (*International Index of Erectile Function - 5*) questionnaire, created for the purpose of providing a sensitive and specific questionnaire for evaluating erectile function in relation to sexual activity in the previous six months.

The eligible patients took an extract of *Serenoa repens* 320 mg, one capsule per day, for 6 consecutive months. The subjects were evaluated at baseline [and] after 6

Table 2.

Initial and final values.

Variable	T_0	T_1	Difference T_1-T_0	p value
PSA (ng/ml)	1.9 (0.79)	1.4 (0.71)	-0.6 (0.71)	< 0.0001
Q_{max}	10.7 (4.00)	13.7 (2.37)	2.9 (4.12)	< 0.0001
IPSS	17.8 (4.18)	12.2 (5.28)	-5.6 (3.76)	< 0.0001
NHI-CPSI	13.3 (6.53)	8.2 (5.72)	-5.1 (5.80)	< 0.0001
IIEF	17.6 (4.01)	18.1 (4.65)	0.5 (4.66)	0.0055

Statistically significant differences were observed for all the variables considered.

months. At the final visit, information relating to the total PSA and Q_{max} values was collected again, and the IPSS, NHI-CPSI and IIEF-5 questionnaires were re-administered.

Statistical analysis

For the subjects entered in the study, the mean values, medians, standard deviations and ranges were calculated for the initial and final visit.

The statistical significance of the difference between the initial and final values for the variables under consideration in the subjects who completed the study was determined using a Student's t-test.

RESULTS

The number of patients enrolled in the study was 591. Table 2 shows the initial and final values for the subjects who completed the study, along with the relevant standard deviations and the Student's t-test value on the differences. The patients treated with the extract of *Serenoa repens* experienced a significant reduction in their serum PSA levels compared to baseline, showing a trend which could be maintained, probably even in the long-term. The analysis of the uroflowmetry results showed that treatment with the extract of *Serenoa repens* distinctly improves bladder emptying and lower urinary tract symptoms (Figure 1); an improvement was also observed in the scores for the IPSS and NIH-CPSI questionnaires which serve as a basis for evaluating the urinary symptoms of patients with prostatic hyperplasia and chronic prostatitis respectively (Figures 2, 3).

The results also suggest that using the extract of *Serenoa repens* for 6 months in patients with chronic benign prostate diseases gives rise to an improvement in erectile function, as demonstrated by the increase in the scores for the IIEF-5 questionnaire after 6 months of treatment (Figure 4).

Figure 1.

Uroflowmetry (Q_{max}) at T_0 and after 6 months of treatment with the extract of Serenoa repens.

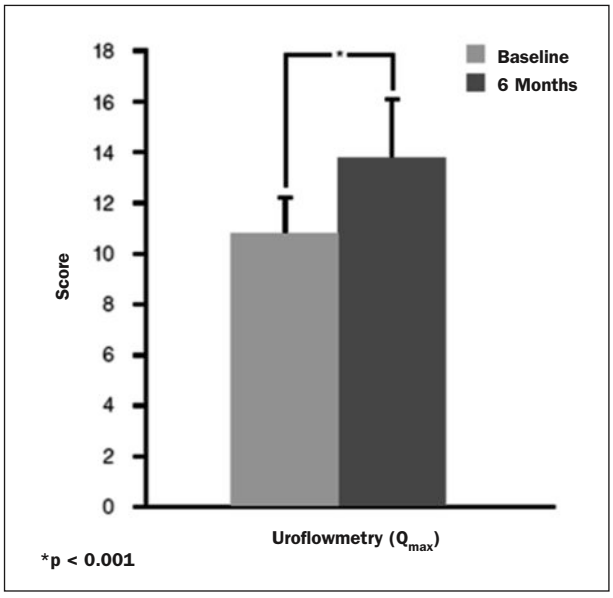


Figure 2.

IPSS score at T_0 and after 6 months of treatment with the extract of Serenoa repens.

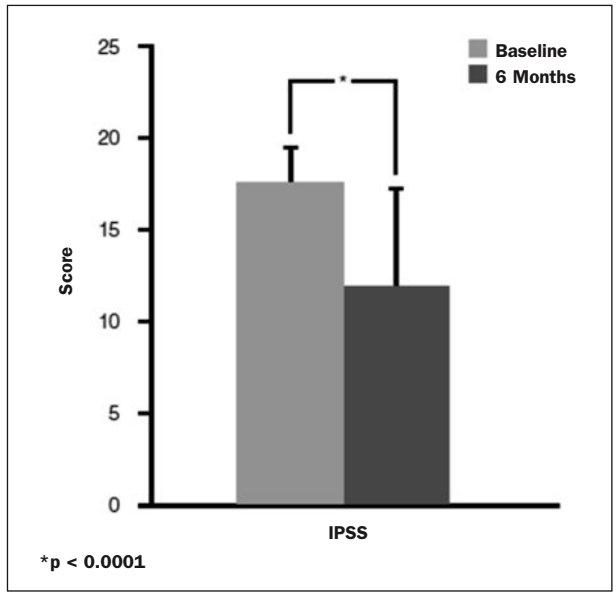


Figure 3.

NIH-CPSI scores at T_0 and after six months of treatment with the extract of Serenoa repens.

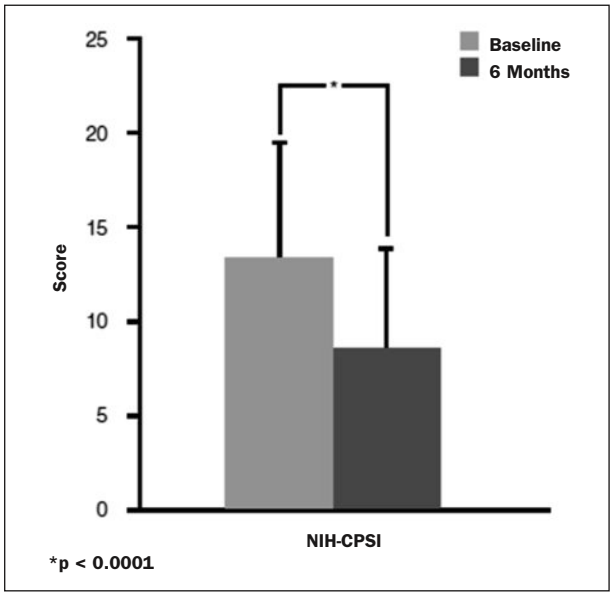
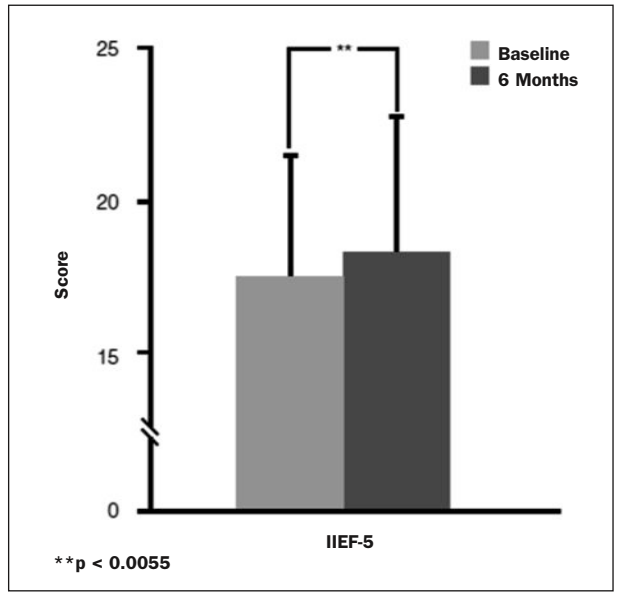


Figure 4.

IIEF-5 scores at T_0 and after six months of treatment with the extract of Serenoa repens.



Discussion

The results of this study demonstrate how treatment for 6 months with a medicinal product based on *Serenoa repens* in routine clinical practice improves Q_{max} values and the scores for the IPSS, NHI-CPSI and IIEF-5 questionnaires, also bringing about a reduction in the total PSA value. The study evaluated the effect of the extract of *Serenoa repens* in respect of urinary and sexual function aspects and finally on the basis of the PSA values.

The strengths of the study include the very large sample size and the fact that the study was conducted as part of routine clinical practice in primary and secondary care centres nationally. The experience of treatment with this medicinal product is wide-ranging (1, 2).

The data in the literature on the efficacy of this medicinal product are numerous (3-5) and the efficacy of the product has been demonstrated in various studies conducted in large populations of patients, including in comparison with other widely used medicinal products such as 5α-reductase inhibitors (finasteride) or alpha blockers (tamsulosin).

In one randomized double-blind study (3) conducted in 1,098 patients with moderate BPH treated for 6 months with the extract of *Serenoa repens* 320 mg (160 mg twice daily) or finasteride 5 mg, for example, both treatments improved the symptoms of BPH in approximately two thirds of the patients. Unlike finasteride, however, the extract of *Serenoa repens* exhibited only a slight effect on the "androgen-dependent" parameters. This is in keeping with what was observed in our study on the basis of the IIEF-5 questionnaire. In this study, in fact, although the improvements in the IPSS score (-37% and -39% for the extract of *Serenoa repens* and finasteride respectively), quality of life (+38% and +41%) and the maximum urinary flow rate (+25% and +30%) were largely similar, the extract of *Serenoa repens* was judged to be superior to finasteride in terms of its effect on sexual function, and it prompted fewer complaints concerning reduced libido and erectile dysfunction. The therapeutic equivalence between the extract of *Serenoa repens* 320 mg/day and pharmacological treatment was also confirmed in the PERMAL study (4), a large-scale European study conducted in 704 patients with BPH (IPSS ≥ 10) to evaluate the effects of the extract and tamsulosin 0.4 mg/day on various clinical efficacy parameters (IPSS, QoL, Q_{max}) and on changes in prostate volume and serum PSA levels. In particular, after 12 months of treatment, the same reduction in the IPSS score (-4.4) was observed in both groups, with no differences in terms of irritative and obstructive symptoms, along with an almost identical improvement in the Q_{max} (1.8 ml/s for the extract of *Serenoa repens* and 1.9 ml/s for tamsulosin): both treatments also maintained stable PSA levels with a slightly better reduction in prostate volume under extract of *Serenoa repens* and a greater incidence of retrograde ejaculation in the tamsulosin group. One subsequent study conducted by the same authors (5) also demonstrated how treatment with extract of *Serenoa repens* can actually give rise to a greater improvement than that achievable with tamsulosin when patients with particularly severe LUTS (IPSS > 19) are taken into consideration. These observations confirmed that the efficacy of extract of *Serenoa repens* can be attributed to its triple mechanism of action, or to its anti-androgen (via inhibition of type 1 and 2 5α-reductase), anti-proliferative (via shrinkage of prostate epithelial cells and reduction of tissue dihydrotestosterone levels) and anti-inflammatory (via inhibition of arachidonic acid metabolites) effects. As such, these may constitute an advantage over alpha blockers in the treatment of BPH with severe symptoms when

obstructive and irritative symptoms are involved at the same time. The use of the extract of *Serenoa repens* has been the subject of numerous pharmacological and clinical investigations in recent years: its equivalent and in some cases superior efficacy in BPH compared with 5α-reductase inhibitors or alpha blockers is closely correlated with the particular product formulation. As already observed in a review published in the *British Journal of Urology* (6), not all *Serenoa repens* extracts have the same composition and consistency, and they cannot therefore be treated as equivalent in terms of their relative therapeutic efficacy. The lack of standardization between the various extracts can actually lead to dosage variations ranging between -97% and +140%, with major implications from the pharmacodynamic and pharmacokinetic viewpoints. In particular, the presence of high levels of unbound fatty acids in the extract of *Serenoa repens* is associated with a greater degree of inhibition of 5α-reductase activity and significant superiority in terms of its effects on symptoms, on urodynamic variables and on quality of life compared with what is observed with other extracts. Another important fact to come out of this study is the effect of *Serenoa repens* in reducing PSA values, which is an important factor in the management of subjects with BPH, particularly with regard to the decision to perform a prostate biopsy. Reducing this value therefore has major clinical implications.

In one randomized, controlled clinical study conducted on *Serenoa repens* versus placebo, the PSA value after one year of treatment was more or less unchanged in the subjects assigned to *Serenoa repens* (-0.005 ng/dl). The baseline value for these subjects was 1-7 (SD 1.4) ng/dl (7), however. In the present study, the reduction was greater in subjects with higher PSA values. In fact, the reduction observed in subjects with a PSA of < 1.7 ng/dl was 0.09 ng/dl. It should be stressed that all the subjects included in the present study had a PSA value of < 4 on inclusion. This reduction in the PSA value can probably be attributed to an anti-inflammatory effect of *Serenoa repens* (8).

Conclusions

In conclusion, the results of this study demonstrate how treatment for 6 months with the extract of *Serenoa repens* under routine clinical conditions gives rise to a statistically significant improvement in Q_{max} values and in the IPSS, NHI-CPSI and IIEF-5 questionnaire scores, resulting not only in an improvement in urinary symptoms but also in an overall improvement in the patient's quality of life.

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Correspondence
Roberto Giulianelli, MD
Urology Department - Clinica Villa Tiberia, Roma, Italy
roberto.giulianelli@virgilio.it

Stefano Pecoraro, MD
Giuseppe Sepe, MD
Urology Department - Clinica Malzoni, Avellino, Italy

Rosario Leonardi, MD
Urology Department - Clinica Musumeci GECAS Clinic, Catania, Italy

Barbara Cristina Gentile, MD
Luca Albanesi, MD
Stefano Brunori, MD
Luca Mavilla, MD
Francesco Pisanti, MD
Urology Department - Clinica Villa Tiberia, Roma, Italy

Renato Giannella, MD
Urology Department - Clinica Malzoni, Avellino, Italy

Patrizia Morello, MD
Urologic Service - ASL RM H, 4 District, Roma, Italy

Domenico Tuzzolo, MD
Urology Department - Casa del Sole, Formia, Italy

Mario Coscione, MD
Fabio Galasso, MD
Urology Department - Clinica S. Rita, Benevento, Italy

Tammaro D'Angelo, MD
Urology Department - Clinica S. Pio, Mondragone, Italy

Paolo Ferravante, MD
Surgical Department - Fatebenefratelli Hospital, Benevento, Italy

Emilio Morelli, MD
Urology Department - Clinica Villa Maria Clinic, Mirabella Eclano, Italy

Antonio Miragliuolo, MD
Urology Department
S. Maria della Pietà Hospital, Casoria, Italy

ORIGINAL PAPER

Clinical importance of the micro-focal prostate cancer on a single sample of a trans-rectal 8-core biopsy

Giandomenico Passavanti, Michele Gnech

U.O. Urologia - Ospedale Misericordia, Grosseto, Italy.

Summary

Objective: *We tried to verify retrospectively, the clinical importance of a single micro-focal prostate cancer at biopsy (as microscopic aspect of a group of 12 neoplastic glands 40x) in patients subsequently treated with radical prostatectomy (RP).*
Materials and Methods: *from January 2008 to November 2010 we carried out 760 eight-core prostate biopsies for increased PSA in patients with a prostatic volume of </= 40cc. A total of 252 patients (33.15%) had a prostate cancer and out of them 17 (6.7%) had a microscopic prostate cancer -16 a single microscopic focus and a case 2 microscopic foci in two different specimens. PSA ranged 5 to 7.4 ng/ml (mean 6.2 ng/ml), age ranged 61 to 75 (mean 68.29), Gleason score was G6 in all cases; in 4 cases a microscopic focus of PIN3 was associated.*
Results: *All patients had a RP and the pathologic stage was T2a in 4, T2b in 1, T2c in 9 (3 of these had microscopic PIN3 at biopsy) and T3a in 3 (including the one with 2 microscopic foci of prostate cancer on 2 different bioptic samples). Gleason was G6 in 12 cases and G7 in 5.*
Discussion: *The single microscopic focus of prostate cancer has always raised diagnostic problems, in fact some authors report these patients have 30 to 90% of probability to have a significant prostatic cancer (volume > 0,5 ml) whereas other authors found an insignificant prostatic cancer in 30% of the patients with a single microscopic focus of prostate cancer. It is really very difficult to predict the extent of the tumor in these cases because the different parameters employed are not reliable. Our series, although very small, support the hypothesis that significant cancers are more frequently associated with a single microscopic focus of prostate cancer at biopsy (in fact 17 out of 17 patients had a significant cancer) and consequently we feel that it is more oncologically correct to choose an aggressive therapy in these cases (RP, radiotherapy or androgen deprivation according to the individual case) rather then a "wait and see" which could be less cautious.*

KEY WORDS: *Prostate cancer; Prostate biopsy; Microscopic focus.*

Submitted 13 November 2011; Accepted 31 March 2012

INTRODUCTION

The single micro-focal prostate cancer at an 8-core prostate biopsy, always raises problems for diagnostic and therapeutic choices because the biopsy parameters are not reliable in staging the disease.
We tried to better understand this topic studying the results of our series and the evidences of literature.

MATERIALS AND METHODS

From January 2008 to November 2010 we carried out 760 eight-core prostate biopsies.
PSA ranged from 0.81 to 94.91 ng/ml (mean 8 ng/ml) and prostate volume was always =/< 40 cc.; patient's age ranged 49 to 84 (mean 69.53).
A prostate cancer was diagnosed in 252 patients; PSA of this group ranged from 1.14 to 94.91 ng/ml (mean 9.2 ng/ml) and age from 53 to 84 (mean 71.1); out of these patients with prostate cancer 17 presented with a micro-focal prostate cancer; 16 had a single microscopic focus on a single sample of biopsy and 1 had a microscopic focus on two biopsy samples.
The definition of microscopic focus of prostate was 12 prostate glands at 40x magnification (Figure 1) (1).
The PSA of this last group ranged 5 to 7.4 ng/ml (mean 6.2 ng/ml), age ranged 61 to 75 (mean 68.29) and Gleason score at biopsy was 6 (3 + 3) in all cases. In 4 cases we found a microscopic focus of high grade PIN.

RESULTS

The 17 patients with microscopic focus of prostate cancer had a radical prostatectomy: the post-operative stag-

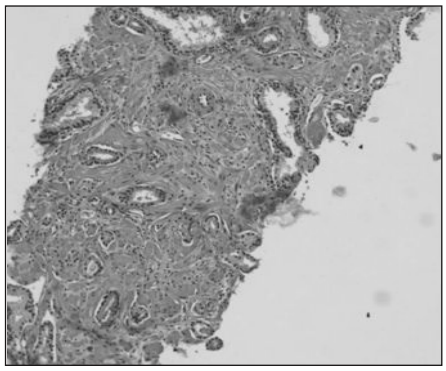

Figure 1.

Morphological aspect of a micro-focal prostatic cancer on a single bioptic sample.

ing was T2a in 4, T2b in 1, T2c in 9 (3 patients of this group had an high-grade PIN micro-focus) and T3a in 3. Postoperative Gleason scores were equal to biopsy – G6 (3 + 3) – in 12 cases (70.58%) whereas in 5 cases (29.41%) it was higher – G7 (3 + 4) – than the biopsy Gleason.

Discussion

The single micro-focal prostate cancer in 8-core prostate biopsy raises many difficulties in the pre-operative staging of the disease and doesn't show clearly the full extent of the prostate cancer, so it could be almost impossible to choice the correct therapeutic option.

In these cases the incidence of an insignificant cancer after radical prostatectomy, was found about 42% when the definition of significant cancer was a tumor >/= 0,5 ml (2).

Another relevant aspect of this condition is that the biologic parameters of the tumor are not enough reliable to evaluate these cancers: PSA </= 10 ng/ml is not reliable for staging (3) and the biopsy Gleason often is not equal to the Gleason of the surgical specimen. In fact the biopsy Gleason is equal to the definitive one in only 70% of the cases (4), and also in our series, the biopsy Gleason was coincident the Gleason of the surgical specimen in only 12 cases out of 17 (70.58%).

Therefore these biologic parameters of the disease were not helpful for the staging (5, 6) and also others parameters (e.g. PSA density, ultrasonography…) are also often unreliable because of technical difficulties or because operator-dependent (7).

Some Authors reported that the incidence of significant cancer in patients with biopsy single microfocal prostate cancer ranged from 61 to 92% (8, 9), and our series confirms this finding; for this reason it is difficult to propose a correct therapeutic strategy.

The therapeutic choice has to be tailored case by case and it have to take into accouint the different biological parameters of the cancer, age and general condition of the patients too.

Conclusions

On the basis of our experience and in reference to previous papers on this subject which present contrasting opinions, we feel that it is more cautious to make an active therapeutic choice in the case of single micro-focal prostate cancer at biopsy; in fact we propose a radical prostatectomy or an external beam radiotherapy for patients under 75 in good general condition and with parameters suggesting a local significant tumor; for more aged or compromised general condition patients we suggest an hormonal therapy.

Only in carefully selected cases a "*wait and see*" strategy could be proposed and in these cases the patients need to have a high compliance to frequent clinical examinations and re-biopsies.

Finally we feel that it is desirable to develop further research in order to investigate others laboratory tests and imaging modalities, such as PCA3 or NMR 3/T with or without endorectal probe (10), to better evaluate the local extension of the tumor in the case of single microfocal prostate cancer at biopsy.

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Correspondence

Giandomenico Passavanti, MD
Via Oberdan 44 - 58100 Grosseto, Italy
mpeppina@infinito.it

Michele Gnech, MD
U.O. Urologia - Ospedale Misericordia, Grosseto, Italy

CASE REPORT

Partial priapism secondary to idiophatic segmental thrombosis of corpora cavernosa

Pietro Pepe [1], Paolo Panella [1], Giuseppe Candiano [1], Antonio Garufi [2], Giandomenico Priolo [2], Francesco Aragona [1]

[1] Urology Unit - Cannizzaro Hospital, Catania, Italy;
[2] Imaging Department - Cannizzaro Hospital, Catania, Italy.

Summary

A 51-year-old man presented at our Department 2 days after the onset of a painful mass in the perineum and dysuria. Diagnosis of partial priapism secondary to proximal segmental corpora cavernosa thrombosis was made through colordoppler ultrasound (CDU) and magnetic resonance imaging (MRI). Treatment consisted of administration of systemic anticoagulation drugs (acenocumarol) and local injection of ethylephrine chloridrate. The thrombosis resolved after two months with incomplete restoration of erectile function (loss of rigidity). In conclusion, on the basis of previous reports (23 cases reported in literature) and our experience, in presence of painful mass in the perineum, CDU and MRI evaluation allows to make diagnosis of the rare proximal partial priapism that as first option should be treated conservatively.

KEY WORDS: Partial priapism; Corpora cavernosa; Thrombosis; Perineum pain.

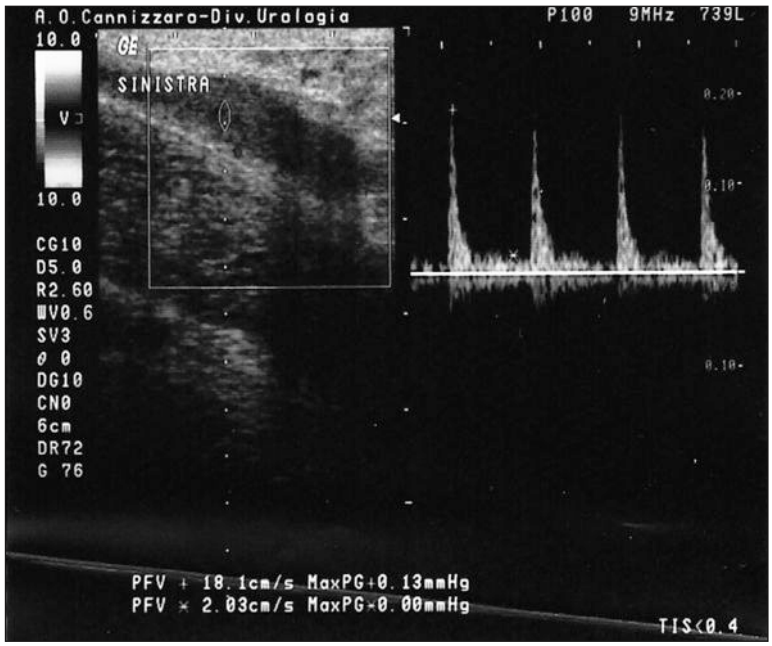
Submitted 2 October 2011; Accepted 31 December 2011

CASE REPORT

A 51-year-old white male presented at our Department 2 days after the onset of a painful mass in the perineum combined with dysuria; no sexual trauma or urethral discharge was referred by the patient. On the physical examination, a painful mass was found in the proximal cavernous body, however the pendulous part of the penis had a normal appearance. Further physical examination, routine blood and coagulation tests, urinalysis showed no abnormalities. Color-Doppler-ultrasound (CDU) of the penis showed the presence of a ipoechoic pattern of either posterior cavernosa corpora combined with decreased flow in the cavernosa arteries (peak velocity equal to 18 cm/sec; telediastolic velocity equal to 0.5 cm/sec) (Figure 1). MRI T1-weighted images demonstrated an hypo-intense signal of proximal corpora cavernosa suggesting the presence of a massive thrombosis (Figure 2). The treatment consisted of intracavernosa corpora injection of ethylephrine chloridrate (5 mg) and heparin solution, moreover systemic oral analgesic for 14 days and anticoagulation drugs (acenocumarol) for two months were administrated. Six months later physical examination and repeat CDU showed absence of pain and thrombosis; on the contrary MRI T2 weighted images showed decreased signal of corpora cavernosa suggesting the presence of fibrosis (Figure 3). After a follow up of four years the patient needs oral drugs (5 phosphodiesterasi inhibitors) to have a good erectile performance because the loss of rigidity.

CONCLUSIONS

In literature only 23 cases (1) of partial segmental thrombosis of corpus cavernosum have been reported and the aetiology still today remains unclear (2). Some authors believe that thrombosis could be secondary to the presence of a membranous septum between the pendular and proximal intracorporal tissues (3, 4); other authors suggest the post-traumatic development of a fibrous scar that could change the free-flowing venous lake of corpus cavernosum (5). In the 50% of the cases thrombosis has been related to a trauma (coitus or cycling injury) (6, 7) and in rare cases to malignancies, sickle cell disease or alpha-blocker administration (8). Usually, partial proximal priapism is not an urologic emergency, however prolonged ischemia secondary to thrombosis could induce erectile failure and fibrosis of corpora cavernosa. Clinical



presentation combined with CDU and MRI evaluation lead to the diagnosis (9). At first presentation the thrombus is hyper-intense on T1-weighted images and hypo-intense on T2-weighted images; later, intensity increases because the formation of methemoglobin (6).

Several treatment options have been suggested; initially surgical corporotomy and clot evacuation have been evocated, but recently conservative therapy using systemic anticoagulation drugs to prevent fur-

Figure 1.

Basal color-Doppler ultrasound of the penis: ipoechoic pattern of proximal corpora cavernosa combined with decreased systolic peak velocity (18 cm/sec) and absence of telediastolic signal (0.5 cm/sec) of cavernosa arteries.

Figure 2.

Sagittal (a) and axial (b) MRI T1 weighted images: hypo-intense signal of proximal corpora cavernosa secondary to thrombosis.

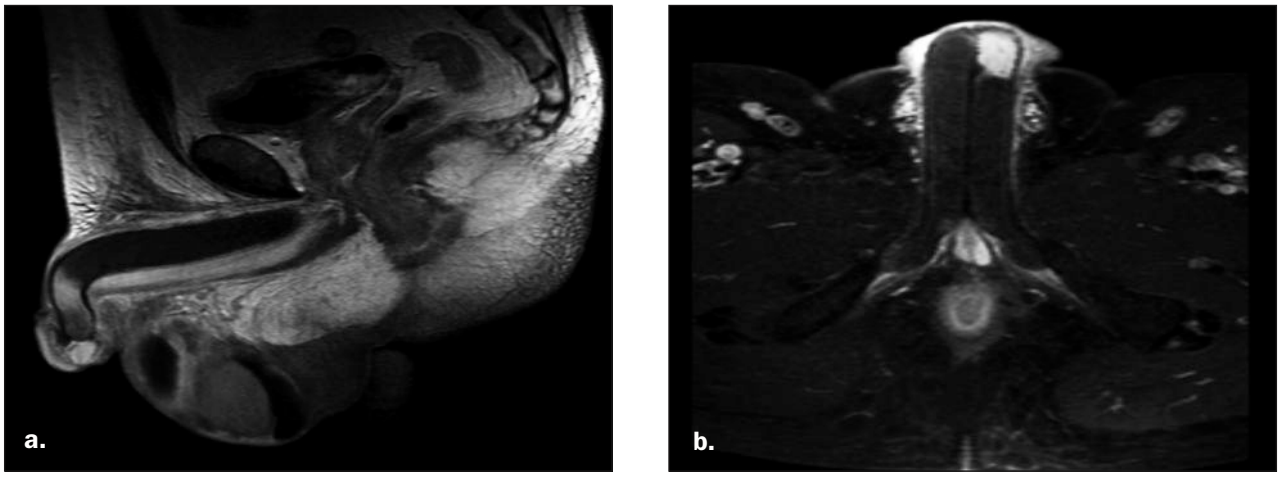
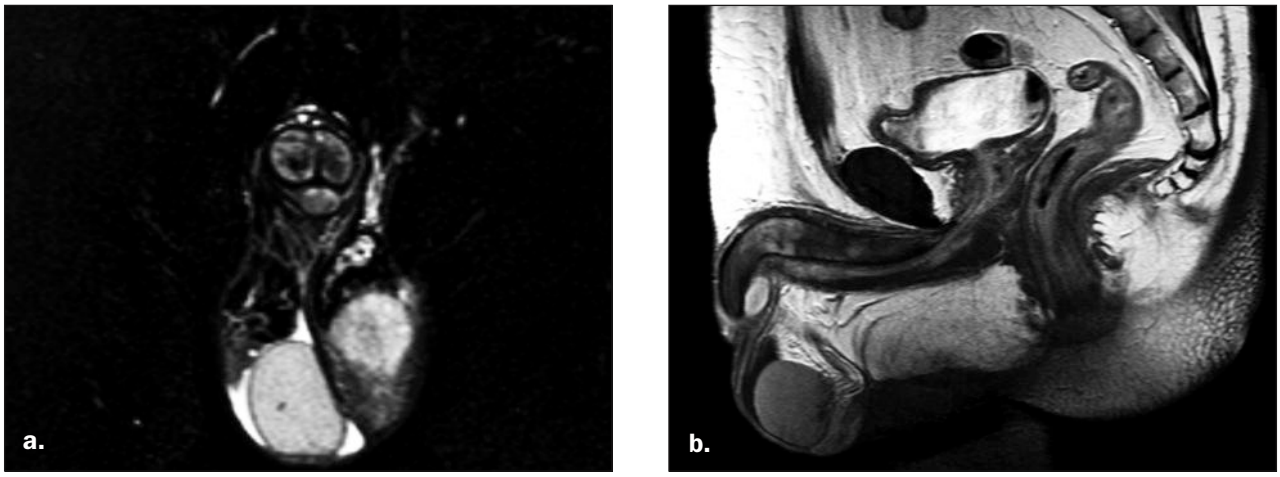


Figure 3.

(after six months). Coronal (a) and sagittal (b) T2 weighted MRI images shows decreased signal of corpora cavernosa suggesting presence of fibrosis.



ther thrombosis allowed to maintain erectile function in the majority of the cases reserving surgery option only when medical treatment fails. Although patients are often able to resume sexual activity in our case the patient needed oral drugs (5 phosphodiesterasi inhibitors) to reach a good sexual performance.
In conclusion, clinical presentation (painful mass in the perineum combined with a rigid proximal and flaccid distal corpus cavernosum) and CDU and MRI evaluation allows to make diagnosis of the rare proximal partial priapism that as first option (10) should be treated conservatively.

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Correspondence

Pietro Pepe, MD
Urology Unit, Cannizzaro Hospital
Via Messina 829 - Catania, Italy
piepepe@hotmail.com

Panella Paolo, MD

Candiano Giuseppe, MD

Aragona Francesco, MD
Urology Unit, Cannizzaro Hospital
Via Messina 829 - Catania, Italy

Garufi Antonio, MD

Priolo Giandomenico, MD
Imaging Department, Cannizzaro Hospital
Via Messina 829 - Catania, Italy

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