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S.C.D.U. Urology

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TITLE OF THE STUDY: Evaluation of the efficacy of the treatment of benign prostatic hypertrophy with Serenoa Repens extracted with CO2 + PEA (Palmitoylethanolamide) in monotherapy or in combination with tamsulosin. ProSeRePEA trial.

1. Introduction and rationale

Lower urinary tract symptoms (LUTS) can be divided into filling, micturition and post-void symptoms [1]. LUTS include: diurnal and nocturnal pollakiuria, urinary urgency, incontinence, hypovalid voiding, voiding hesitation, prolonged urination time, voiding dribbling and paradoxical iscuria. LUTS cause disturbance and compromise quality of life [2-5]. Lower urinary tract symptoms are strongly associated with aging [2, 3], so costs and patient numbers are likely to increase with future demographic changes [3, 7].

Most older men have at least one symptom [3], however, symptoms are often mild and tolerable [5, 6, 8]. The progression of this symptomatology in each individual is very subjective, in some patients the symptoms are worsening and dynamic, for others they remain more stable over time [3].

LUTS are mainly related to bladder outlet obstruction from benign prostatic hypertrophy (BPH). [1, 4]. However, they can also be related to bladder and urinary tract abnormalities, such as anatomical or functional abnormalities (detrusor hyperreactivity, urinary infections, neoplasms, lithiasis) [3, 9]. Prostatic hypertrophy is due to hyperplasia of both the epithelial and stromal components and originates in the periurethral region of the gland. In the initial stages, there is a development of micronodules of stromal and glandular tissue in the periurethral area; over the years these nodules increase in size by compressing and distorting the prostatic urethra, hindering the urinary flow. Hormonal, immune, dietary, neurological and genetic factors are involved in the genesis of BPH. An alteration of the balance at a local level between estrogens and androgens is recognized. This phenomenon increases the ability to capture testosterone which stimulates cell growth and therefore prostatic hyperplasia. Glandular growth, i.e. of the adenoma, causes both urethral compression and peripheral compression of the remaining part of the parenchyma. This situation causes an intraglandular inflammatory picture which results in asymptomatic abacterial chronic prostatitis which can be found at the histological level of patients undergoing endoscopic resection of prostate adenoma. This inflammation aggravates and worsens the underlying urinary symptoms. According to European guidelines (UAE), the diagnosis of BPH must make use of a complete anamnestic collection to know any comorbidities of the patient. It must make use of the use of questionnaires to be submitted to each patient (e.g. IPSS, International Prostate Symptom Score), with the aim of quantifying voiding symptoms and monitoring worsening/improvements over time after medical therapy [10]. The patient should maintain a voiding diary to evaluate micturition characteristics, including voided volume in 24 hours, voiding frequency, and fluid intake. It is important for the

doctor to perform an objective examination of the patient, abdominal and genital, including rectal exploration to evaluate the prostate volume, consistency, any irregularities and tenderness. Urinalysis with urine culture should be included in the primary evaluation of any patient with LUTS to identify conditions such as urinary tract infections (UTIs), microhematuria, and diabetes mellitus. It is important to determine the PSA (prostate specific antigen), a protease produced exclusively by prostatic epithelial cells, as it has a good positive predictive value since it increases in the course of both benign and malignant prostate diseases. In fact, it increases with the increase in the volume of the gland, increases in the course of inflammatory processes and in the course of prostate adenocarcinoma. Second level tests will have to be performed to make a correct differential diagnosis between these pathologies having a different therapeutic approach. The normal reference PSA value is <4 ng/ml and can be associated with its ratio (ratio between free PSA and total PSA, the higher it is, the more likely it is to be a benign disease).

Kidney function can be assessed by serum creatinine and estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more frequent in patients suffering from BPH. One study reported that 11% of men with LUTS had renal insufficiency [11].

Uroflowmetry is a non-invasive urodynamic (time-volume) test widely used and recommended by guidelines for the initial diagnosis of LUTS. The parameters to consider are: Qmax, voided urine volume and flow morphology. These parameters, to be considered optimal, must be obtained when the volume of urine emptied remains between 150 and 400 ml. The morphology of the flow is "bell" shaped with a Qmax > 15 ml/s as a rule. A curve with a flattened and lengthened morphology over time is pathological.

Uroflowmetry is limited as a diagnostic test because it cannot provide a diagnosis of the underlying disease but can be used for monitoring treatment outcomes and for correlating symptoms with objective findings [12].

With regards to imaging, renovesical ultrasound is recommended if, in addition to the LUTS mentioned above, there is hematuria or a history of kidney stones. Prostate ultrasound can be performed suprapubically or transrectally; it is essential to perform if surgery for BPH is planned, as the calculation of the prostate volume can decide which therapeutic procedure to perform [13]. The prostatic volume calculated by the suprapubic approach appears to be overestimated compared to that by the transrectal approach. Diagnostic cystoscopy is not recommended in patients with BPH.

Treatment of obstructive prostatic hypertrophy can be classified into three types:

- watchful waiting

-Pharmacological treatment

-surgical treatment

The choice of therapy is based on the severity/severity of symptoms estimated by the IPSS questionnaire.

In the presence of an IPSS score < 8, watchful waiting is possible (pharmacological therapy is not indicated). When the IPSS score > 8, it is indicated to start pharmacological therapy according to international guidelines. Surgery is confined to patients who do not respond to drug therapy and/or develop complications of an obstructive nature: obstructive renal failure, bladder stones with recurrent urinary tract infections, recurrent macroscopic haematuria.

Pharmacological treatment of prostatic hypertrophy mainly consists of alpha-blocker drugs, 5 alpha reductase inhibitors and herbal medicines.

α1-blockers (e.g. tamsulosin, alfluzosin) aim to inhibit the effect of norepinephrine released on the smooth muscle cells of the prostate and thus aim to reduce the tone of the prostate and bladder neck [14]. These drugs also act on other receptors in other parts of the body, such as blood vessels, resulting in adverse effects, such as hypotension.

The different α1-blockers available on the market have similar efficacy in appropriate doses [16]. The effects take a couple of weeks to develop completely burned, but significant efficacy versus placebo can occur within hours or days [15].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Qmax by approximately 20-25% [17]. α1-blockers do not reduce prostate size [18]. The most frequent adverse events of α1-blockers are asthenia, dizziness and orthostatic hypotension. They do not negatively affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [19]. Originally, abnormal ejaculation was associated with retrograde ejaculation, but more recent data show that it is due to a decrease or absence of seminal fluid during ejaculation.

Thus, α1-blockers are often considered the first-line pharmacological treatment of LUTS due to their rapid action, good efficacy, low frequency and severity of adverse events. However, α1-blockers do not prevent the onset of acute urinary retention and the need for surgery for BPH.

Another category of drugs involved in the treatment of BPH are the 5 alpha reductase inhibitors (5-ARIs). The effects of androgens on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α-reductase. There are two isoforms of this enzyme:

• 5α-reductase type 1, activity predominant in extraprostatic tissues, such as skin and liver.

• 5α-reductase type 2, predominant in the prostate.

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits type 2 5α-reductase only, whereas dutasteride inhibits type 1 and type 2 5α-reductase with similar potency. 5α-reductase inhibitors work by inducing apoptosis of prostate epithelial cells [20] leading to a reduction in prostate size by approximately 18-28% and a decrease in circulating PSA levels by approximately 50% after six to twelve months of treatment [21].

Placebo-related clinical effects are observed after a minimum treatment duration of at least six to twelve months. An indirect comparison and a direct comparative trial (twelve months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [21, 23]. The greater the baseline prostate volume, the greater the symptomatic benefit of dutasteride over tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term risk (> 1 year) of acute urinary retention or the need for surgery [22, 24].

The most notable adverse effects of 5-ARIs are related to sexual function and include decreased libido, erectile dysfunction (ED), and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [21]. Gynecomastia develops in 1-2% of patients.

According to guidelines (EAU), in addition to the two categories of drugs mentioned above, there are also treatments for BPH based on natural extracts (phytotherapy).

Herbal medicines are made from roots, seeds, pollen, bark or fruit. There are single herbal preparations and preparations that combine two or more plants in one tablet. The most used plants are Cucurbita pepo (pumpkin seeds), Hypoxis rooperi (South African star grass), Pygeum africanum (African plum tree bark), Secale cereale (rye pollen), Serenoa repens (dwarf palm) and Urtica dioica (roots of 'nettle). In vitro, plant extracts may have anti-inflammatory, anti-androgenic and estrogenic effects; they can inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostate cells, α-adrenoreceptors, 5α-reductase, muscarinic cholinoceptors, dihydropyridine and vanilloid receptors, and neutralize free radicals [25-26]. Pharmacokinetic properties can vary significantly depending on how Serenoa repens is extracted.

Herbal therapeutic agents are a heterogeneous group and may contain different concentrations of active ingredients. In general, no herbal agent has been shown to reduce prostate size and a decrease in the progression of BPH has not been demonstrated [27-28]. Side effects during herbal medicine

are usually mild and comparable to placebo. Gastrointestinal disturbances are the most common reported.

Short-term studies have recently been performed on the combination of plant extracts with alpha-blockers and 5-ARIs.

PROCOMB study (2014): randomized double-blind multicenter study for 12 months of treatment in which patients were divided into 3 groups; group A, who received only Serenoa Repens + Lycopene (Ly) + Selenium (Se); group B, who received only tamsulosin 0.4 mg; group C, who received tamsulosin 0.4 mg + SerR + Ly+Se. The aim of the study was to achieve an improvement in some parameters (IPSS, post-void residual and Qmax at uroflowmetry) in patients in group C compared to those in group B. The results demonstrated a better efficacy of the combined therapy of group C compared to the single therapy of group B, (increase in Qmax and decrease in IPSS value). [29]

QUALIPROST study (2015): prospective, longitudinal, observational and multicenter study with the evaluation of 6 months of treatment. We included patients not taking any therapy, patients on monotherapy (with alpha-blockers, 5-ARIs and Serenoa Repens hexane extract) and patients on combined therapy (alpha-blockers + 5-ARIs and alpha-blockers + Serenoa Repens) .

The results obtained demonstrated comparable efficacy in the use of combined therapy with alpha blocker + Serenoa repens and with alpha blocker + 5-ARI [30].

To date, there are no scientific studies in the literature that evaluate the efficacy of the treatment of BPH with Serenoa Repens extracted with CO2 and PEA (palmitoylethanolamide) (PEAPROSTIL 600, FARMITALIA®). PEA is a substance produced by all living beings with analgesic and anti-inflammatory properties. It protects cells and tissues from oxidative damage, reduces chronic pain and restores the physiological tissue balance. It was discovered in 1957 and studied by Rita Levi di Montalcini, who won the Nobel prize in 1993. This synergistic action deriving from the combined activity of Serenoa Repens and PEA can lead to a reduction of the chronic prostatic inflammatory process (chronic abacterial prostatitis) in patients with BPH. PEAPROSTIL 600 (FARMITALIA®) is a supplement that is administered in orodispersible form without the need for the use of water and each sachet is 2.45 gr.

2. Objectives of the study

The objective of this study is to evaluate the efficacy of the PEAPROSTIL 600 (FARMITALIA®) supplement composed of Serenoa Repens associated with PEA combined with alpha-blocker in the reduction of LUTS symptoms in patients with IBP. During the entire study period, any adverse events, intolerance, allergic reactions, complications related to the products used will be recorded.

2.1 Primary Outcomes:

1) Evaluate the efficacy of the treatment in terms of subjective improvement of urinary symptoms by performing IPPS and SF-36 questionnaires and evaluate the objective improvement of urinary symptoms by performing uroflowmetry before and during treatment (during control visits follow-up at 1,3,6 and 12 months) by evaluation of the ultrasound post-voiding residue, comparing patients receiving combined therapy with tamsulosin+peaprostil (Arm 1) with patients receiving monotherapy with tamsulosin (Arm 3).

2.2 Secondary Outcomes:

1). Evaluate the tolerability profile of the study therapy, analyzing the side effects.

2). Evaluate the efficacy of the treatment in terms of subjective improvement of urinary symptoms by performing IPPS and SF-36 questionnaires and evaluate the objective improvement of urinary symptoms by performing uroflowmetry before and during treatment (during follow-up visits -up at 1,3,6 and 12 months) by means of ultrasound evaluation of the post-voiding residue, comparing the patients of the 3 study groups (Arm 1, 2 and 3).

3. Study design

The study is a single-center, 3-arm, prospective randomized clinical trial.

• Arm 1: PEAPROSTIL 600 + Tamsulosin 0.4 mg/dl
• Arm2: PEAPROSTIL 600
• Arm 3: Tamsulosin 0.4 mg

Upon enrollment in the study, each patient will be randomized into one of the 3 arms described. Randomization will take place in a 1:1:1 pattern.

Based on clinical-scientific considerations inherent to the typology of patients and to reality clinic, the experimental design indicated above currently corresponds to the best possible.

3.1 Composition of the therapy

• PEAPROSTIL 600 is a food supplement based on Palmitoylethanolamide and Serenoa Repens, respectively for each sachet there are 600 mg of PEA and 320 mg of Serenoa oil. The net content of a sachet is 2.45 g and can be orodispersible without the need for the use of water. The drug does not contain gluten or lactose.

• Tamsulosin 0.4 mg is a drug belonging to the category of alpha-blocker drugs used as first choice drugs (according to EAU lines) for the treatment of LUTS/BPH. The recommended dose is 0.4 mg per day (1 administration), to be taken preferably at the same time during the day, indifferently with or without meals.

4. Patient selection

4.1 Target population

Patients referred to outpatient visits eligible for study at the S.C.D.U. of Urology of the Maggiore Hospital of Charity of Novara.

4.2 Inclusion criteria

o Male patients aged 40 years or older

o Patients with baseline IPSS questionnaire between 8 and 14

o Patients with prostate volume ≤ 60 cc assessed by transrectal ultrasound (TRUS)

o Patients who have a Qmax ≤ 15 ml/sec on uroflowmetry

o Patients who show a post-voiding residue ≤ 120 ml on extemporaneous ultrasound

o Patients who have signed the informed consent for participation in the study

o Patients able to understand the conditions of the study and to participate for the full duration.

4.3 Exclusion Criteria

o Patients suffering from urinary incontinence

o Patients with overactive bladder

o Patients with neurological bladder

o Patients with active malignancies and who have been treated for malignancy in the previous 6 months

o Patients suffering from local or systemic infections (UTI, osteomyelitis, sepsis, etc.)
o Patients with renal insufficiency
o Patients with bladder stones
o Patients with gross haematuria

5. Study procedure

5.1 Data Collection Method

Each patient participating in the study will be uniquely identified by an alphanumeric code. All the data required by the protocol, relating to the patient, to the medical record, to the therapeutic intervention, to the checks following discharge from the hospital, will be recorded by a co-investigator who will directly follow the study and its correct conduct for its entire duration. duration. All data will initially be recorded on forms in paper format which will form the data collection folder (CRF).

A file containing all completed forms and signed informed consent will be kept for each patient.

Information concerning patients (identification codes, personal data, medical records, consent, information privacy policy) will be kept by the Investigator in special confidential archives (patients file) to guarantee the privacy of the subjects and exhibited in the event of audits, inspections or monitoring visits. All the variables under study will be entered in a dedicated and password-protected database, kept at S.C.D.U. Urology, The database will be shared on a cloud-protected server with the Biostatistics department of the University of Catania which will carry out the statistical analysis (Prof. Martina Barchitta). The Investigator and co-Investigators will be the only ones to have access to the database.

5.1.1 Method of randomization

Randomization will take place in a 1:1:1 pattern. Based on considerations
clinical-scientific inherent to the typology of patients and to the clinical reality, the design
experimental above currently corresponds to the best possible.

5.2 Pre-treatment assessment

All patients will undergo an accurate analysis of the following parameters (T0).

- Personal data: identification number and initials of the patient's name and surname, date of birth, telephone number and e-mail address.
- General characteristics: gender, weight, height, smoker, coffee and/or tea intake, allergies, job, sport, diabetes mellitus.
- Medical therapy in progress.
- Remote pathological history: previous surgical interventions, underlying pathologies and number of deliveries.
- Past pathological history and diagnosis: starting date and type of symptomatology
- Assessment of quality of life (QoL questionnaire).
- Voiding assessment (IPSS questionnaire)
- Physical examination: abdominal, urological including rectal examination.
- Uroflowmetry (morphology of the curve, Qmax, Vol, RPM-residual evaluation post urination)

5.3 Measurements during the treatment cycle

All data collected during the administration of the therapy will be collected and reported in the appropriate data collection folder (CRF) by a co-investigator doctor from the team of Prof. Alessandro Volpe.

5.3.1 Safety assessment and appearance of adverse events:

An adverse event is considered any unfavorable and unwanted sign, symptom or disease found in a patient participating in a clinical study temporarily associated with the use of an experimental product, even if it does not necessarily have a causal relationship with the treatment received. Clinical and/or pathological conditions present prior to initiation of study treatment are considered adverse events only if they worsen after initiation of study treatment.

Every adverse event that occurred during the execution of the study will be recorded.

In the event of an adverse event, the Investigator will promptly institute the appropriate investigations and therapeutic measures. Any adverse event occurring during the study should be treated according to recognized treatment standards. If necessary, the patient will be withdrawn from the study.

The procedures foreseen by the study do not involve any additional risk for the patient's health.

The Investigator must promptly report, within 24 hours, any adverse event that occurs to patients during the study to the Ethics Committee, to the Promoter, in accordance with the provisions of the law.

In the event of accidents (defined by article 9, paragraph 1 of Legislative Decree 46/97 and by article 11, paragraph 1 of Legislative Decree 507/92) that may have occurred during the project, the reports will be sent to the Office V (Medical Device Supervision) of the DGDFSC (General Directorate of Medical Devices, Pharmaceutical Service and Care Safety) of the Ministry of Health, according to the procedures set out in Meddev 2.12-1 rev 6 year 2009, by the Promoter. The information relating to the accidents will also be sent to the Manufacturer.

5.3.2 Expected Adverse Events

Predicted adverse events include all those events that are expected to occur in association with any routine treatment. No serious adverse events have ever been reported in the literature regarding the use of tamsulosin.

Common effects (<1/10 cases, > 1 100 cases (1-10%)): dizziness, particularly on sitting or standing up. Abnormal ejaculation (ejaculation disorder). This symptom means that the seminal fluid does not leave the body through the urethra but enters the urinary bladder (retrograde ejaculation) or that the volume of seminal fluid is reduced or absent (ejaculation failure). Uncommon effects (>1/1000 cases, <1/100 cases (0.1-1%)): headache, palpitations (heart beats more frequently than normal and is also noticeable), decrease in blood pressure to example rising quickly from sitting or lying down often associated with dizziness, stuffy or runny nose (rhinitis), diarrhoea, nausea and vomiting, constipation, weakness (asthenia), rash, itching and hives.

Rare effects ((>1/10000 cases, <1/1000 cases (0.01-0.1%)): fainting and cases of sudden localized swelling of soft tissues of the body (e.g. of the throat and tongue), difficulty breathing and/or itching and rash (rash), as frequently in an allergic reaction (angioedema).

Very rare effects (<1/10,000 cases (<0.01%)): priapism (painful and prolonged involuntary erection requiring immediate medical treatment).

The most frequent adverse events from the use of tamsulosin were orthostatic hypotension, retrograde ejaculation and ejaculation failure, gastrointestinal disorders [31].

5.3.3 Adverse event reporting period

The adverse event baseline period for this study begins on day 0 and ends 30 days after study completion. All adverse events should be documented in the data collection record (CRF), as well as any other events considered potentially related to the device.

5.4 Post-treatment evaluation protocol

All the variables will be collected by a co-investigator of Prof. Alessandro Volpe's team during check-ups at pre-established intervals of 1, 3, 6 and 12 months (T1, T2, T3 and T4 respectively) and will be reported in the specific data collection folder (CRF).

- at 1 month (T1), 3 months (T2), 6 months (T3) and 12 months (T4):
- Personal data: identification number and initials of the patient's name and surname, date of birth, telephone number and e-mail address
- Medical history: IPSS, SF-36
- Physical examination: abdominal, urological including rectal examination
- Uroflowmetry: morphological analysis of the flow curve, Qmax, Volume of urine emptied, RPM).

6. Sample size and statistical analysis of the data

A total of 250 patients will be recruited. The sample analysis was performed by the “GF Ingrassia” Department of Medical, Surgical Sciences and Advanced Technologies of the University of Catania. In particular, the design foresees a 1:1:1 randomization process in 3 arms. Expect a difference of at least 2 points in IPSS and Qmax and a standard deviation of 4, as described in previous studies (Morgia et al., 2014; Alcaraz et al., 2016), it is necessary to enroll 250 patients to obtain a power 90% statistic at a significance level of 0.05.

The statistical analysis of the data collected during the study, according to an intention-to-treat procedure, will be performed using statistical software such as IBM SPSS statistics version 23.0. The variables that will be collected in order to evaluate the efficacy of the therapy will be: chronological age, weight, BMI, smoking, diabetes, PSA, IPSS, Postvoiding Residual, Qmax, QMed, Voided volume, SF-36 score. A descriptive analysis of the patients included in the three arms will be performed using the appropriate frequency measures and indices of central tendency and dispersion. Considering one pair of the three arms at a time (1 vs. 2; 1 vs. 3; 2 vs. 3), the qualitative variables will be compared using the chi-squared test; the quantitative variables will be

compared using Student's t-test. The level of significance will be set at $p < 0.05$. For the variables that will be significant in the univariate analysis, multivariate analyzes will be performed using appropriate regression models to control for the effect of the covariates.

7. Duration of the study

The duration of the study will be 1 year. The enrollment of patients will take place for 1 year, the follow-up will be concluded 1 year after enrollment. A preliminary statistical analysis will be performed with the data obtained at 3 and 6 months. The final analysis will be conducted upon completion of the study.

8. Publication Policy

The results of this study will be summarized and presented in a final report which will have the aim of drawing reliable conclusions regarding the effective efficacy of using PEAPROSTIL 600 in the treatment of benign prostatic hypertrophy. The scientific article will then be sent to a peer-reviewed journal in the sector to be published in order to disseminate the results obtained to the scientific community. The data produced in this survey will be owned by the Ospedale Maggiore della Carità, Corso Mazzini 18, 28100, Novara, Italy.

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10. Abbreviations index

LUTS: low urinary tract symptoms

BPH: benign prostatic hypertrophy

PSA: prostate specific antigen

IPSS: International Prostatic Symptoms Score

QoL: quality of life questionnaire

CO2: Carbon dioxide

PEA: Palmitoylethanolamide

Qmax: maximum flow

5-ARI: 5α-reductase inhibitors

DE: erectile dysfunction

RPM: post-voiding residue

Vol: volume

Cr: creatininemia

eGFR: glomerular filtration rate

UTI: urinary tract infection

CRF: data collection folder

TRUS: transrectal ultrasound

DHT: dihydrotestosterone

Echo: ultrasound

s: seconds

ml: millilitres

ng: nanograms

T0: zero time

T1: 1 month

T2: 3 months

T3: 6 months

T4: 12 months

Novara, 17/02/2021 Dr. Michele Billia