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Is there an effect of oral anticholinergics on the clinical and molecular parameters of prostate and bladder of patients with benign prostatic hyperplasia and overactive bladder?

Submission date
09/04/2017

Recruitment status
No longer recruiting

Registration date
18/04/2017

Overall study status
Completed

Last Edited
23/01/2019

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Benign prostatic hyperplasia (also known as prostate enlargement) is a common condition in men after the age of 50. It usually causes people to have to urine (pee) often and urgently. This can be very difficult to handle. An overactive bladder (where urine is collected and held) could be a symptom of an enlarged prostate. A prostatectomy is a surgical procedure that removes either part of or the whole prostate is done to try to help relieve an overactive bladder. However, research has shown that people who have undergone a prostatectomy still have overactive bladder symptoms. Therefore it is unclear if only the prostate should be treated or both the prostate and the bladder should be treated to help relieve the symptoms. There are medications that can be used to treat the symptoms such as tamsulosin which help improve urination and solifenacin which helps treat the muscle movement in the bladder. The aim of this study is to explore whether the medications used in the treatment of benign prostatic enlargement-associated Lower Urinary Tract Symptoms (LUTS) has an effect on the prostate as well as on the bladder.

Who can participate?
Adults who are aged 50 and older who have lower urinary tract symptoms and adults who are 50 years or older who do not have symptoms.

What does the study involve?
This study involves two parts. Participants in the first part of the study are randomly allocated to one of two groups. Those in the first group receive a single tablet taken by mouth of tamsulosin (0.4mg) that they take nightly for six months. Those in the second group receive a tablet of tamsulosin (0.4mg) that also includes solifenacin (5mg) that they take nightly for six months. Participants are assessed at the start of the study and at the end of the study for their bladder and urine symptoms as well as quality of life and blood tests. After the six months, participants are asked if they would like to continue with the medicine or undergo a prostatectomy. The second part of the study includes the samples taken from participants, who agreed to undergo a

prostatectomy, and compares their samples with participants (with both symptoms of overactive bladder and those without) who have agree to provide tissue samples during other procedures.

What are the possible benefits and risks of participating?
Participants may benefit from receiving additional diagnostic tests. There are risks associated with the tamsulisin medication including blurred vision, hypotension (low blood pressure), retrograde ejaculate (where the semen enters the bladder as it cannot leave through the penis). There are also risks with solifenacin which include dry mouth, dry eyes, constipation (unable to have a bowel movement), cognitive dysfunction (mental problems) and hypertension (high blood pressure). There are risks with some of the diagnostic procedures including bleeding, infection, painful urination, and discomfort. There are also risks associated with prostatectomy which include bleeding, infection, retrograde ejaculation, incontinence (leakage of urine or feces).

Where is the study run from?
1. Hippokrateion General Hospital of Thessaloniki (Greece)
2. Papageorgiou Hospital of Thessaloniki (Greece)

When is the study starting and how long is it expected to run for?
January 2013 to June 2015

Who is funding the study?
1. European Social Fund (EU)
2. Greece National Resources (Greece)

Who is the main contact?
Dr Vasileios Sakalis

Contact information

Type(s)
Scientific

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Protocol serial number
71/13.03.2014

Study information

Scientific Title
Changes in lower urinary tract cholinergic pathways in patients with Benign Prostatic Hyperplasis-associated Lower Urinary Tract Symptoms and Overactive Bladder symptoms: The effect of oral antimuscarinics

Study objectives
The aim of this study is to explore whether the antimuscarinics used in the treatment of benign prostatic enlargement-associated Lower Urinary Tract Symptoms (LUTS) have an effect on the prostate as well as on the bladder.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Aristotele University of Thessaloniki, Greece, School of Medicine, Ethics Committee, 13/03/2014, ref: 71/13.03.2014

Primary study design
Interventional

Study design
Prospective multi-centre open-label active comparator randomised controlled study

Study type(s)
Other

Health condition(s) or problem(s) studied
Benign prostatic hyperplasia, Overactive Bladder

Interventions
This study involves two study arms, one clinical and one molecular.

Arm 1: Clinical
Potential participants are identified during an assessment in the male Lower Urinary Tract Symptoms (LUTS) clinic. They are given a study information pack and asked to return a three-day bladder dairy within two weeks. Those who documented the required number of daily urgent episodes are asked to join the study. Participants are randomly allocated using SPSS software (1: 1) into one of two groups.

Group 1 Tamsulosin monotherapy: Participants receive tamsulosin 0.4mg tamsulosin once at night (Tamsulosin OCAS 0.4mg, Astellas) for six months.

Group 2 Tamsulosin & Solifenacin Combination therapy: Participants receive solifenacin 5mg plus tamsulosin 0.4mg to take once at night (Astellas) for six months.

Titration of solifenacin dose (10mg) is possible in the combination therapy patients who have inadequate symptom control after 4 weeks. Patients are followed up at baseline and at 26 weeks to assess their urinary symptoms, quality of life and to complete tests including transrectal and transabdominal ultrasonography, free uroflowmetry and pressure-flow study, basic biochemistry, PSA and Testosterone blood tests. At week 26 they are asked to repeat a bladder diary. Participants have interim follow-up assessments at four and 12 weeks that include questionnaires, uroflowmetry and transabdominal ultrasonography. At study completion participants are asked whether they would like to continue on medical therapy or undergo prostatectomy (transurethral resection, for prostates <80mls or open procedure, for prostates>80mls). If they choose the prostactectomy they are included in the second arm of the study.

Arm 2: Molecular
This arm compares tissue samples from different symptomatic patients. Participants in this group include those from the first arm of the study who have agreed to a prostatectomy and from three control groups. Participants from the first arm of the study undergo a prostatectomy. This is done using a transurethral resection for prostates <80mls or an open procedure for >80mls.

The control groups consist of the following:

Control group 1: Treatment naive patients with benign prostatic hyperplasia (BPH) and Overactive Bladder (OAB). Participants in this group are asked to provide a tissue sample during a procedure for another problem (typically ureteroscopic lithotripsy or small volume bladder tumour disease).

Control group 2: Asymptomatic men (Bladder biopsies). Participants are recruited based on their IPSS (International prostate symptom score questionnaire) score. These participants undergo a procedure for another problem (usually to treat ureteric stones and small volume bladder tissue. The sample is obtained from a macroscopically healthy bladder area.

Control group 3: Asymptomatic men (Prostate biopsies) Participants are recruited based on their IPSS (International prostate symptom score questionnaire) score. Participants in this group provide a undergo a transrectal biopsy of their prostate, and are asked to provide an additional biopsy for this study.

The samples collected from the treatment group are compared to samples from the control groups (the symptomatic group, asymptomatic bladder tissue and one asymptomatic prostate tissue).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tamsulosin, Solifenacin

Primary outcome(s)
Muscarinic receptor expression is measured using the immunohistochemistry (Western Blot and RT-PCR) at 6 months

Key secondary outcome(s)
1. Urinary symptoms are measured using IPSS Questionnaire at three and six months
2. Storage ability is measured using IPSS Questionnaire Storage subscale at three and six months
3. Amount of prostate specific antigen (PSA) in the blood is measured using standard laboratory biochemistry tests at three and six months
4. Semen parameters are measured using standard laboratory biochemistry tests at three and six months
5. Total prostate and adenoma volume is measured using Transabdominal and transrectal ultrasonography at three and six months
6. Quality of life is measured using the QoL question of the IPSS at three and six months
7. Adrenergic receptor expression in prostate and bladder is measured using immunohistochemistry (Western Blot and RT-PCR) at six months
8. Sensory receptor TRPV1 expression is measured using immunohistochemistry (Western Blot and RT-PCR) at six months
9. eNOS and VEGF expression in prostate and bladder using immunohistochemistry (Western Blot and RT-PCR) at six months

Completion date
30/06/2015

Eligibility

Key inclusion criteria
Treatment arms (Group 1 and 2):
1. Treatment-naïve men
2. Age 50 years or older
3. Predominantly storage LUTS as defined by the IPSS (storage subscore ≥ voiding subscore and score ≥ 3 in the urgency question) and at least 3 urgency episodes per 24h as documented in a 3-day bladder diary
4. Prostate volume ≥30ml
5. Maximum flow rate (Qmax) ≥10ml/s
6. Post-void residual (PVR)≤100ml
7. PSA value ≤ 4 ng/ml. Patients with positive DRE and/or PSA values 4-10ng/ml are included only after negative prostate biopsy.

Control group 1:
1. Treatment-naïve men
2. Age 50 years or older
3. Predominantly storage LUTS as defined by the IPSS (storage subscore ≥ voiding subscore and score ≥ 3 in the urgency question) and at least 3 urgency episodes per 24h as documented in a 3-day bladder diary
4. Prostate volume ≥ 30ml
5. Maximum flow rate (Qmax) ≥ 10ml/s
6. Post-void residual (PVR) ≤ 100ml
7. PSA ≤ 4ng/ml. Patients with positive DRE and/or PSA values 4-10bng/ml are included only after negative prostate biopsy
8. Consent to provide prostate or bladder tissue

Control group 2 and 3: Asymptomatic men
1. Treatment-naïve men
2. Age 50 years or older
3. Total IPSS <7 and/or a score of 0-1 in the IPSS ‘urgency’ question.
4. Prostate volume ≥ 30ml
5. Maximum flow rate (Qmax) ≥ 10ml/s
6. Post-void residual (PVR) ≤ 100ml
7. PSA ≤ 4ng/ml. Patients with positive DRE and/or PSA values 4-10 ng/ml were included only after negative prostate biopsy.

Healthy volunteers allowed
No

Age group
Adult

Sex
Male

Key exclusion criteria
1. Patients with neurogenic lower urinary tract dysfunction
2. Patients with a history of urinary tract malignancy
3. Any contraindication to the use of α-blockers or antimuscarinics
4. Metabolic conditions that may affect lower urinary tract (LUT) function
5. Psychiatric illnesses
6. Chronic kidney, hepatic or cardiac failure
7. History of urinary stone disease
8. History of urethral instrumentation
9. Urethral stricture
10. Acute urinary tract infection (UTI) or history of recurrent UTI’s
11. Use of medications known to affect LUT function including PDE-5 inhibitors
12. Positive urine culture
13. Microscopic haematuria, proteinuria or glucosuria. Subjects with pyuria were included only after a negative urine culture.

Date of first enrolment
01/10/2013

Date of final enrolment
01/02/2015

Locations

Countries of recruitment
Greece

Study participating centre

Hippokrateion General Hospital of Thessaloniki
Thessaloniki
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Study participating centre
Papageorgiou Hospital of Thessaloniki
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Sponsor information

Organisation
Aristotele University of Thessaloniki

ROR
https://ror.org/02j61yw88

Funder(s)

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Funder Name
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Alternative Name(s)
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Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
Greece National Resources

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Vasileios Sakalis MSc, FEBU at vsakkalis@hotmail.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2018	23/01/2019	Yes	No