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RESEARCH PROTOCOL

Access this article online

Website: www.ijrh.org

DOI: 10.4103/0974-7168.135639

Quick Response Code:

Homoeopathic therapy for lower urinary tract symptoms in men with Benign Prostastic Hyperplasia: An open randomized multicentric placebo controlled clinical trial

Central Council for Research in Homoeopathy

ABSTRACT

Background: Benign Prostatic Hyperplasia (BPH) is the most common condition in ageing men, associated with Lower Urinary Tract Symptoms (LUTS). Being a cause of significant morbidity in ageing man, various observational studies were conducted by the Council with a positive outcome. This protocol has been prepared to further ascertain the usefulness of constitutional/organ remedies in LUTS for men with BPH in a randomized control setting.
Objectives: The primary objective is to compare the changes in IPSS (International Prostate Symptom Score) within the three groups enrolled for the study (Constitutional remedy/Constitutional + Organ remedy/Placebo). The secondary objectives are to compare the changes in Prostate volume, Post Void Residual Urine (PVRU), Uroflowmetry and in WHOQOL–BREF.
Material and Methods: It is an open randomized placebo controlled clinical trial. The prescription of the constitutional remedies/organ remedies/placebo is done as per the randomization chart and the selection of these remedies is done as per the guidelines laid in the Organon of Medicine. The outcome measures including IPSS (monthly), prostate volume, post void residual urine, uroflowmetry and the WHOQOL–BREF are assessed at baseline, three and six months interval.
Discussion: Results from this trial will help in constructing treatment strategy for BPH patients with lower urinary tract symptoms in improving their quality of life.
Trial Registration: Clinical Trial Registry - India: CTRI/2012/05/002649.

Keywords: Homoeopathy, Prostate, Post void residual urine, Prostate volume, Uroflowmetry

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Received: 12-06-2014
Accepted: 13-06-2014

BACKGROUND

Benign Prostatic Hyperplasia (BPH) is the most common condition in ageing men, associated with Lower Urinary Tract Symptoms (LUTS). The prevalence of BPH increases with age. The lifetime risk of developing histologically confirmed BPH has been approximately 8% between the age 31 to 40 years, 50% between 51 to 60 years, 70% between 61 to 70 years and 90% between 81 to 90 years.[1] Correspondingly, symptomatic (clinical) BPH is present in approximately 26% of the men in the fifth decade, 33% in the sixth decade, 41% in the seventh decade and 46% in the eighth decade of life and beyond.[2] The various risk factors of BPH are the

demographic factors; genetic factors including family history, role of Vitamin D3 and its receptor which regulates both epithelial and cell growth proliferation; and behavioural and co-morbid factors including obesity, which increases the risk of BPH by 10% for each 0.05 increase in the waist-to-hip ratio. Obesity is also associated with an increase in sympathetic tone, which promotes prostatic cellular proliferation. Moderate to vigorous exercise reduces the risk by 25%. The dietary factors including high intake of polyunsaturated fats and a diet high in beef products increases the risk by 25%. Alcohol consumption appears to have a protective effect on BPH development. The risk decreases by 50% in men who consume three drinks of alcohol per day. The association is believed to be related to alcohol's cardiovascular effects and modulation of steroid hormone metabolism.[2] The enlarged gland produces Lower Urinary Tract Symptoms (LUTS) complex via at least two routes: (a) direct Bladder Outlet Obstruction (BOO) from enlarged tissue (static component) and (b) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to BOO. Detrusor overactivity is a contributor to the storage symptoms.[3]

The specific approach used to treat BPH depends upon number of factors like age, prostate size, weight, prostate-specific antigen level and severity of the symptoms. Alternative treatment available for the moderate to severe symptoms of BPH include watchful waiting, medical therapies including Alpha-blockers, 5-Alpha-reductase inhibitors (5-ARIs), Anticholinergic agents, their combination therapy and minimally invasive and surgical therapies.[4] Conventional therapies such as Alpha adrenergic blocking agents, 5-Alpha–reductase inhibitors result in 25% shrinkage of prostate gland and 20% improvement in symptom scores. These drugs are expensive in comparison with their effectiveness. However 65% of men undergoing prostatectomy develop retrograde ejaculation. Erectile impotence occurs in about 5% of men. Moreover, patients with very mild symptoms of BPH receive little or no benefit from surgery.[5,6] BOO secondary to BPH is the most common cause of LUTS. Although voiding symptoms (e.g. slow stream, hesitancy, intermittency and terminal dribble) occur with a greater frequency, storage symptoms (e.g. increased daytime frequency, nocturia, urgency and urinary incontinence) are considered to be most bothersome and interfere to a great extent with daily life activities of the patient and his partner's Quality Of Life (QOL).[7]

The results of the observational study carried out by the Council previously had shown promising results, which require further control studies. The IPSS, prostate weight, PSA and average flow rates had shown statistically significant improvement whereas Maximum Flow Rate and Post Void Residual Urine (PVRU) showed some improvement, which was not statistically significant. *Lycopodium, Pulsatilla, Sulphur* and *Calcarea carb*. were found to be most useful.[7]

STUDY OBJECTIVES

Primary

To compare the changes in IPSS (International Prostate Symptom Score) within the groups enrolled for the study (Constitutional remedy/ Constitutional + Organ remedy/Placebo).

Secondary

To compare the changes in prostate volume, post void residual urine, uroflowmetry and in WHOQOL–BREF.

STUDY DESIGN AND SETTINGS

It is a multi-centric randomized placebo controlled study being carried out at six centres. The patients are enrolled for six months through OPD screening. The intervention is given for six months, and the evaluation of IPSS is done monthly for six months. The assessment of PSA, prostate volume, post void residual urine and uroflowmetry (Q Max. and Q Avg.) is done at baseline, three months and six months, which is detailed in Figure 1.

Study eligibility criteria

Eligible participants comprise (a) men aged between 50-80 years presenting with (b) presence of BPH symptoms with IPSS score >7 [Table 1]. (c) Prostate Specific Antigen (PSA) level equal to or below 4 ng/mL (to rule out suspected cases of malignancy) and (d) on ultrasonographic examination prostate weight >20 g/20 cc/20 ml) (e) written informed consent from the patients.

The exclusion criteria for the study are (a) patients who are not adequately symptomatic (mild according to IPSS) (b) patients with serious underlying medical condition like severe renal, hepatic disease etc., (c) complete retention of urine for more than 24

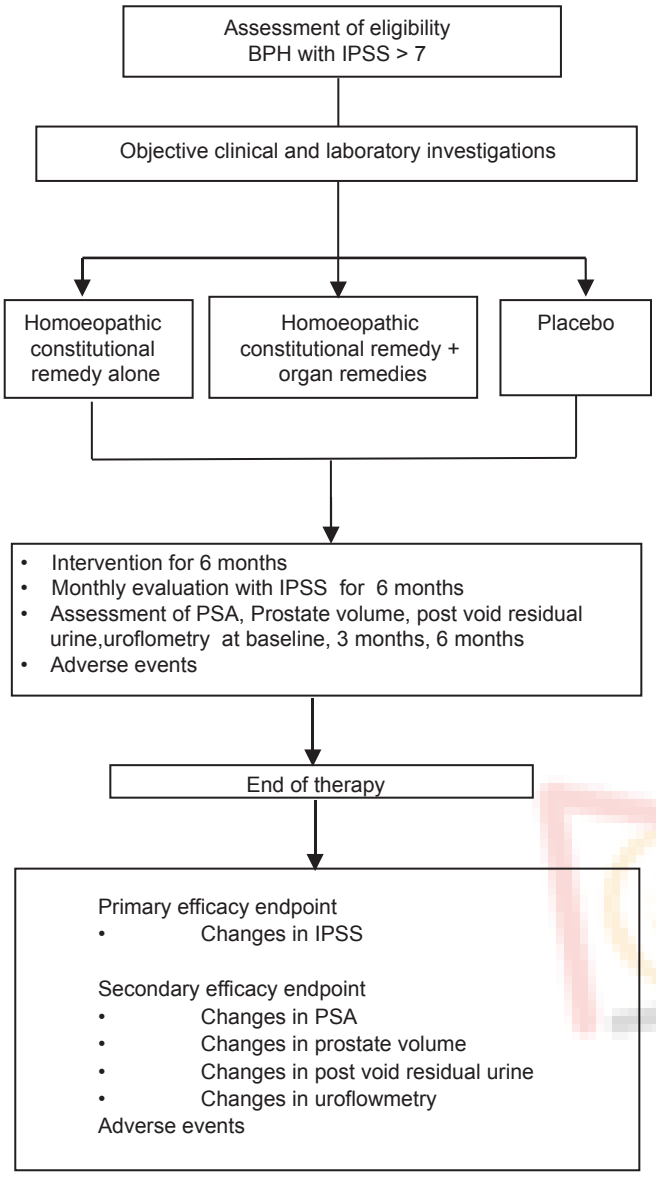

Figure 1: Consort flow diagram

hours (d) prostatic carcinoma (e) patients interested for surgery during the next 6 months (f) other possible causes such as recurrent urinary tract infection, neurogenic bladder or urethral stricture.

Total score

0-7: Mildly symptomatic; 8-19: Moderately symptomatic; 20-35: Severely symptomatic.

Sample size

The sample size was calculated keeping in view the outcome of the earlier observational study. Using the effective size of 0.6, with power 90%, $\alpha = 0.05$, Homoeopathic Constitutional (HC): Homoeopathic Constitutional (HC) + Organ Remedy (OR): Placebo: 2:2:1, the calculated sample size was 90:90:45. The target sample size is 225.

Randomization and intervention

Patients fulfilling the eligibility criteria are enrolled and randomized as per computer generated randomized chart to receive constitutional homoeopathic medicine alone in LM potency, constitutional homoeopathic medicine in LM potency along with organ remedy in trituration/mother tincture and placebo in the ratio of 2:2:1. Constitutional medicines are selected and administered on the basis of individualizing characteristic symptoms. Organ remedies like *Sabal serrulata* Q, *Hydrangea arborescens* Q, *Chimaphila umbellate* Q, *Berberis vulgaris* Q, *Ferrum pic.* 3X, *Pareira brava* Q, *Sabal serrulata* Q and *Solidago* Q are being used as an adjuvant to constitutional medicine in accordance with their indications.

Periodic assessment and follow up

At baseline, all enrolled subjects are examined by experienced qualified homoeopathic doctors having variable experience (10-20 years) for all outcome measures [IPSS, prostate volume, post void residual urine, uroflowmetry, PSA and WHO QOL – BREF] along with individual characteristics on pre-designed proforma. The final selection has to be done using repertorization, materia medica consultation and outcome of previous study. The periodicity of assessment has been given in Table 2. Adverse events are noted in all the groups during the treatment period.

Study endpoints

Primary study endpoint is to compare the changes among three groups in IPSS at 6 months and secondary study endpoints are the changes in prostate volume, post void residual urine and uroflowmetry at 3 and 6 months. The changes in WHOQOL– BREF shall be at 6 months. Primary safety endpoint is any adverse event amongst the groups.

Study duration

18 months. (6 months for enrolment + 6 months for treatment + 6 months for data analysis and manuscript preparation).

Data collection

Data collection starts with the screening of patients above the age of 50 years with urinary discomfort. After obtaining the written informed consent, further detailed screening is undertaken using IPSS scale and investigated for PSA level, Prostate volume and Post void residual urine.

Table 1: International Prostate Symptom Score (IPSS)

In the past month	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	
Nocturia Over the past month, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Table 2: Month-wise evaluation of outcome parameters of screened and enrolled patients

Day/month	Baseline	Study period in months					
		1st	2nd	3rd	4th	5th	6th
Screening	√						
Informed consent	√						
CRF		√					
IPSS	√	√	√	√	√	√	√
PSA	√			√			√
Prostate volume	√			√			√
Post void residual urine	√			√			√
Uroflowmetry	√			√			√
WHOQOL-BREF	√			√			√
Adverse events		√	√	√	√	√	√

CRF: Case Recording Form; IPSS: International Prostate Symptom Score; PSA: Prostate Specific Antigen

Data management

The information of all patients screened and enrolled is to be recorded. The case history of each case is to be recorded in the Case Recording Format and the relevant annexure pertaining to base line assessment, IPSS, WHOQOL–BREF, Acute Phase Information Sheet, Adverse Event Reporting Form and details of medicine dispensing are filled and maintained.

Data analysis

Data obtained from all study centres would be verified and analyzed using Paired *t*-test, ANOVA repeated measures and other appropriate statistical tools.

Ethical clearance

The study has been approved by the ethical committee.

DISCUSSION

There is sufficient homoeopathic literature wherein a number of constitutional as well as organopathic medicines are listed for the treatment of BPH. Several rubrics related to the symptoms of BPH with indicated constitutional remedies and organ remedies are seen in many repertories.[7-11]

Council also carried out various multicenter observational studies on BPH. In a pilot study, eleven cases of BPH were assessed on the basis of American Urological Association Symptom Index (AUASI). Constitutional remedies including *Pulsatilla nigricans* and *Thuja occidentalis* proved useful.[12]

In another observational study undertaken by the Council, the clinical as well as laboratory/diagnostic parameters were assessed using 20 pre-selected homoeopathic medicines and of those *Lycopodium, Pulsatilla, Sulphur* and *Calcarea carb*. were found useful.[13]

Another clinical trial conducted by AK Hati *et al.* comparing the homoeopathic treatment strategies using Constitutional Medicines (CM) or Organopathic Medicines (OM) alone or in combination of both Constitutional and Organopathic Medicines (BCOM) in patients suffering from BPH reports the highest treatment response in patients prescribed BCOM. However, this study was not randomized and instead sequentially allocated.[14]

As the previous studies were not randomized, the present study is a randomized open label three arm study with one arm consisting of homoeopathic constitutional remedy alone, second of homoeopathic constitutional and organ remedies and third arm comprising of the placebo group. The organ remedies were selected from among the medicines found useful in the study by AK Hati *et al.* and the rest were selected from the available literature. The outcome shall be assessed on composite endpoints mainly IPSS, post voidal residual urine, prostate volume, uroflowmetry (Q_{max} and Q_{avg}), PSA level and WHOQOL–BREF, a validated questionnaire used for evaluation of quality of life in cases of BPH. All the domains of Model Validity of Homoeopathic Trials (MVHT)[15] are covered in this protocol as BPH study is amenable to homoeopathic intervention, the specific intervention used is consistent with homoeopathic principles, the rationale for the intervention used is supported by a significant body of homoeopathic practitioners, the main outcome measures reflect the key effects expected of the intervention used and is capable of detecting the change. Furthermore, the length of the follow up for the main outcome is appropriate to detect the intended effect of the intervention used.

The overall risk of bias[16] appears to be minimal as only one domain (allocation concealment) out of six has high risk of bias. Although the primary objective i.e. comparison of IPSS is subjective but the secondary outcomes are objective and shall not be influenced by lack of blinding. The study is not blinded due to multiple prescription in the second arm and because an identical control group for mother tinctures cannot be created. It is hoped that the data generated shall be useful for the profession in general and researchers in particular.

Trial status

The study was initiated in the month of July 2012 and till date 430 patients have been screened and 217 have been enrolled.

CONTRIBUTIONS

Study concept and design: Praveen Oberai[1], GRC Reddy[2], Varanasi Roja[3]
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How to cite this article: Central Council for Research in Homoeopathy . Homoeopathic therapy for lower urinary tract symptoms in men with Benign Prostastic Hyperplasia: An open randomized multicentric placebo controlled clinical trial. Indian J Res Homoeopathy 2014;8:75-80.

Source of Support: Nil, **Conflict of Interest:** None declared.

सौम्य प्रोस्टैटिक हाईपरप्लासिया (बीपीएच) से पीड़ित पुरूषों में लोअर यूरिनरी ट्रैक्ट लक्षणों का होम्योपैथिक उपचारः एक खुला यादृच्छिक बहुकेंद्रीय प्लासिबो नियंत्रित नैदानिक परीक्षण

पृष्ठभूमिः बढ़ती आयु वाले पुरुषों में सौम्य प्रोस्टैटिक हाईपरप्लासिया (बीपीएच) व सम्बंधित लोअर यूरिनरी ट्रैक्ट (एलयूटीएस) के लक्षण एक बहुत सामान्य सी स्थिति है। परिषद् के पिछले अवलोकन अध्ययनों के परिणाम सकारात्मक थे। इस प्रोटोकॉल को बीपीएच वाले पुरुषों में एलयूटीएस के संगठनात्मक उपचार में लाभप्रदता को सिद्ध करने के लिए तैयार किया गया है।

उद्देश्यः इस अध्ययन का प्राथमिक उद्देश्य छह महीनों के बाद आईपीएसएस (इंटरनेशनल प्रोस्टेट सिम्पटम स्कोर) में परिवर्तन को नापना है।अन्य उद्देश्य प्रोस्टेट वॉल्यूम,पोस्ट वोयड रेसिडुअल यूरिन,यूरोफ्लोमेट्री और डब्ल्यूएचओक्यूओएल–बीआरईएफ में परिवर्तन हैं।

सामग्री और विधिः यह एक खुला यादृच्छिक बहुकेन्द्रीय प्लासिबो नियंत्रित नैदानिक परीक्षण है जहाँ मरीज की दशा के अनुसार दवाइयों का चयन किया जाता है। परिणामों में आईपीएसएस के साथ डब्ल्यूएचओ क्यूओएल बीआरईएफ, प्रोस्टेट वॉल्यूम, पोस्ट वोयड रेसिडुअल यूरिन, यूरोफ्लोमेट्री (क्यूमैक्स और क्यूएवीजी) नापा जाता है और पीएसए स्तर को आधार रेखा, तीन और छह महीनों के अंतराल पर नापा जाता है।

चर्चाः इस परीक्षण के उपरान्त प्राप्त परिणामों द्वारा बीपीएच से पीड़ित मरीजों के उपचार की रणनीति बनाने और उनके जीवन की गुणवत्ता को सुधारने में सहायता मिलेगी।

परीक्षण पंजीकरणः चिकित्सीय पंजीकरण परीक्षण/(क्लिनिकल ट्रायल रजिस्ट्री)–भारतः सीटीआरआई/2012/05/002649

मुख्य शब्दः प्रोस्टेट, होम्योपैथी, यूरोफ्लोमेट्री, पोस्ट वोयड रेसिडुअल यूरिन, प्रोस्टेट वॉल्यूम