A Study of Effectiveness of Medical Therapy in Benign Prostatic Hyperplasia Patients in HUSM

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Abstract: Introduction: Benign prostate hyperplasia (BPH), a progressive disease, can cause various urinary complications if left untreated.

Aims and Objective: The current study was designed to compare international prostate symptom score (IPSS), urine flow rate (Qmax), Prostate specific antigen (PSA) in pre and post treatment among patients with Benign prostatic hyperplasia and to assess their quality of life.

Methodology: A cross sectional study was designed at Hospital Universiti Sains Malaysia, including all patients diagnosed as BPH from year 2007 to 2010. Based on inclusion and exclusion criteria 307 subjects were selected. New set of International Prostate Symptom Score (IPSS) and urine flow rate (Qmax) was obtained from all selected patients. SPSS version 19 was used for statistical analysis.

Result: Out of the 307 patients currently treated at Hospital University Sains Malaysia (HUSM), 268(87.3%) were Malays, 38(12.4%) were Chinese and 1(0.3%) was Indian. Majority of the patients having BPH were above 50 years of age. One hundred and seven (34.9%) patients were associated with hypertension, followed by diabetes mellitus 12 (3.9%). urine peak flow rate (Qmax) had mean difference of 11.74 and 14.41 ml/sec, which shows the medical therapy do improve urine flow rate and benign prostatic hyperplasia (p<0.001). The prostate size also showed an increase having mean difference from 36.12 to 38.14 cc (p<0.001). There is significant relation between prostate gland volume and serum prostatic specific antigen (p<0.001).

Conclusion: Benign prostatic hyperplasia although a benign condition, but still interferes with the normal life style of the patients. By initiating medical treatment this disease can not only be treated but also significantly improves the quality of life of the patients.

Keywords: Benign Prostatic Hyperplasia (BPH), International Prostate Symptom Score (IPSS), Quality of Life, Treatment Outcomes.

INTRODUCTION

Benign prostate hyperplasia (BPH) is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. It involves the stromal and epithelial elements of the prostate arising from the periurethral and transition zones of the gland. Cellular accumulation and gland enlargement may result from epithelial and stromal proliferation, impaired preprogrammed cell death (apoptosis), or both [1-3]. BPH is considered as a normal part of the aging process in men and is hormonally dependent on testosterone and dihydrotestosterone (DHT) production.

BPH is one of the most common urinary problems in male after the age of 50 years. In UK, it is estimated that about 3.6 million men over the age of 50 years will have moderate to severe Lower urinary tract symptoms (LUTS); 1.2 million men were diagnosed as BPH [4,5]. The presence of histological BPH at autopsy is approximately 8% in men aged 31-40, 50% in those aged 51-60 years, 70% in those aged 61-70, and 90% in those aged 81-90 years [6]. In USA the prevalence of BPH is common in African American when compared with white population [7].

BPH is a progressive disease and causes various urinary complications if left untreated. Incomplete voiding results in stasis of urine in the bladder with concomitant increased risk of developing urinary tract infection. On the other hand, it also increases the incidence of urinary bladder stones due to crystallization of salts in the residual urine. Sometimes patients may even present with acute urinary retention that might need a bladder catheter insertion. In chronic urinary retention, the residual urinary volume gradually increases and this eventually causes high bladder pressure and develops vesico-ureter reflux, resulting in hydronephrosis. Given enough time it may eventually
progress to renal failure. Hyperplasia of the gland results in enlargement of the prostate that restricts the flow of urine from the bladder [8-10].

The voiding dysfunction that results from prostate gland enlargement and bladder outlet obstruction (BOO) is termed as lower urinary tract symptoms (LUTS). LUTS symptoms can be classified into 2 types. 1. Storage symptoms include urinary frequency, urgency (compelling need to void that cannot be deferred), urgency incontinence, and voiding at night (nocturia). 2. Voiding symptoms include poor urinary stream, hesitancy (needing to wait for the stream to begin), intermittency (when the stream starts and stops intermittently), straining to void, and dribbling [11,12].

These storage and voiding symptoms are evaluated using the International Prostate Symptom Score (IPSS) or American Urological Association Prostate Symptoms Score (AUA) questionnaire, designed to assess the severity of BPH [11-13].

METHODOLOGY
A cross sectional study was designed including all patients diagnosed as BPH by using IPSS (International Prostatic Symptom Score), uroflowmetry and digital rectal examination during prostate awareness campaign conducted by urological department in Hospital Universiti Sains Malaysia (HUSM) from the year 2007 to 2010.

The patient's data was obtained from outpatient clinic census. All medical folders and record of the patients were traced and reviewed thoroughly. Multiple blood and urine test were performed as a part of routine procedure pre and post treatment, this also included prostate specific antigen detection. Once the patients were diagnosed as benign prostate hyperplasia using IPSS, digital rectal examination, urine flow rate using uroflowmetry during prostate awareness campaign, and on α-1 adrenergic receptor inhibitor, Alfuzosin 10mg once daily were included for current study. During follow up, if the patients were diagnosed as prostatic cancer or underwent transurethral resection of prostate (TURP) operation then they were excluded from the study.

Post treatment data was collected by calling the patients and giving appointment to clinic for further evaluation using IPSS and urine flow rate by uroflowmetry, and transabdominal ultrasound to assess prostate size after giving informed consent. Digital rectal examination was not included, because digital rectal examination is a subjective assessment, and varies from person to person. IPSS is an international validated questionnaire by American Urology Association in year 1992, translated version were applied as it is a subjective scoring system [2]. A direct question was asked and explained to the patient and scoring was recorded accordingly to avoid biasness and confusion because some patients don't really understand exactly what the question is about. The patient followup varied from 2 to 3 months depending upon the availability of patients and organisational constraints.

Urine flow rate was recorded by using uroflowmetry, which is a machine connected to computer, when patient's urine was passed into the uroflowmeter, the peak urine flow rate was recorded as Qmax. Transabdominal ultrasound was performed for all the patients and prostate size measurement was recorded. Since the study was conducted at urological department, Hospital University Sains Malaysia, an approval prior to conduct the study was taken from the hospital management.

All the data was entered and analysed by using SPSS version 19.0. The statistical analysis result will consider as significant if the p-value ≤0.05. The descriptive statistics and paired t-test were used.

RESULTS
Out of 340 patients, 9 patients who were diagnosed as prostatic cancer during follow up period while 24 patients were lost to follow up. Hence 307 patients were included in the study. Out of the 307 patients, 268(87.3%) were Malays, 38(12.4%) were Chinese and 1(0.3%) was Indian. Majority of the patients having BPH were above 50 years of age. Only 9(2.9%) out of 307 lies in the age group of 40-50 years. While 298 (97.1%) patients were more than 50 years of age (Table 1).

Benign prostatic hyperplasia has been associated with co-morbid factors. Of 307, 107 (34.9%) patients were associated with hypertension, followed by diabetes mellitus 12 (3.9%). Furthermore, majority of the patients had multiple co-morbid conditions like 5 (1.6%) patients had diabetes, hypertension and hyperlipidaemia, 41(13.4%) had ischaemic heart disease, hypertension and hyperlipidaemia (Table 2).
Table 1: Distribution of Age

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td>9</td>
<td>2.9</td>
</tr>
<tr>
<td>51-60</td>
<td>77</td>
<td>25.1</td>
</tr>
<tr>
<td>61-70</td>
<td>140</td>
<td>45.6</td>
</tr>
<tr>
<td>71-80</td>
<td>64</td>
<td>20.8</td>
</tr>
<tr>
<td>&gt;80</td>
<td>17</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Table 2: Co-Morbidities in the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Comorbid</td>
<td>60</td>
<td>19.5</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td>12</td>
<td>3.9</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>107</td>
<td>34.9</td>
</tr>
<tr>
<td>Ischemic Heart Disease (IHD)</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Hyperlipidaemia (HLP)</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>2.6</td>
</tr>
<tr>
<td>DM+ HTN</td>
<td>35</td>
<td>11.4</td>
</tr>
<tr>
<td>DM+HTN+HLP</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>HTN+IHD+HLP</td>
<td>41</td>
<td>13.4</td>
</tr>
<tr>
<td>DM+HTN+IHD+HLP</td>
<td>15</td>
<td>4.9</td>
</tr>
<tr>
<td>HTN+HLP</td>
<td>21</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Paired t-test showed that the mean difference was 15.55 and 5.53 for IPSS. The urine peak flow rate (Qmax) had mean difference of 11.74 and 14.41 ml/sec, which shows the medical therapy do improve urine flow rate and benign prostatic hyperplasia with p-value <0.001. The prostate size also showed an increase having mean difference from 36.12 to 38.14 cc and p-value of <0.001 (Table 3).

Table 3: Comparison between IPSS, Qmax, PSA in Pre and Post Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-treatment Mean (SD)</th>
<th>Post-treatment Mean (SD)</th>
<th>Mean Difference (95% CI)</th>
<th>t-test (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS</td>
<td>15.55 (6.45)</td>
<td>5.53 (5.44)</td>
<td>10.02 (9.34, 10.69)</td>
<td>29.21 (306)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qmax</td>
<td>11.74 (5.77)</td>
<td>14.51 (5.41)</td>
<td>-2.77 (-3.32, -2.21)</td>
<td>-9.78 (306)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA</td>
<td>4.69 (6.5)</td>
<td>3.33 (4.99)</td>
<td>1.35 (0.99, 1.71)</td>
<td>7.38 (306)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate Size</td>
<td>36.14 (23.6)</td>
<td>38.14 (22.1)</td>
<td>-2.01 (-3.01, -1.00)</td>
<td>-3.92 (306)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There is significant relation between prostate gland volume and serum prostatic specific antigen, with p-value <0.001, based on Pearson’s correlation test. The Correlation Coefficient (r) is 0.52 (Figure 1).

Out of 307 patients, 122 (39.7%) patients had no differences in their sexual satisfaction either pre or post receiving medical therapy for benign prostatic hyperplasia. Whereas, 8 (2.6%) patients complaint of worsening in sexual satisfaction after receiving medical therapy (Table 4).

DISCUSSION

Previously, the understanding about lower urinary tract symptom (LUTS) was limited by the belief that it was always caused by bladder outlet obstruction (BOO) due to benign prostatic enlargement (BPE). Hence the strategy of treating LUTS was based on symptoms. If the symptoms were mild to moderate, patients were given medication. If severe or treatment fails, patients will be subjected for surgery either by open technique or endoscopically.

BPH is non-malignant enlargement of the prostate. The prostate has both stromal and glandular component and divided into various zones like central, peripheral, transitional, periurethral and anterior zone. Of all these zones, BPH commonly arises from transitional and periurethral zone whereas prostatic cancer commonly arises from peripheral zone [2]. The incidence of BPH increase with age, as the men grow older the risk of BPH is higher. Prostatic enlargement causes bladder outlet obstruction, in turn causing LUTS.
symptoms [7-9]. Prostate gland begins to progressively enlarges in size with age [14]. From previous study, it was noted that BPH occurs in 20% of the men at age of 40-50 years, 40% in 50-60 years old, 55% in 60-70 years old, 80% and 90% at the age of 70-80 and 80-90 years respectively [1].

A study conducted on 6486 patients from Boston, United States of America; Boxmeer, the Netherlands; Auxerre, France; Birmingham, UK; and Seoul, Korea; showed that prevalence was higher in blacks as compared with white; In USA, the prevalence of BPH is common in African American when compared with white population [7]. In 2008, a study involving 21,949 men was conducted in United States of America. Majority (79.8%) of patients with BPH were black in 6 community health centres. It was found that blacks were less likely to present with Lower urinary symptoms, but they had higher incidence of operation rate [14,15].

Malaysia in a multiethnic country. There are no previous studies to compare the prevalence of BPH among the various races in Malaysia. Since current study was carried out in Kelantan which consists mainly of Malay population (94%) hence, it was not rational to analysis our results within different ethnicities in Malaysia.

Patients who were diagnosed with benign prostatic hyperplasia with lower urinary tract symptoms, also frequently had associated hypertension and cardiovascular disease. Colon & Payne in 2008 and Parsons et al. in 2006 reported that patients with metabolic disorder like diabetes, hyperlipidaemia are prone for benign prostatic hyperplasia [16, 17]. Hence it was postulated that, metabolic disorder and benign prostatic hyperplasia have underlying dysfunction in insulin uptake of glucose and resulting in hyperinsulinaemia. Second reason might be prostatic gland experiences hypoxia due to vascular damage secondary to metabolic disorder like diabetic vasculopathy [18, 19].

According to American Urology Association guideline, medical therapy should be the first line of treatment in benign prostatic hyperplasia. Prostate contains α-1 adrenergic receptor; stimulation of this receptor can lead to contraction of smooth muscle and increase the detrusor activity, leading patients to complain of lower urinary tract symptoms. Alpha adrenergic receptor inhibitor regardless of selective like Alfuzosin, Doxazosic or non- selective like Prazosin, Terazosina can improve the lower urinary tract symptoms due to benign prostatic hyperplasia.

A recent study conducted on using Alfuzosin 10mg once a day in treating benign prostatic hyperplasia showed that α-1 adrenergic receptor inhibitor can improve the symptoms score. The patients showed IPSS improved ≥4 points, reduced the risk of acute urinary retention and prostate related surgery [20]. A previous study also showed that α-1 inhibitor can improve IPSS from 17.1 to 9.3 and urine peak flow rate from 9.1 to 11.3ml/sec [21]. McVary in 2006 also showed that, α-1 inhibitor does improved IPSS by average of 2-4 points, reduced post voiding residual urine and improved quality of life of the patients [22].

Furthermore, 5-α reductase inhibitor like Finesteride, Dutasteride etc. can also be used in the treatment of BPH. It is known that, the growth of prostate gland is regulated by the hormone-Dihydrotestosterone (DHT) which is converted from testosterone in the presence of 5-α reductase isoenzyme, hence blocking this isoenzyme can prevent the growth of prostate gland.

A previous study showed that, 5-α reductase inhibitor reduces 98% of DHT in the body over a period of 24 months [11]. Dubruyne et al. in 2004 also reported improved IPSS and urine peak flow rate in 24-48 months. Therefore, 5-α reductase inhibitor is not the drug of choice in the treatment of acute urinary symptoms caused by BPH [23]. A recent study showed that 5-α reductase inhibitor can reduce the total prostate size by 25% [24].

### Table 4: Comparison of Sexual Satisfaction in BPH Patient’s Pre and Post Receiving Treatment for LUTS; McNemar’s Test

<table>
<thead>
<tr>
<th>Sexual function pre-treatment</th>
<th>Satisfactory n (%)</th>
<th>Reduce Satisfactory n (%)</th>
<th>Not Satisfactory n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory</td>
<td>122 (39.7)</td>
<td>8 (2.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reduce Satisfactory</td>
<td>15 (4.9)</td>
<td>54 (17.6)</td>
<td>17 (5.3)</td>
</tr>
<tr>
<td>Not Satisfactory</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>91 (29.6)</td>
</tr>
</tbody>
</table>
The results from present study showed that the mean of IPSS pre and post treatment reduces from 15.55 to 5.53, a difference of around 10 points. The inference when compared with the literature suggests Malaysian population showed a better improvement. It should be interesting to find out what is the optimal dose of α-1 inhibitor in Malaysian population. It is probable that the current dose recommended by the American Urology Association is too high for Malaysian population. In terms of urine peak flow rate, the study showed mean of pre and post treatment improved from 11.74 to 14.51, which is close to normal limit.

Prostate specific antigen (PSA) is a protein produced in prostate cells and is mainly found in seminal fluid, some escapes from prostate and expressed in the serum [9]. PSA mainly produced in transitional zone, which is common for BPH to occur and only very little produce in peripheral zone which is common for cancer to occur. Therefore, increase in PSA level usually indicate prostate cancer but it also increases in conditions like benign prostate hyperplasia (BPH) or prostatitis. Berges & Oelke in 2011 and Mochtar et al. in 2003 reported an increase in PSA level and prostate volume with age [9, 12]. Moreover, the PSA can be used as predictor for prostate volume and treatment of BPH. It means if the PSA level is high, these patients should receive treatment automatically. The half-life of PSA is about 2-3 days, thus minimum of 2-3 weeks is required for the PSA to come to normal [25, 26]. Babaijan et al. in 2001 also noted that, men older than 50 year old have 20-30% possibility of developing cancer prostate if PSA level >4ng/ml, if PSA level >10ng/ml, the possibility of detecting prostate cancer during biopsy is about 42-64% [27].

With present study it was observed that mean serum prostate specific antigen level decreased from 4.69 to 3.33ng/ml. According to Mochtar et al. an increase in serum prostate specific antigen (PSA) is associated with increases in prostate gland [9]. From our data, although there is slight increase in mean prostate gland size, but surprisingly there is reduction in serum PSA level. This may be because there are 6 (2%) patients in our study who presented with high PSA level in the initial assessment due to acute urinary retention. A previous study reported that serum PSA level does not increase when inserting urinary catheter but stretching of prostate gland due to acute urinary retention does cause increase in serum PSA [28]. This might be the cause of drop in serum PSA in our study data. There is strong correlation between prostate gland size and PSA level. Rise in PSA represents that there are prostate gland enlargement as well. This should probably be taken into account when initiating the treatment in patient with benign prostatic hyperplasia.

Sexual dysfunction is also an aging process like benign prostatic hyperplasia. Van Moorselaar et al. in 2005 showed that Alfuzosin can improve sexual function but Doxazosin will worsen it [29]. From present study, 15(5%) out of 307 study population had improvement of sexual function after receiving medical therapy. Hence it is safe to use for long term therapy, and patient counselling were conducted that medical therapy is safe in terms of affecting their sexual function.

Phosphodiesterase-5 inhibitor is a drug used in treatment of erectile dysfunction. Recent studies also showed that phosphodiesterase-5 inhibitor are effective in treatment of erectile dysfunction, at the same time it does improve the lower urinary tract symptoms caused by benign prostatic hyperplasia. Therefore, they can be used as an alternative in patients who were not responding to the α-1 inhibitor and 5-α reductase inhibitor treatment [30, 31].

One of the main limitations involved in current study is our sample size. With limited number of patients and being single center study, the current study does not represents an overall scenario for Malaysia and the results can not be generalised. Due to patient and organisational constraints the patients were followed up once only. Multiple patient follow up would have provided us a more detailed picture

CONCLUSION

Medical therapy is effective for benign prostatic hyperplasia hence it improves the patient’s quality of life in term of improving their urine peak flow rate (Qmax), reduces their lower urinary tract symptoms and incidence of acute urinary retention.

SOURCE OF THERAPY

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