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Original Research Article

Efficacy of a polyherbal formulation in the management of benign prostatic hyperplasia: a randomized, controlled trial

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) affects a significant number of men beyond the age of 40 years with its incidence reaching up to 90% in 80's. Despite multiple treatment innovations, BPH still remains a nightmare for ageing men, mostly due to its distressing lower urinary tract symptoms (LUTS) and sexual dysfunction. The severity of LUTS is graded by international prostate symptom score or American urological association symptom index (AUA-SI) along with impact on quality of life (QOL). The objective of this study was to evaluate the efficacy of an Unani polyherbal formulation, Habb-i-muqil, in improving the AUA-SI and QOL in patients with BPH.
Methods: In an open, standard controlled study, 76 men, diagnosed with clinical BPH, aged between 40 and 80 years were randomly allocated for treatment for duration of 90 days with Habb-i-muqil (test drug) or Tamsulosin (standard control) after ethical approval. AUA-SI and QOL were assessed at baseline (0 day) and days 15, 30, 45, 60, 75 and 90.
Results: Analysis of 60 men showed that after 90 days of treatment the percentage changes in the AUA-SI from baseline were 59.4 and 49.4% by Habb-i-muqil and tamsulosin, respectively. The test drug produced statistically significant improvement ($p<0.001$) in overall AUA-SI and QOL compared with standard control.
Conclusions: The Unani polyherbal formulation, Habb-i-muqil, was effective in improving AUA-SI and QOL in men with BPH in comparison to tamsulosin. Both the treatments were generally well tolerated.

Keywords: Benign prostatic hyperplasia, LUTS, Habb-i-muqil, Quality of life

INTRODUCTION

Benign prostatic hyperplasia (henceforth BPH) is one of the commonest non-malignant neoplasms to affect men beyond middle age.[1] The incidence of BPH increase with age so that it affects approximately 20% of men in their 40s reaching up to 90% in 9th decade.[2]

Despite multiple treatment innovations, BPH still remains a nightmare for the ageing men, mostly due to its distressing lower urinary tract symptoms (LUTS) affecting quality of life (QOL) and sexual functions.[3] Dihydrotestosterone (DHT) derived from testosterone through the action of 5-α reductase seems to be the major stimulus for proliferation of prostate in men with nodular hyperplasia.[3,4]

Inflammatory mediators and local growth factors are also considered to be responsible for prostatic hyperplasia.[5-7] Moreover, inheritance, metabolic syndrome, obesity and decreased physical activity increase the risk factors of prostatic hyperplasia.[8] Unani, an age-old traditional system of medicine, which is based on the 'humoral theory' proposed by Hippocrates (480-370 BC), the father of medicine, states that any disturbance in the ratio of four humors is responsible for the disease. One of the major humor to which our hormones also belong is phlegm (Balgham).[9] So, according to this very system of medicine

BPH is a phlegmatic disorder caused by derangement of phlegm, a cold humor.[10]

For evaluating suspected BPH patients, American Urologic Association, European Association of Urology and 'WHO international consultation on urologic disease' has recommended the routine use of International prostatic symptom score (IPSS).[11,12]

Most commonly used class of drug for treating bothersome LUTS in BPH is α-adrenergic receptor antagonist and selective α1-receptor blocker. Although these are effective in alleviating bothersome LUTS, they have various side effects like, dizziness, fatigue, asthenia, postural hypotension and ejaculatory disturbances.[13]

In Unani system of medicine natural herbs which are comparatively safer have been in use for centuries in alleviating urinary symptoms. These herbs, however, need to be evaluated on scientific parameters. To avoid the side effects of conventional medicine, a study was conducted to evaluate the efficacy of a polyherbal formulation, Habb-i-muqil, in the treatment of LUTS due to BPH.

Habb-i-muqil was selected for this study because of its following properties; it is deobstruent, anti-inflammatory, anti-tumor, phlemagogue, laxative and aphrodisiac.[14-16] *Commiphora mukul*, one of its major ingredients, is effective in urinary disorders and is also a potent androgen receptor antagonist and estrogen receptor agonist.[17,18] Guggulsterone and gallic acid, like constituents in it are considered as ideal chemopreventive, apoptotic and robust therapeutic agents for prostate cancer.[19,20]

METHODS

An open, randomized, standard controlled trial was conducted from December 2018 to December 2019 at Regional Research Institute of Unani Medicine, Srinagar Kashmir, after gaining approval on 09-12-2017 from institutional ethical committee (Regional Research Institute of Unani Medicine, Central Council for Research in Unani Medicine, Ministry of Ayush Government of India). A written informed consent was obtained from all the participating patients. Diagnosis and selection of the cases was made on the basis of clinical features, American Urological Association-Symptom index (IPSS) (AUA-SI), QOL, ultra-sonography (USG) per abdomen for prostate volume and serum prostate specific antigen (PSA) along with other safety parameters [LFT, KFT, CBC, ESR, blood sugar, ECG, and X-ray (KUB)].

Case selection criteria

Inclusion criteria

Males in age group of 40-80 years complaining of LUTS and clinically stable patients of BPH with serum PSA level <10 ng/ml were included.

Exclusion criteria

Patients below 40 and above 80 years of age; with intellectual disability and who fail to give consent; with other debilitating diseases like CHD, CKD, liver disease and hypertension; and complete retention of urine and serum PSA ≥10 ng/ml.

Intervention

Test drug formulation, Habb-i-muqil, consisting of following ingredients- (a) *Commiphora muqul* (Muqil) (85 g); (b) three different forms of *Terminalia chebula* (Halela Zard, Halela Siyā, Halela Kābli) (60 g each), *Emblica officinalis* (Āmla Khushk) (60 g), *Ferula persica* (Sakbīnaj) (20 g); *Bressica nigra* (Khardal) (10 g), all the ingredients were powdered and mixed with 20 ml sweet almond oil (Roghan-i-Bādām shīrīn) and 100 ml Āb-i-Gandana, to make the pills of 250 mg.

1 g of it was given to the cases of test group twice a day orally with water, leaving a twelve hours gap between the two doses.

The other group that is the control group was given a standard conventional drug, tamsulosin, 0.4 mg in tablet form, only once a day orally, thus leaving a 24 hours gap between the two doses.

Both the drugs were continued for a period of 90 days in each patient after taking a written consent from them.

Assessment

All the BPH patients having LUTS were assessed for AUA-SI and QOL at baseline (0 day) and days 15, 30, 45, 60, 75 and 90.

In addition to this prostate volume and PSA were assessed before initiation and after completion of the treatment. Various safety parameters were also checked before and after study to evaluate the safety of the test drug. The patients' summary is given by consort flow diagram below in Figure 1.

Data analysis

Data was entered in a spread sheet and then exported to data editor of SPSS version 20.0 and Graph pad prism software. The continuous variables were expressed as mean±SD and categorical variables were expressed in terms of frequency and percentage. Students' independent t-test was employed for inter-group (test group vs. control group) analysis of data, and for intra-group analysis paired t-test was applied. Chi square test was employed for comparison of categorical variables. The graphical representation of data was presented by means of bar and line graphs. A p value of less than 0.05 was considered statistically significant.

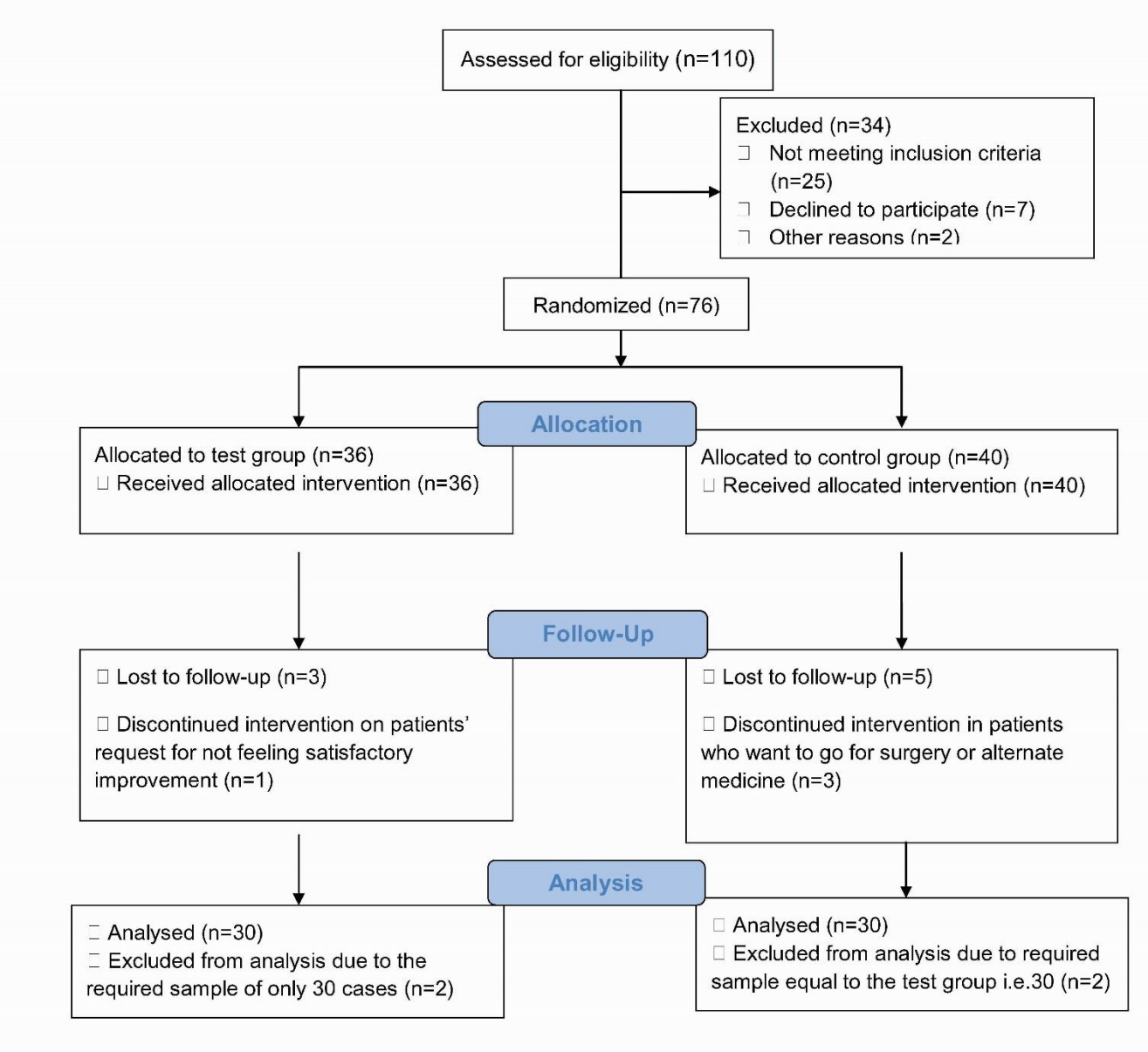

Figure 1: Patients deposition (Consort flow diagram).

RESULTS

Out of 76 randomly allocated patients only 60 were analyzed statistically for the results, 30 from each test group and control group. Distribution of patients as per their age in both the groups and total percentage of each age group thereafter is shown in the Table 1. Mean±SD of urinary symptoms before and after trial i.e.; at 0^{th} day and at 90^{th} day was calculated and the effect in both the groups was derived statistically as can be easily understood in Table 2.

Comparing the values of baseline and post treatment, the effect of test drug was seen highly significant ($p<0.001$) in the six parameters whereas less significant for 'weak stream' ($p<0.007$). Moreover, in comparison to standard drug the effect of test drug was highly significant ($p<0.001$) for 'frequency of micturition', 'urgency', 'weak stream' and 'nocturia', whereas it was less significant for 'straining' ($p=0.0324$) and insignificant for 'incomplete emptying of bladder' ($p=0.869$) and 'intermittency' ($p=0.781$).

Baseline values of mean±SD of AUA-SI and QOL in test group comparison to control group (17.16±4.99 vs 17.66±3.95) and (4.76±0.67 vs 4.93±0.58) improved after treatment to (6.96±2.87 vs 8.93±3.09) and (2.36±0.66 vs 3.06±0.58) respectively. Statistically effect of test drug formulation was found to be highly significant comparison to standard drug ($p<0.001$) with respect to AUA-SI and QOL (Table 3). Although the effect of the test drug in reducing prostate volume was not significant, but when compared with the control group the effect of the former was found to be significant ($p<0.001$) statistically. Contrarily, the effect on PSA was found to be insignificant ($p=0.723$) at 5% level of significance.

Table 1: Age distribution in test and control group.

Age (years)	Test		Control		Total %
	N	%	N	%	
40-49	10	33.3	8	26.7	30
50-59	4	13.3	6	20.0	16.65
60-69	14	46.7	12	40.0	43.35
70-79	2	6.7	4	13.3	10
Total	30	100	30	100	100
Mean±SD	57.23±10.50		57.23±9.73		

Table 2: Effect on urinary symptoms individually in test and control group.

Groups		Test	Control	Test vs control (p value)
Incomplete emptying	Before	3.33±1.18	3.46±1.18	0.869
	After	1.17±0.69	1.76±0.72	
Frequency	Before	3.50±1.06	3.23±0.97	<0.001*
	After	1.23±0.50	1.86±0.57	
Intermittency	Before	0.70±0.95	0.96±1.09	0.781
	After	0.23±0.43	0.40±0.67	
Urgency	Before	3.73±0.86	3.80±0.66	<0.001*
	After	1.23±0.67	2.16±0.59	
Weak stream	Before	0.95±1.03	1.26±0.87	<0.001*
	After	0.73±0.86	0.40±0.60	
Straining	Before	1.63±1.06	1.96±0.92	0.0324
	After	0.82±0.64	0.70±0.65	
Noctura	Before	3.33±0.80	2.96±0.80	<0.001*
	After	1.00±0.58	1.63±0.61	

Table 3: Effect on AUA-SI and QOL in test and control group.

Follow ups	AUA-SI (mean±SD)		QOL (mean±SD)		Test vs control (p value)
	Test	Control	Test	Control	
0 day (base line)	17.16±4.99	17.66±3.95	4.76±0.67	4.93±0.58	<0.001*
15th day	16.33±4.97	15.83±3.53	4.66±0.71	4.60±0.67	
30th day	13.10±4.23	12.16±3.15	3.83±0.64	3.80±0.55	
45th day	12.10±4.11	11.46±3.31	3.66±0.71	3.73±0.58	
60th day	8.90±3.11	9.56±2.84	3.03±0.49	3.26±0.58	
75th day	8.43±2.97	9.30±2.89	2.86±0.57	3.06±0.58	
90th day	6.96±2.87	8.93±3.09	2.36±0.66	2.90±0.60	
Percentage of improvement	59.44	49.43	50.42	41.17	
P value	<0.001*	<0.001*	<0.001*	<0.001*	

Note: AUA-SI- American Urological Association Symptom Index; QOL- Quality of life; SD- Standard deviation.

Table 4: Effect on prostate volume and PSA in test and control group.

Groups	Prostate volume (Mean±SD)		PSA (Mean±SD)	
	0 day	90th day	0 day	90th day
Test	34.73±15.02	29.64±13.01	1.08±1.08	0.96±0.93
Control	42.56±22.56	42.23±22.50	1.55±1.87	2.06±3.44
P value (test vs control)	<0.001*		0.0723	

Note: PSA- Prostate specific antigen; SD- Standard deviation.

DISCUSSION

In the treatment of symptomatic BPH physicians have given too much emphasis on International Prostatic Symptom Score (IPSS) (AUA-SI and QOL), prostate volume and urodynamic parameters. Subjective outcome measures are now widely used to assess treatment outcomes for LUTS and BPH.[12,21,22] Among the conventional medicines alpha-1 adrenergic antagonist,

tamsulosin, is the most commonly recommended because of its tolerability, efficacy and safety.[13] Herbal medicine, though in use for centuries in treating LUTS, is still lacking a comprehensive scientific validation except a few.[23,24] However, some common side effects like loss of libido and retrograde ejaculation associated with the conventional medicine become strong factors for patients choosing herbal medicine.

Evaluating the safety and efficacy of the polyherbal formulation *(*Habb-i-muqil*)* in treating LUTS compared to the standard control (tamsulosin) was important in this context. This formulation so far has been evaluated to be effective for treating internal hemorrhoids (I and II), constipation, and osteo-arthritis.[25,26] Most of its ingredients are having anti-tumor, anti-inflammatory, deobstruent, resolvent and aphrodisiac properties.[27] This helps in effective urine outflow, reduce the volume of post void residual urine, decrease bladder irritation and lessen the frequent desire to micturate. Moreover, most of the ingredients in the test drug are hot in temperament according to the unani system of medicine which counteracts the effect of excess phlegm in the body and hence diminish the symptoms produced by it.[14,27] *Commiphora mukul*, one of its major ingredients acts as a potent androgen receptor antagonist and estrogen receptor agonist.[18] It possesses anti-oxidant, apoptotic, anti-tumor and anti-cancerous property as well.[19,20] Because inflammation and androgens are considered to be the main culprits for developing BPH, Habb-i-muqil was thought to be the best alternative for its management.[28]

In the current randomized, standard controlled trial, 60 patients, who completed the trial duration as per the designed protocol, were analyzed (Figure 1). The mean age of the study group was 56.24±10.11 and maximum numbers of patients belonged to the age group of 60-69 years (Table 1). However, the data depicts least number of patients in the age group of 70-79 years which contradicts the concept of Baltimore and Krimpen longitudinal study of aging suggesting an increase in prostate volume with age.[29,30] This contradiction is most probably due to the patients' ineligibility as per the inclusion and exclusion criteria for the present study. Since most of the elderly patients having other associated ailments were excluded at the initial assessment.

To achieve 'very satisfied' or 'satisfied' response, a man with very severe symptoms (baseline IPSS 30) would require an improvement of almost 18 points, while a man with moderate symptoms (baseline IPSS 12) would require an improvement of 4 points as reported by Reohrborn et al.[31] Barry et al evaluated a change of AUA symptom index of -8.8, -5.5, -3.0 and -0.7 points depicting marked, moderate, slight or no improvement respectively.[32] However, in many clinical studies greater symptom index changes were associated with higher baseline score.[31] Our study also showed similar tendencies (Table 3). The mean and standard deviation of all the seven subjective parameters most of whom showed significant improvement after treatment with the test drug formulation is illustrated in Table 2. Clearly, the test drug has improved the urgency of urine, its frequency and nocturia to a greater extent. Similarly, 'straining' showed a good improvement but at slower pace so that initially the improvement could be found more with control drug, whereas the test drug showed delayed but better results.

Overall AUA-SI (Table 3) got improved in both the test group and control group as 59.4% and 49.4% from the base line respectively. However, the inter-group comparison, test group vs control group (6.96±2.87 vs 8.93±3.09), depicted comparatively better effects of test intervention and was statistically found highly significant ($p<0.001$). Figure-2 portrays the improvement of AUA-SI in test group which was initially slow but steady and ultimately it surpassed the effect of standard drug which was initially very much prominent but sluggish later on. Likewise, an improvement of QOL by 50.43% and 41.17% in the test group and control group respectively has been observed. Although the effect of both the test drug and standard drug was found statistically significant ($p<0.001$) but the inter-group comparison revealed the test drug as highly significant ($p<0.001$) in comparison to the standard drug for improving the QOL of such patients. Interestingly, the patients having LUTS with BPH from the test group were more satisfied than those from control group at the end of the treatment.

The comparative effect of both the treatments on QOL is better depicted by the line graph in Figure 3. For the volume of prostate mean±SD in the test group was 34.73±15.02 before the onset and 29.64±13.01 after the accomplishment of the treatment period (Table 4). In the control group mean volume was 42.56±22.56 before onset and 42.23±22.50 after completion of the treatment. The change in prostate volume was not noticeable but compared to the control group, the improvement in the test group was statistically significant ($p<0.001$). Since the ingredients of the test drug formulation are concoctive and purgative of phlegm (Mundij wa mushil-i-balgham*)*, removes unwanted phlegm from the body and normalize the ratio of humors, a decrease in volume of the prostate to some extent was observed. The effect on PSA by both the test drug and standard drug was found to be statistically insignificant (Figure 4).[14,27]

Furthermore, calculating the mean and standard error of mean of safety parameters before and after the treatment, both the drugs were found to be safe for such a period. Side effects such as dizziness, somnolence and decreased libido were reported in 8% of patients in control group and gastric upset complained in 3% of patients in the test group which is acceptable. Because almost all the ingredients of test drug are aphrodisiac, the side effects produced by the standard drug were not met with the test drug. Test drug formulation (Habb-i-muqil) overall produced the satisfactory results in our study.

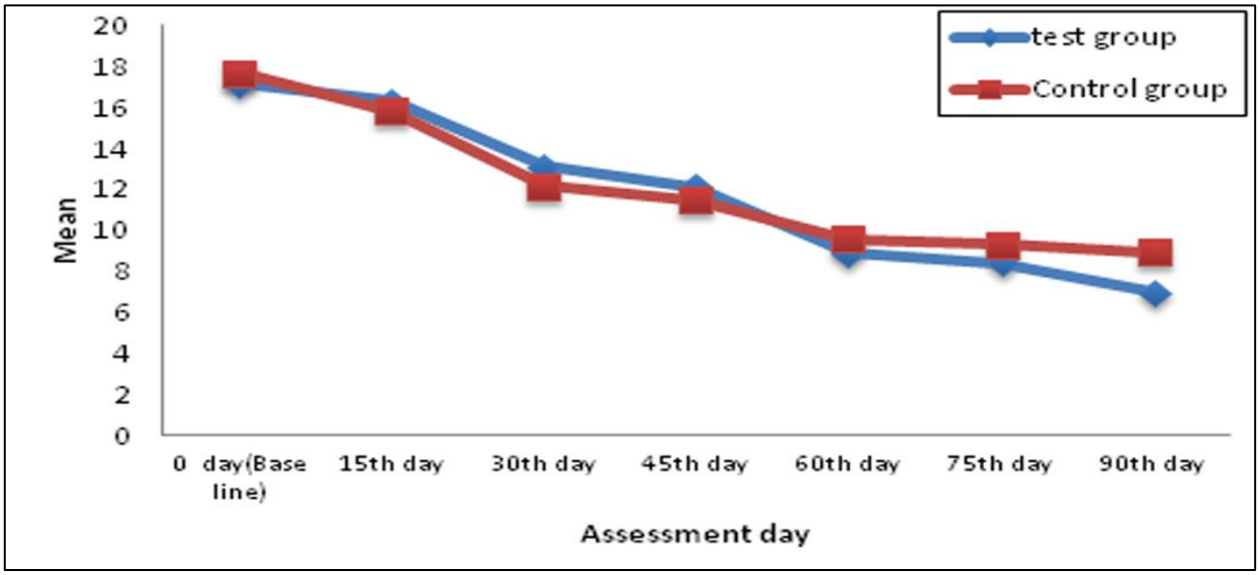

Figure 2: Effect on AUA-SI in test and control group.

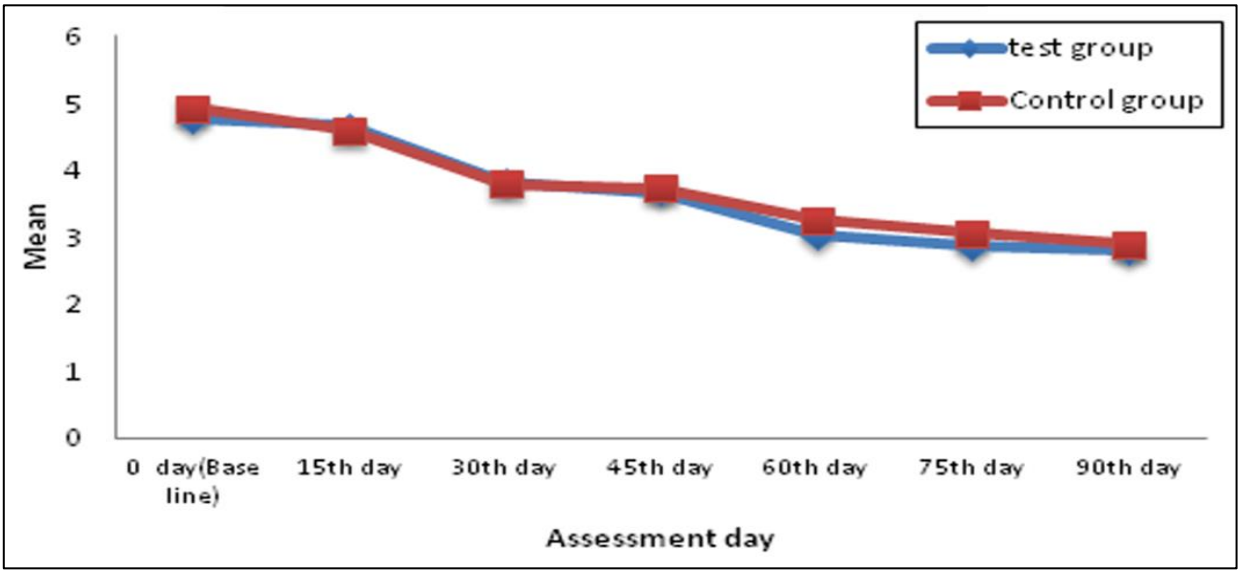

Figure 3: Effect on QOL in test and control group.

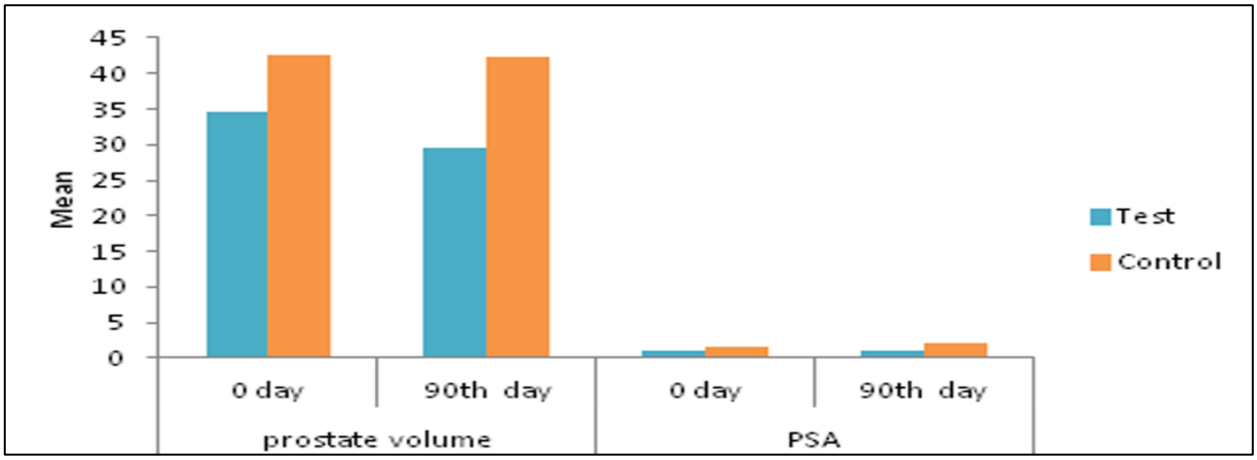

Figure 4: Effect on prostate volume and PSA in test and control group.

CONCLUSION

From this study, it was inferred that Habb-i-muqil was relatively effective in improving the overall AUA-SI and QOL compared to tamsulosin. No clinically significant adverse drug reaction was observed in the test group and overall compliance to the treatment was excellent. These results conclude that the test drug formulation is safe and effective in the management of symptomatic BPH. However, further study with larger sample size and with some additional parameters is required for elucidation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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