Original Article

Effects of Leuprolide as an adjunctive treatment of benign Prostatic Hyperplasia, a randomized-controlled clinical trial

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Abstract

Objective: To observe the effects of adding luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide acetate) to the standard treatment (5-alpha reductase plus alpha-1-adrenergic inhibitor) of benign prostate hyperplasia. We assessed improvement in international prostate symptom score (IPSS), patients' satisfaction of voiding, and catheter removal. **Method:** 77 patients diagnosed with BPH who presented with the first episode of urinary retention were randomly divided into two different groups; intervention group (Leuprorelin acetate + tamsulosin and finasteride) and control group (Placebo injection + tamsulosin and finasteride) as a routine treatment. T-test was used to compare the mean differences in IPSS before and after 12 weeks of the treatment. **Results:** The mean ± SD IPSS reduction in the intervention group was 2.47 ± 1.5 while in the control group was 1.51 ± 1.5. Results indicated a statistically significant mean difference in IPSS reduction of the intervention group compared to the control group, t (75) =2.8, p = 0.007. The odds of patient satisfaction of voiding and the catheter removal after one month of treatment were 1.2 in the intervention group compared with the control group; however, their association was not statistically significant (OR 1.2, 95%CI 0.3-4.3, P=0.78). **Conclusion:** The study showed statistically a significant decrease of IPSS in the intervention group, but did not show any significant differences in the catheter removal and patient's satisfaction of voiding after 12 weeks of treatment.

Keywords: Benign Prostatic Hyperplasia, Leuprorelin, Luteinizing-Hormone releasing Hormone, Combination Drug Therapy

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in elderly men. About 50-75% of men over the age of 50 and 80% of men over the age of 70 are affected [1, 2]. BPH results from progressive hyperplasia of epithelial cells of the prostate. This hyperplasia is focal, not diffuse meaning that some hyperplastic nodules fuse and form an adenoma. This adenoma causes an anatomical disfiguration which results in lower urinary tract symptoms (LUTS), urinary retention, and bladder outlet obstruction [1, 2]. The most important risk factors for BPH are aging, smoking, heavy alcohol consumption, diabetes type 2, hyperlipidemia, cardiovascular diseases. Physical activity, vegetable-rich diet, and a small amount of alcohol consumption are protective factors [3-6]. For the diagnosis, international prostate symptom score (IPSS) is a useful subjective tool for BPH accepted by the American Urology Association (AUA) to evaluate the severity of the disease, degree of LUTS, and quality of life [7]. Treatment options for BPH include watchful waiting/lifestyle modifications, medical therapy, non-surgical techniques, and eventually surgery. The goals of the treatment are to reverse signs and symptoms associated with LUTS, improve quality of life, patient satisfaction, and preventing the progression of the disease.[8, 9]. Medical therapy is the accepted standard of care for BPH since 1990. Among the available medications, the use of 5-alpha reductase inhibitors (5-ARIs) alone or in combination with alpha-1-adrenergic receptors blockers are the approved treatment options by the US Food and Drug Administration (FDA). They have shown an excellent risk reduction for symptomatic BPH progression by targeting

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dihydrotestosterone (DHT). They reduce the serum and intra-prostatic DHT concentrations and decrease the prostate volume. So, the European Association of Urology (EAU) and the AUA suggest 5-ARIs in their guidelines for the management of BPH [10, 11]. Although 5-ARIs and alpha-blockers are the first-line therapeutic option for treatment of symptomatic BPH, these medications do not change the natural advancement of the disease and several side effects have been reported following their prescription including dizziness and possible fainting, Floppy iris syndrome, palpitations, orthostatic hypotension, ejaculatory disturbances, loss of libido, and erectile dysfunction [9]. Development of the luteinizing hormone-releasing hormone (LHRH) agonist is a considerable advance in hormonal therapy of BPH patients. LHRH agonists cause suppression of testosterone production via binding to LHRH-receptors in the pituitary with a greater affinity than intrinsic LHRH. This result in the levels of testosterone is similar to those achieved with orchiectomy [12]. Leuprorelin (leuprolide acetate) was synthesized in 1974 in Japan and is a synthetic non-peptide analog of naturally occurring porcine LHRH. Compared with natural LHRH, it has a longer half-life, improved binding affinity, and greater resistance to peptidase degradation. Administration of leuprorelin has been associated with no considerable side effects or reactions in the injection site [13-17].

This randomized-controlled study investigated the effects of hormonal therapy using leuprolide acetate to assess its efficacy when it is added to standard androgen therapy of BPH.

Material and Method

Study design

This is a double-blinded randomized controlled trial study to observe the effects of intramuscular LHRH-agonist on patients with BPH compared with the standard treatment using a combination of tamsulosin and finasteride. The study was approved by the local Ethics Committee of the Mashhad University of Medical Science under the approval code of IR.MUMSMEDICAL.REC.1398.512. Written informed consent was obtained from each patient.

Study patients

We assessed the eligibility of all patients admitted to the urology department with the diagnosis of clinical BPH. The diagnosis of BPH was made based on the Canadian Urological Association guideline [18]. The guideline suggests thorough history-taking and physical examination, performing Digital rectal examination (DRE), a urinalysis, urine cytology, a serum PSA level, transrectal ultrasonography (TRUS) findings, and post-void residual urine volume (PVR) measurements.

Patients were randomly separated into two different groups by a simple random sampling method using the sequentially numbered in sealed envelopes; intervention group (Leuprorelin acetate + tamsulosin and finasteride) and control group (Placebo injection + tamsulosin and finasteride) as a routine treatment with 5-ARIs and alpha-blockers. The patients were blinded to the group they were assigned, to maintain the double-blind nature of the trial.

The intervention group received a single dose of Leuprorelin acetate (7.5mg) injection in addition to the standard therapy with tamsulosin (0.4 mg/day) and finasteride (5mg/day). The control group had the standard therapy with tamsulosin (0.4 mg/day) and finasteride (5mg/day) plus saline injection as the placebo.

The International Prostate Symptom Score (IPSS) checklist was used and completed by a physician for all the patients before initiating the therapy and 12 weeks after the therapy to evaluate the significance of LUTS improvement as our primary assessment. This checklist covered seven symptoms of the urinary tract including incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia [19]. The secondary endpoint was evaluating the achievement of patients' satisfaction of voiding clear urine after removal of the catheter following 12 weeks of treatment.

Inclusion and exclusion criteria

The inclusion criteria considered any men over the age of 50 years with the first experience of urinary retention, with no previous history of BPH treatment. The patient should not have any indication for surgical treatment.

Exclusion criteria were men with prior prostate or bladder surgeries, history of kidney disease, heart disease, renal disease, and epilepsy. Those with fever more than 38 degrees, elevated serum PSA level (> 2.5 ng/ml) which increases the risk of prostate cancer, patients with recent or current treatment for sexual dysfunction medications, endocrine-related drugs, a-blockers, 5-ARIs or steroids were also excluded. The patients were informed that the Leuprolide injection can cause medical castration and the patient's desire to have kids was an ethical exclusion criterion.

Statistical analysis

Baseline characteristics of patients were evaluated and reported using descriptive statistics for the full enrolled sample. Independent sample T-test was used to examine and compare the mean differences for quantitative data obtained in each group before and after the treatment. All values are presented as mean ± standard deviation. Levene's test is used to test the equality of variance. The chi-square was also used for qualitative data. A value of $P < 0.05$ was considered to be statistically significant. All analyses were conducted using SPSS software version11.5 (SPSS Inc., Chicago, IL, USA).

Results

Study population

77 patients with confirmed BPH were enrolled in our study and randomized in the intervention group (38 patients) and

the control group (39 patients) between October 2019 and February 2020. All randomized patients were included in analyses and completed the study. Evaluating the pretreatment characteristics showed that only the patients' age had a significant difference distribution between groups. However, there was no statistically significant difference between groups regarding other basic characteristics of PSA, prostate size, and PVR before the treatment (**Error! Reference source not found.**).

Table 1. Basic characteristics of the patients in each group

	Intervention group Mean ± SD	Control group Mean± SD	P-Value"
Age	76.89 ± 10	60.00 ± 06	<0.001"
PSA*	2.9 ± 1.8	2.0 ± 0.8	0.01"
IPSS**	23.7 ± 4.2	17.2 ± 4.1	<0.001"
Size (Trans-abdominal US)	71.8 ± 36.6	60.1 ± 28.7	0.123"
Post-Void Residual	42.0 ± 49	60.7 ± 32	0.027#

*PSA: prostate-specific antigen, **IPSS: international prostate symptom score, "Independent sample t-test; #Mann-Whitney test

Primary endpoint

An independent sample t-test was conducted to examine differences between intervention and control groups across the IPSS estimated before and after the therapy. The intervention group revealed a mean ± SD of 2.47 ± 1.5 while the control group revealed a mean ± SD of 1.51±1.5. Levene's test for equality of variances showed no violations, p= 0.376. Results indicated a statistically significant mean difference in IPSS symptoms score reduction of the intervention group compared with the control group, t (75) = 2.8, p = .007 (**Error! Reference source not found.**).

Table 2: The mean of IPSS reduction (after treatment minus before treatment) and catheter removal in each group

	N	Mean IPSS reduction difference ± SD	Catheter removal (Number)	No catheter removal (Number)
Intervention	38	2.47 ± 1.5	33	5
Control	39	1.51 ± 1.5	33	6

Mean IPSS reduction before and after the treatment in each group.

Secondary outpoint

Catheter removal and patients' satisfaction were achieved in 33/38 patients in the intervention group and 33/39 patients in the control group. In 5 patients of the intervention group and 6 of the control, group catheters were not removed after one-month treatment (**Error! Reference source not found.**).OR was used to show the association between two groups regarding the patients' satisfaction of voiding without a catheter. The odds of these measures after one month of treatment was 1.2 in the intervention group compared with the control group; however, their association was not statistically significant (OR 1.2, 95%CI 0.3-4.3, P=.78).

A Chi-square test was used to examine the possibility of catheter removal due to patients' satisfaction of voiding between two evaluated groups. The results of Chi-square showed that the intervention group had no statistically significant difference with the control group regarding the patient's satisfaction voiding of clear urine after catheter removal; X^2 (1, N=77) =.078, p=. 78.

Because the pre-treatment values were significantly different, we performed an adjustment via linear regression. The test showed that the findings are significant even with consideration of primary baseline status (table 3).

Table 3. Adjustment of primary significant variables via linear regression

	Unstandardized B	95% CI for B	p-value
IPSS	1.008	0.932, 1.084	<0.001
Age	0.04	0.0003, 0.079	0.048
Post-Void Residual	0.015	0.007, 0.023	<0.001
PSA	1.565	0.517, 2.613	0.004

Discussion

This randomized-controlled clinical trial was conducted to assess the efficacy and safety of adjunctive Leuprorelin acetate (7.5 mg IM as a single dose) compared with standard therapy (Placebo + tamsulosin and finasteride) in 12 weeks for patients with confirmed BPH. Our population study with a mean age of 69 years old and the mean IPSS of 20 was representative of the condition and the indication for medical treatment of BPH. Accordingly, after one month of treatment, results showed a rapid and significant reduction in mean IPSS. Applying one dose of Leuprorelin acetate adjunctive to the standard treatment, led to a higher reduction of mean IPSS (2.47) compared with the control group (1.51) and this reduction was statistically significant (p = 0.007). There were two previous studies on the effects of Leuprorelin acetate (1 mg/day, SC) on symptoms score of patients with BPH for a minimum of four months which were conducted by one investigating group [20, 21]. Based on the studies of *Gabrilove et al*, the irritative and obstructive symptoms of the prostate such as the urinary flow, nocturia, and frequency were improved in all treated patients following four weeks of therapy, which was similar to our results regarding the improvement symptoms. They also revealed superior improvement in patients with worse symptoms before the treatment. They proposed reversible effects for leuprorelin after discontinuing its application [20, 21]. In another study on BPH patients, 3.75 mg leuprorelin was injected intramuscularly every 28 days and resulted in a reduction of PSA of the patients [22]. Some other studies also reported its application efficacy on patients with prostate cancer. A similar reduction in IPSS score was reported following 6 months treatment with Leuprorelin acetate for BPH patients who have prostate carcinoma [23]. In another study, nafarelin acetate was used as a potent LHRH agonist for the preoperative treatment of prostate cancer patients with BPH which resulted in noticeable clinical improvement [24]. It has

been also suggested that the application of LHRH analogs might become an alternative to surgical castration and estrogen therapy for the treatment of hormone-dependent prostatic carcinoma [21, 25].

There are limited data on the exact effect of LHRH agonists on LUTS symptoms of patients with BPH. The efficacy of applying other LHRH agonists such as Decapeptyl for patients with BPH was also reported in some studies which showed achievement of decline in IPSS symptoms score of patients after one month of treatment [22, 26]. On the other hand, Abo El-Enen *et al*. reported no change of IPSS scores following four weeks of treatment using LHRH agonist of goserelin acetate (a single SC injection of 3.6 mg)[27]. Similar to our results no side effects have been reported by previous studies following a single dose injection of LHRH agonists in patients with BPH and after four weeks of follow up.

In our study, the application of LHRL agonist of leuprorelin resulted in catheter removal and satisfaction of voiding well in 86.8% of patients (33/38). These results were confirmed by previous studies of Gabrilove *et al* [20, 21]. Although a one-month treatment with leuprorelin led to catheter removal and voiding clear urine in the majority of patients, according to the results of our clinical trial, there was no statistically significant difference between the effect of LHRH synergic with standard therapy compared with the routine treatment with 5-ARIs and alpha-blockers. Similarly, the obtained OR showed that although the odds of catheter removal and patients satisfaction following treatment with LHRH combined with standard therapy is higher compared with standard therapy alone, but also this improvement is not statistically significant (OR 1.2, 95%CI 0.3-4.3, P = 0.78).

All the evaluated basic characteristics were similar between groups except the patients' age that showed statistically significant different distribution between the two groups, which is the limitation of this study.

In conclusion, the synergic effects of leuprorelin with standard therapy led to a statistically significant decrease of IPSS symptoms score compared with standard therapy alone; but did not show any significantly different effects on the catheter removal and patients' satisfaction compared with 5-ARIs and alpha-blockers. Due to limited literature on the efficacy of LHRH agonists further studies with larger sample sizes are still warranted to evaluate its effects on patients with BPH and increase the power of the study.

Study limitations

Despite random sampling method via using the sealed envelopes, IPSS, age, post-void residue, prostate volume, and prostate size were different between two groups at baseline.

Data Availability Statement

The supporting data for our findings are available within the supplementary information file.

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