Effect of Hormonal Therapy for Volume Reduction, Lower Urinary Tract Symptom Relief and Voiding Symptoms in Prostate Cancer: Leuprolide vs Goserelin

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Purpose: The complaints of lower urinary tract symptoms in cases with prostate carcinoma (Pca) are associated with coexisting benign prostate hyperplasia or aging bladder. The aim of this study was to investigate and compare the effect of goserelin acetate with leuprolide acetate on total prostate volume (TPV), post voiding residue (PVR), International Prostate Symptom Score (IPSS) and maximum flow rate (Qmax) reduction in cases of advanced Pca.

Materials and Methods: The study initially enrolled 71 patients who presented at our clinic for hormonotherapy because of advanced prostate carcinoma between May 2015 and August 2016. A total of 51 patients were found suitable for the study and were divided into two groups as Group 1 who received goserelin acetate (10.8 mg /3 months) and Group 2 who received leuprolide acetate (22.5 mg /3 months). Age, Gleason score, T stage, pre and post treatment Prostate specific antigen (PSA) and testesterone level, TPV, IPSS, PVR, and Qmax values were recorded retrospectively. Changes in parameters were assessed every 3 months.

Results: Analysis was made on 51 patients in this study. No statistically significant difference was determined between the two groups in respect of the mean percentage decrease in PSA (98.7% and 98.4%, respectively; $P = .9$) and testosterone (92.9 % and 96.4 %, respectively; $P = .15$) from baseline to 6 months but TPV reduced by -20.2 % ± 4.8 and -15.6 % ± 1.04, the median total IPSS score decreased by -34.77 % ± 8.8 and -19.77 % ± 6.1, median Qmax increased by 45.34 % ± 10.16 and 23.21 % ± 6.93, and median PVR decreased by -31.54 % ± 8.4 and -19.23 % ± 5.5, respectively for the two groups (all parameters $P < .05$)

Conclusion: In this study, the improvement observed in voiding parameters with the use of goserelin acetate was better than with leuprolide acetate. The superiority of the goserelin acetate group was determined in particular on the reduction of TPV, PVR and IPSS. Although the PSA follow-up time was short, no significant difference was determined between the groups in the early oncological outcomes.

Keywords: androgen deprivation therapy; total prostate volume; post voiding residue; voiding symptoms; prostate carcinoma

INTRODUCTION

Prostate carcinoma (Pca) is one of the most common malignant cancers and the second greatest malignancy-related cause of death in males[(1)]. In 2014, the prostate cancer incidence rate was reported as 35 cases per 100,000 in Turkey[(2)]. Androgen deprivation therapy (ADT) is a main stage in the treatment of metastatic or advanced prostate cancer and has been shown to improve overall survival[(3)]. Gonadotropin releasing hormone (GnRH) agonists remain the most widely used form of ADT.

As 70% of prostate carcinomas originate from the peripheral zone, they are frequently asymptomatic until growth is of a size that compresses the prostatic urethra, bladder neck or there is metastasis[(4)]. Therefore, complaints of lower urinary tract symptoms (LUTS) in cases with Pca are associated with the coexistence of benign prostate hyperplasia (BPH) or aging bladder[(5)]. In these cases, total prostate volume (TPV), post voiding residue (PVR), the International Prostate Symptom Score (IPSS) and maximum flow rate (Qmax) are important in the planning of the treatment. Published data show that ADT can reduce TPV ranges by 30 % to 55 %[(6,7)]. Hormonal therapy reduces TPV as well as the tumor volume and this downsizing of the prostate gland has an effect on PVR, IPSS and Qmax values[(8)]. However, to the best our knowledge, there are no published studies that have investigated the effect of different GnRH agonists on LUTS. To adress this knowledge gap, the effect of goserelin and leuprolide acetate on LUTS of prostate cancer were investigated in this study. The aim of the study was to show that there may be regression of symptoms only with hormonotherapy in cases of prostate cancer with LUTS complaints.

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Table 1. Demographic characteristics

Baseline characteristics	Goserelin acetate (10.8 mg) N=24	Leuprolide acetate (22.5 mg) N=27	*P*
Age, years	67.4 (48-80)	64.25 (46-83)	0.035*
Time from diagnosis to initial treatment	61	57	
T stage			
T1	8	11	
T2	12	10	
T3/4	4	6	
Gleason score			
≤7	7	9	
≥8	17	18	
TPV (mL) day of 0	64.12 (28-136)	81.18 (24-110)	0.06
IPSS day of 0	13.45 (4-29)	12.39 (6-26)	0.06
Qmax day of 0	12.4 (5-23)	12.19 (4-21)	0.11
PVR day of 0	73.02 (29-156)	75.9 (20-98)	0.27
PSA levels, ng/mL (mean)	25.6 (4-100)	30.45 (4-81)	0.09
Testosterone, ng/mL (mean)	2.77 (1.1-6.6)	2.98 (1.53-6.2)	0.11

Abbreviations: TPV: Total prostate volume, IPSS: International Prostate Symptom Score, Qmax: maximum flow rate, PVR: post voiding residue, PSA: Prostate specific antigen

MATERIALS AND METHODS

Study population and design

A retrospective review was made of the data of 71 patients who received ADT only for advanced prostate cancer between May 2015 and August 2016. Patients with an indwelling urinary catheter, treatment with 5 alpha reductase inhibitors or alpha adrenoceptor blocker, had evident nervous system disorder or had undergone pelvic or urinary tract surgery were excluded from the study. After exclusion of these patients, the data of the remaining 51 patients were analyzed. Written informed consent was obtained from patients who participated in this study. All study procedures were applied in compliance with the Helsinki Declaration and the Good Clinical Practice Guidelines. Age, Gleason score, T stage, pre and post treatment prostate specific antigen (PSA) and testesterone level, TPV, IPSS, PVR, and Qmax values were recorded for each patient. In this study, patients with advanced prostate cancer received leuprolide or goserelin acetate for at least 6 months at the discretion of the attending physician (T.N.Y. & E.Ö.). Three-month doses were applied to all cases. The cases were divided into 2 groups, as Group 1 patients who received goserelin acetate (10.8 mg/3 months) and Group 2 patients who received leuprolide acetate (22.5 mg/3 months). In all cases bicalutamide (50 mg once daily) was given for the first 10 days for flare protection and on the 10th day GnRH agents were inserted subcutaneously into the abdominal wall.

Blood samples were collected to analyse testosterone and PSA levels with a validated chemiluminescence method at the beginning of the ADT and the analyses were repeated at the 3rd and 6th month. Ultrasonography and uroflowmetry were also performed before administration of the drug and at each 3-monthly visit by the same urologist using the same equipment.

Total prostate volume and PVR were calculated by an elliptical approximation (width x height x length x 0.5) with transrectal ultrasound (using a Sono Scape SSI-5500BW ultrasound scanner, Shenzhen, China). Ultrasound was performed on day 0 and repeated 3 and 6 months later to assess evaluate the change in volume due to ADT with the same equipment by the same urologist. Ultrasound was also performed to measure PVR pre and post ADT. The changes were recorded.

The IPSS questionnaire was completed by all the cases enrolled in the study. This score system is used to assess LUTS[9]. It includes 7 symptoms of urinary tract: incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia[8]. Mild LUTS was defined as IPSS of 1-7, moderate LUTS as IPSS of 8-19 and severe as IPSS of 20-35[10]. A clinically significant response was defined as a change of at least 3 points in IPSS[10]. The IPSS form was administered to the patients at the beginning of the treatment and was repeated at the 3rd and 6th months.

Statistical analysis

SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistically analysis. All values are presented as mean ± standard deviation. Values of the clinical factors were analyzed using the Mann Whitney U-test to determine the significance of differences between groups, and Spearman rank correlation analysis was applied to evaluate the relationship between ADT and the IPSS score, Qmax, TPV and PVR. A value of $P < .05$ was considered to be statistically significant.

RESULTS

The mean age of the patients was 63.9 ± 4.2 years (range, 46-83 years). Group 1 (goserelin acetate) comprised 24 patients and Group 2 (leuprolide acetate), 27 patients. Patient characteristics (age, stage, Gleason score, PSA variables, total testosterone, TPV, IPSS, Q max and PVR) are shown in **Table 1**.

A statistically significant difference was found in mean age between the treatment groups ($P = .035$). Serum PSA, total testosterone, TPV, IPSS, Q max and PVR values were not statistically significant between the two groups ($P = .09$, $P = .11$, $P = .06$, $P = .06$, $P = .11$, $P = .27$, respectively)

No statistically significant difference was determined between the groups in respect of mean percentage decrease in PSA from baseline to month 6 (98.7 % and 98.4 %, respectively; $P = .9$). No significant difference was determined between the two groups in the changes of testosterone values in the 6th month of treatment compared with baseline values (92.9 % and 96.4 %, respectively; $P = .15$).

Table 2. Changes parameter from baseline to 6th month in patients treated with goserelin acetate and leuprolide acetate

	Goserelin acetate	Leuprolide acetate	*p*
PSA (initial to 6th month)	-98.7 % ±0.9	-98.4 % ±0.4	0.9
TT (initial to 6th month)	-92.9 % ±5.8	-96.4 % ±6.9	0.15
TPV (initial to 6th month)	-20.2 % ±4.8	-15.6 % ± 1.04	0.02*
IPSS (initial to 6th month)	-34.77 % ±8.8	-19.77 % ±6.1	0.001*
Qmax (initial to 6th month)	45.34 % ± 10.16	23.21 % ± 6.93	0.001*
PVR (initial to 6th month)	-31.54 % ±8.4	-19.23 % ±5.5	0.01*

Abbreviations: TPV: Total prostate volume, IPSS: International Prostate Symptom Score, Qmax: maximum flow rate, PVR: post voiding residue, PSA: Prostate specific antigen, TT: Total testesterone

Total prostate volume (TPV) was reduced significantly from baseline to month 6 in both groups with mean ±standard error percentage decreases of -20.2 % ± 4.8 and -15.6 % ± 1.04 for goserelin acetate and leuprolide acetate, respectively. Statistical evaluation showed that goserelin acetate was superior to leuprolide acetate (*P* = .02). From baseline to 6th month, the median total IPSS score decreased by -34.77 % ± 8.8 and -19.77 % ± 6.1, median Qmax increased by 45.34 % ± 10.16 and 23.21 % ± 6.93, median PVR decreased by -31.54 % ± 8.4 and -19.23 % ± 5.5, respectively in the two groups. Statistically significant Goserelin acetate was observed to be statistically significantly superior in all of these parameters ($P < .05$) (**Table 2 and Figure 1**).

DISCUSSION

Hormone therapy is the main treatment for locally advanced and metastatic prostate carcinoma patients who are not eligible for radical treatment options. Gonadotropin-releasing hormone (GnRH) receptor agonists are successful in obtaining the required therapeutic levels (serum testesterone < 0.5 ng/mL) in 90 % of patients[11]. The first administration may create a sudden increase in serum T levels. Therefore, because of this effect, the patient is given antiandrogen treatment for 10 days before the first injection to prevent clinical symptoms such as flare phenomenon, spinal cord compresion, bone pain and urethral obstruction[1].

Low urinary tract symptoms are one of the main concerns of prostate cancer patients. Although studies have indicated that endocrine treatments have a diminishing effect on LUTS complaints, there are no studies that have measured the efficacy of goserelin acetate and leuprolide acetate on the improvement on IPSS, TPV, PVR and Qmax[8,12,13]. The results of the current study show that hormonal therapy has a positive effect on LUTS symptoms and prostate volume within 6 months. Prostate cancer frequently coexists with BPH, which can cause LUTS. Lehrer et al. reported that 55.6 % of PCa patients have mild LUTS, 37.1 % have moderate symptoms, and 7.3 % have severe symptoms[14]. Hamilton et al. reported a significant improvement in LUTS complaints and reductions in PVR and TPV values after 12 months of hormonal therapy in patients with prostate cancer[4]. In 2012, Klarskov et al. showed 50 % reduction in IPSS levels, 38 % increase of Qmax, 26 % decrease in PVR value and 37 % decrease in TPV levels within 12 months of hormone therapy[13]. As a result of that study, the best improvement in these parameters was observed to be in the first month of the ADT. A few studies have detected the reduction in TPV to be in the range of 21 % to 48 % within 3.7 months as a result of ADT[15,16]). In the current study, TPV reduction secondary to hormone therapy was 20.2 % in the goserelin group, and 15.6 % in the leuprolide group in 6 months, which was similar to the findings of previous studies.

The effects of testosterone suppression on bladder outlet obstruction have been determined in vitro and in vivo animal studies. Blockage of GnRH receptors in the prostate smooth muscle and epithelial cells allows the down-regulation of pro-inflammatory cytokines, growth factors and □1-adrenoreceptors involved in these cells. An improvement in LUTS and a decrease in TPV were accepted in this patient group with the provided smooth muscle relaxation[10,17]. It is believed that hormone therapy in the elderly bladder contributes to IPSS scores through the effect on prostate carcinoma. In a study that compared degarelix and goserelin acetate, it was observed that the improvement was better in cas-

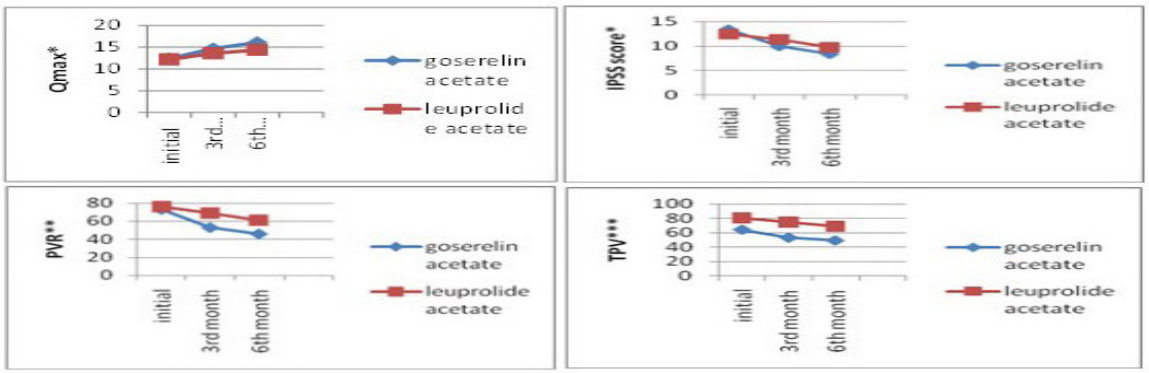

Figure 1. Voiding parameters and prostat size from initial to 6th month. Comparison chart of the effects of goserelin acetate and leuprolide acetate on parameter (*$p < 0.001$, **$p < 0.01$, ***$p < 0.02$)

es with low IPSS scores in the 3rd month and degarelix was superior to goserelin acetate[10]. In the current study, although IPSS scores were not divided into voiding and storage scores, goserelin acetate was found to be statistically more significant in total score improvement (-34.77 % ±8.8 vs -19.77 % ± 6.1, respectively). The storage score of IPSS is associated with PVR while Qmax value is related to voiding scores. Improvement in IPSS has been similarly observed at Q max and PVR levels[13]. In the results of the current study, the increase in maximum flow rate (45.34 % ± 10.16) and decrease in postvoid residual volume (-31.54 % ± 8.4) were significanty higher in the goserelin acetate group than in the leuprolide acetate group in the 6th month ($P < .01$). There are different opinions that assume the upper level of testosterone as 0.2 ng/mL or 0.5 ng/mL as the ideal castration level. It is often accepted as adequate at 0.5 ng/mL as there has been seen to be no difference regarding the decrease in PSA and progression in the follow-up of patients[3]. In terms of comparing GnRh agonists, some studies have shown no statistically significant difference between goserelin acetate and leuprolid acetate[3]. Goserelin groups have shown some superiority over leuprolide[18]. In the current study, for castration level < 0.5 ng/mL of testesterone, there was no significant difference between the groups ($P = .15$). Similar results were observed in the changes in PSA level, with no statistically significant difference observed between the groups in respect of the PSA decrease ($P = .9$).

There were some limitations to this study. Although the number of patients was sufficient, the study was conducted at a single center. To the best of our knowledge, this is the first study to have compared the effect of goserelin acetate and leuprolide acetate on voiding parameters and reduction of prostate volume and postvoiding residue.

CONCLUSIONS

The main goal of hormonal therapy is to treat patients with locally advanced and metastatic prostate carcinoma who are not eligible for radical treatment options, and in the current study, the effect of ADT was observed on voiding symptoms and prostate volume. The improvement in voiding parameters of goserelin acetate was determined to be better than leuprolide acetate. In particular, the superiority of goserelin acetate was observed in the reduction of TPV, PVR and IPSS.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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