Effects of Goserelin Treatment on Microvessel Density and Blood Loss Associated with Transurethral Resection of the Prostat

Goserelin Tedavisinin Prostatın Transüretral Rezeksiyonu ile İlişkili Kan Kaybı ve Mikrovasküler Dansite Üzerindeki Etkisi

Goserelin ve Prostatın Mikrovasküler Dansitesi / Goserelin and Microvessel Density in Prostate

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Özet

Amaç: Prostat'ın transüretral rezeksiyonundan (TUR-P) önce uygulanan tek doz goserelin' in, benign prostat hiperplazisi (BPH) olan hastalarda kan kaybı ve prostat subüretral dokunun mikrovasküler dansitesi (MVD) üzerine olan etkilerinin belirlenmesi amaçlandı. Gereç ve Yöntem: TUR-P planlanan hastalar iki gruba randomize edilerek ayrıldı. Ameliyattan 1 ay önce 3,6 mg subkütan goserelin asetat uygulanan 18 hasta Grup 1'i oluşturdu. Grup 2 ise goserelin verilmeyen 21 hastadan oluşturuldu. İntraoperatif kanama miktarı ölçüldü. Her hasta için toplam kan kaybı, toplam kan kaybı/ ameliyat süresi, toplam kan kaybı/ rezeke edilen doku gramı hesaplandı. Prostat subüretral doku kesitleri mikrovasküler dansitesi açısından incelendi. Bulgular: Ameliyattan hemen sonra yapılan kontrolde; grup 1'deki hemoglobin (Hb) düşüşü grup 2'ye göre daha fazlaydı ve ortalama Hb seviyesi grup 1'de grup 2'ye kıyasla istatistiksel olarak anlamlı derecede düşük bulundu (p=0.028). İstatistiksel olarak anlamlı olmamasına rağmen irrigasyon sıvısında Hb konsantrasyonu ve ameliyat süresince kan kaybı grup 1'de grup 2'ye oranla daha yüksekti, buna karşılık TUR-P süresine göre ve rezeke edilen prostat doku ağırlığına göre kan kaybı ise grup 1'de grup 2'ye gore daha düşüktü. Mikrovasküler dansite grup 2'de belirgin olarak daha azdı. Tartışma: Bir aylık tek doz goserelin tedavisi, TUR-P boyunca olan kan kaybını azaltmada etkili değildir ve prostat dokusunda mikrovasküler dansitesi üzerinde süpresif etkisi yoktur.

Anahtar Kelimeler

Benign Prostat Hiperplazisi; Goserelin; Mikrovasküler Dansite; Kan Kaybı; Prostatın Transüretral Rezeksiyonu

Abstract

Aim: To determine the effects of one dose goserelin before transurethral resection of the prostate (TUR-P) on blood loss and microvessel density (MVD) of prostatic suburethral tissues in the patients with benign prostatic hyperplasia (BPH). Material and Method: The patients who planned to have a TUR-P were randomly divided into two groups. Group-1 consisted of 18 patients who were pretreated with 3,6 mgr subcutaneous injection of goserelin acetate one month before the operation. Group-2 was constructed from 21 patients without goserelin acetate pretreatment. The amount of intraoperative haemorrhage was calculated. Total blood loss, total blood loss/duration of surgery and total blood loss/gram of resected tissue were calculated for each patient. Sections from the prostatic suburethral tissues were examined for microvessel density. Results: Quantitative decreases in Hb were greater in group 1 than in group 2, and mean Hb level was statistically significantly lower in group 1 than in group 2 at the control just after the operation (p=0.028). Although all the differences were statistically insignificant, Hb concentration in irrigation fluid and total blood loss during surgery were higher in the group 1 than in the group 2, contrarily, blood loss by duration of TURP and blood loss by weight of resected prostate tissue were less in the group 1 than in the group 2. The MVD was significantly lower in group 2 than in the group 1. Discussion: Single dose goserelin treatment given for one month is not effective in reducing blood loss during TURP and has not suppressive effects on MVD in prostatic tissues.

Keywords

Benign Prostatic Hyperplasia; Goserelin; Microvessel Density; Blood Loss; Transurethral Resection Of Prostate

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Introduction

Benign prostatic hyperplasia (BPH), a common disease among elderly men, usually is treated with surgery. Even though the development of various minimally invasive surgery for BPH, transurethral resection of the prostate (TUR-P) remains the gold standart method in the treatment of BPH. However, the operation is associated with complications such as haemorrhage, postoperative clot retention and blood transfusion [1]. Therefore, it is crucial for both surgeon and patient to control the blood loss associated with TUR-P. Recent reports show that taking the 5α-reductase inhibitor finasteride before surgery is effective in controlling the blood loss associated with TUR-P [2- 4]. The exact mechanism by which intraoperative blood loss is reduced by finasteride is unknown, but seems to involve a decrease in prostate blood flow and microvessel density (MVD) within the prostate.

BPH with increased acinar and stromal cell proliferation stimulates increased vascularity (angiogenesis) of vessels, which may be easily disrupted, providing the basis for recurrent bleeding. Because of androgens enhance prostatic hyperplasia; their withdrawal seems a logical way to treat this situation. Recently gonadotropin-releasing hormone analogues, by producing "chemical castration," have been tried in cases of benign prostatic hyperplasia [5]. Marshall and Narayan [6] postulated that angiogenesis is critical in BPH and androgen deprivation leads to the suppression of angiogenesis.

Goserelin acetate, a synthetic decapeptide analogue of luteinizing hormone-releasing hormone (LHRH), has been widely used in treating BPH and prostatic cancer [7].

The present prospective randomized study was designed to compare the men treated with goserelin acetate before TURP with that not taking goserelin acetate with regard to effect on blood loss during and after surgery, and for the MVD of the resected prostate tissue; the correlation between MVD and blood loss was also evaluated.

Material and Method

After all patients were counseled and provided verbal informed consents, study was carried out at Inonu University Faculty of Medicine between March 2003 and June 2004. Thirty-nine consecutive patients who agreed to undergo TURP for bladder outlet obstruction were randomly divided into two groups. Group-1 consisted of 18 patients who were pretreated with 3,6 mgr subcutaneous injection of goserelin acetate (Zoladex Depot® 3,6 mgr subcutaneous injection, İstanbul, Turkey) one month before the operation. Group-2 (control group) was constructed from 21 patients without goserelin acetate pretreatment. Because of the possible effects on operational bleeding, patients with serious hematological, oncological, cardiovascular, hepatic, renal diseases and coagulation disorders and those having a history of previous invasive procedures on the prostate were excluded in the study. We also excluded the men who previously or currently on gonadotrophin releasing hormone anologous treatment other than gosereline, on drugs with anti-androgenic activity (finasteride or dutasteride), or gonadal hormones and men with histopathoogically documented prostate cancer. Men with a suspected malignancy because of a raised Prostate Specific Antigen (PSA) level (PSA> 4 ng/ml) or an abnormal digital rectal examination (DRE) were included if diagnostic tests (transrectal needle biopsy) were negative and TURP was considered clinically appropriate. Intake of nonsteroidal anti-inflammatory drugs and aspirin was discontinued 2 weeks before surgery. All patients underwent TURP at one institution during the same period. Prostate specimens were blindly evaluated by the same pathologist for pathologic diagnosis, weight and microvessel density (MVD) determinations. Preoperative characteristics of all patients were presented in table-1.

The patients with an indwelling urethral catheter were included to ascertain whether the presence of a catheter increased hematuria during TURP, and MVD, as haematuria is a known sequel of indwelling urinary catheters.

Preoperative evaluation included general systemic and digital rectal examination, urine analysis and culture, abdominopelvic and transrectal ultrasonography for the determination of the kidney, bladder and prostate morphologies, volume of the prostate and post-voiding residual urine, uroflowmetry measurements for maximum (Qmax) and average (Qave) urine flow rate determinations, serum biochemistry (blood urea nitrogen-BUN, creatinine-Cr, sodium-Na, potassium-K, chlorine-Cl, free-PSA, total-PSA, free/total PSA rate), hemogram (hemoglobin-Hb, hemotocrit-Hct concentrations), and serum coagulation parameters (international normalization rate-INR, protrombine time-PT, activated partial tromboplastine time-aPTT) findings. Serum hemogram and biochemistry parameters were also determined postoperatively in the recovery room and the next morning.

Surgical Procedure: The premedication consisted of oral diazepam. Spinal anesthesia was used in all patients. Most of the operations were performed by same surgeon using a 24 or 27-Ch resectoscope (Karl Storz, Tuttlingen, Germany) and 3% mannitol during surgery as irrigation fluid maintained 50 to 75 cm above the prostate. The fluid returns were collected in a hepa-

Table 1. Preoperative characteristics according to the groups.

	GROUP 1	GROUP 2	P value
Age-year (range)	69,29 ± 8,04 (55-90)	63,12 ± 5,97 (52-75)	0,013
Hematuria history-no. of pts. (%)	1 (5,88)	2 (11,76)	0,545
No. of pts. with urethral catheter (%)	3 (17,65)	7 (41,18)	0,132
INR (range)	1,06 ± 0,11 (0,93-1,32)	1,11 ± 0,10 (0,96-1,31)	0,108
PT-second (range)	13,05 ± 0,92 (12,1-15,3)	12,94 ± 1,75 (8,3-14,9)	0,429
aPTT-second (range)	29,45 ± 2,94 (23,7-33)	28,95 ± 3,08 (25,7-38,4)	0,290
Transrectal prostate weight-gram (range)	38,71 ± 14,3 (16-63)	40 ± 18,52 (19-85)	0,796
Total PSA-ng / mL (range)	8,27 ± 6,89 (1,04-26,10)	4,83 ± 5,79 (0,63-19,4)	0,031
Free PSA-ng / mL (range)	1,99 ± 1,35 (0,3-4,43)	1,33 ± 2,06 (0,13-6,68)	0,020
Free / Total PSA (%)	27,6 ± 13,38 (12,8-63,07)	24,82 ± 8,24 (9,69-37,23)	0,823
Qmax-mL / second (range)	8,5 ± 4,4 (0-14)	8,2 ± 3,08 (3-13)	0,617
Qave-mL / second (range)	4,1 ± 2,13 (2-9,4)	3,2 ± 1,03 (2-5)	0,336
Post voiding residual urine-mL (range)	94,33 ± 102,19 (15-410)	29,82 ± 22,32 (0-80)	0,021

rinized bucket. At the beginning of the resection, a deep bite of the prostate tissue was resected from each of the prostate lobe for MVD measurement.

After the irrigation fluid was pooled and thoroughly stirred, blood loss during TURP was calculated by the RBC method which was calculated as the volume of the collected irrigation fluid × concentration of Hb (gr/dL of collected irrigation fluid) divided by the concentration of serum Hb (gr/dL) before surgery. Additionally, the blood loss per gram of resected prostate tissue and the mean blood loss per duration of surgery were calculated for each patient.

Histological and immunohistochemical testing: At operation surgical specimens that included the prostatic urethra and prostatic hyperplastic nodules were identified and used for histological analysis. Prostate chippings collected from each patient were fixed in 10% buffered formalin. They were processed routinely with paraffin-wax embedding and sectioned at 5 µm, stained with haematoxylin and eosin, and suburothelial sections of the prostate were identified. BPH (epithelial and fibromuscular hyperplasia) was histologically confirmed in each case. One and four patients had histological evidence of prostate cancer in group-1 and group-2, respectively. Therefore, these patients were not included in the statistical analysis.

Relevant blocks containing the prostatic urethra as well as nodular hyperplasia were then re-sectioned and stained using mouse monoclonal immunohistochemical antibody to CD-34, an endothelial cell antigen specific for nascent blood vessels and an effective immunohistochemical marker for prostatic microvessel density analysis, Ab-1 (Clone QBEnd/10) (NeoMakers, Fremont, CA), to assess the effects of gosereline on microvessels in the prostate. Each section was examined by a single blinded histopathologist who was unaware of drug administration.

MVD was calculated by counting the number of positively stained blood vessels on 10 consecutive, nonoverlapping fields within a 10 × 10 reticulated imprinted grid at x200 magnification (×20 objective and × 10 ocular, 0.754 mm2) in the suburethral compartment, which is the connective tissue within a margin 1 to 2 mm. beneath the urethral epithelial basement membrane, and in the stroma of nodular hyperplasia. The average vessel density per unit grid was obtained as the mean of 10 grids per patient and expressed as vessels/0.754 mm2. Large vessels with thick muscular walls and large vessels of lumina more than eight blood cells in diameter were excluded from the counts. The groups were compared, and the correlation between mean MVD and blood loss during surgery was assessed.

Statistical analysis: All data management and statistical analyses were performed using commercially available software (SPSS 10.0, Chicago, IL, USA). Unless indicated otherwise, continuous data were expressed as means ± standard deviation. Chi-square test, Mann-Whitney U test and Friedman test were used because the variables are not normally distributed. Correlation analysis was based on the Spearman correlation coefficient (rho), its value supported by the respective p values. All tests of statistical significance were two-tailed and were considered significant at a 0.05 level.

Results

Preoperatively, mean age, serum free and total PSA levels and post-voiding residual urine volume were statistically higher in group 1 than in group 2 (Table-1). However, there was no statistically significant difference between the groups in hematuria history, presence of a urethral catheter, coagulation parameters, weight of prostate before surgery, free / total PSA rate and uroflowmetry measurements (Table-1).

Preoperatively, any significant difference was not recorded in serum BUN, Cr and electrolyte levels between the groups (Table-2). There were no significant alterations in serum BUN concentrations after the operation in both groups. Although some statistically significant changes developed following operation in serum Cr and electrolyte levels in either group 1 or 2 or in both, mean values were within the laboratory ranges in both groups at all measurements (Table 2). Significant distortion at clinic appearance which was related to these changes was observed in no patient. Also, the differences in postoperative mean Cr and electrolyte measurements were insignificant between the groups at al periods.

Statistically more significant changes were noted in mean serum Hb and Hct levels (Table-2). Although both Hb and Hct concentrations decreased very significantly in both groups following operation, quantitative decreases were greater in group 1 than in group 2, and mean Hb level was statistically significantly lower in group 1 than in group 2 at the control just after the operation. There was no significant difference in mean Hb and Hct concentrations between the groups preoperatively and at postoperative day 1.

Intra and postoperative characteristics were presented in table-3. No statistical difference was observed in mean duration of operation and TURP, volume of irrigation fluid, and resected weight of prostate tissue between the groups. Although all the differences were statistically insignificant, Hb concentration in irrigation fluid and total blood loss during surgery were higher in the group 1 than in the group 2, contrarily, blood loss by duration

Table 2. Changes of the hemogram and biochemistry parameters.

		Preoperative	Just after oper	Postop. day 1	P value*
HGB	Group 1	13,96 ± 1,37	11,55 ± 2,18	10,89 ± 1,75	<0,0001
	Group 2	14,25 ± 1,16	13,01 ± 1,43	11,55 ± 1,23	<0.0001
	P value&	0,490	0,028	0,270	
HCT	Group 1	41,74 ± 4,25	34,53 ± 6,36	31,27 ± 4,55	<0,0001
	Group 2	41,99 ± 3,53	37,52 ± 4,97	33,27 ± 3,63	<0.0001
	P value&	0,593	0,102	0,234	
BUN	Group 1	20,59 ± 7,19	18,71 ± 4,61	19,82 ± 6,95	0,458
	Group 2	18,41 ± 11,12	19 ± 10,45	18,94 ± 10,87	0,813
	P value&	0,137	0,316	0,293	0,002
CRE	Group 1	0,94 ± 0,24	0,92 ± 0,37	1,12 ± 0,37	0,005
	Group 2	0,98 ± 0,65	0,92 ± 0,6	1,02 ± 0,58	
	P value&	0,300	0,362	0,077	0,005
NA	Group 1	143,41 ± 3,22	132,88 ± 9,52	138 ± 8,37	0,291
	Group 2	141,82 ± 4,13	134,94 ± 8,21	139,59 ± 3,5	
	P value&	0,404	0,501	0,359	0,291
K	Group 1	4,49 ± 0,48	4,36 ± 0,42	4,2 ± 0,73	0,020
	Group 2	4,52 ± 0,3	4,25 ± 0,55	4,02 ± 0,44	
	P value&	0,809	0,522	0,388	0,021
CL	Group 1	107,47 ± 3,24	100,53 ± 7,87	104,06 ± 5,98	0,867
	Group 2	105,59 ± 4,05	102,06 ± 7,54	105,12 ± 4,18	
	P value&	0,200	0,730	0,717	

P * : in-group P & : between-groups

Table 3. Operative and postoperative characteristics according to the groups.

	GROUP 1	GROUP 2	P value
Operation duration - min (range)	90 ± 17,23 (60-130)	87,06 ± 37,54 (50-210)	0,150
Duration of TURP - min (range)	68,24 ± 15,1 (30-90)	59,12 ± 16,42 (35-90)	0,084
Irrigation fluid volume - L (range)	20,82 ± 5,89 (9-28)	21,56 ± 7,61 (9-42)	0,917
Hemoglobin concentration in irrigation fluid - gr / dL (range)	0,25 ± 0,18 (0,01-0,7)	0,21 ± 0,14 (0,01-0,5)	0,585
Resected weight - gr (range)	32,47 ± 18,18 (10-75)	24,18 ± 12,89 (7-50)	0,138
Total blood loss - mL (range)	344,8 ± 205,77 (15,48-782,61)	287,88 ± 158,51 (20,98-579,31)	0,344
Blood loss / duration of TURP - mL / min (range)	5,04 ± 2,79 (0,18-9,78)	5,05 ± 2,71 (0,28-10,71)	0,796
Blood loss / resected weight - mL / gr (range)	12,24 ± 7,19 (0,22-23,98)	14,74 ± 9,31 (0,55-36,11)	0,593
MVD -vessels/ 0.754 mm2 (range)	10,72 ± 3,1 (6,2-16,7)	7,71 ± 3,19 (5-17,8)	0,003
No of pts. requiring blood transfusion	7 (41,2%)	2 (11,8%)	0,052
Volume of the transfused blood - mL (range)	243 ± 336,15 (0-854)	83,65 ± 237,11 (0-772)	0,059
Duration of macroscopic hematuria in urethral catheter after TURP - day (range)	1,0 ± 0,71 (0-2)	1,94 ± 0,77 (1-3)	0,002

Table 4. Effects of the preoperative presence of a urethral catheter (UC) on MVD and total blood loss (TBL) during TURP (ranges).

		UC negative	UC positive	P
MVD	group 1	10,46 ± 3,13 (6,2 - 16,7)	11,93 ± 3,28 (9,7 - 15,7)	0,529
	group 2	7,48 ± 2,21 (5 - 11,4)	8,03 ± 4,43 (5,3 - 17,8)	0,845
TBL	group 1	318,12 ± 184,52 (15,48 - 592,11)	469,3 ± 298,62 (187,9 - 782,6)	0,378
	group 2	259,7 ± 149,8 (99,3 - 538)	328,15 ± 173,54 (21 - 579,3)	0,329

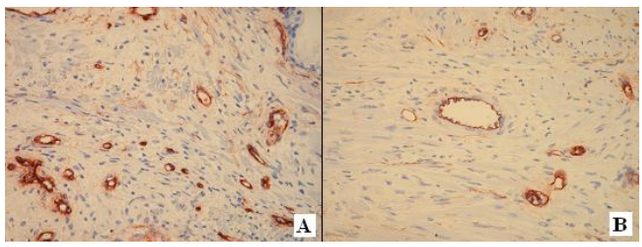


Figure 1. Immunohistochemistry of CD34 stained sections demonstrates suburethral prostatic microvessel density in goserelin treated (A) and control (B) prostates. (X 400)

of TURP and blood loss by weight of resected prostate tissue were less in the group 1 than in the group 2. Although the differences were not significant, rate and mean volume of the blood transfusion after TURP were greater in group 1 than in group 2. Duration of macroscopic hematuria in urethral catheter after TURP was significantly lower in group 1 than in group 2.

All patients in the group 1 and 2 were evaluable for MVD in the prostate sections. The MVD was significantly lower in group 2 than in the group 1 (Table-3). Histopathologic examination of the prostate sections in the groups was presented in figure (Figure 1). There was no significant correlation between the MVD and total blood loss during TURP (rho = 0,142 and p = 0,423 without grouping the patients rho = 0,029 and p = 0,911 in the group 1 and rho = 0,146 and p = 0,576 in the group 2). Although both the MVD and total blood loss were greater in the patients with a urethral catheter in both groups, the differences between the patients with and without urethral catheter were statistically insignificant (Table-4).

Discussion

BPH is a common problem especially in man over 50 years of age. TUR-P remains a common procedure for the relief of urinary obstructive symptoms associated with BPH. However, the operation is associated with complications such as hemorrhage, postoperative clot retention and blood transfusion. Mebust et al [1] reported a 3.9% transfusion rate and a 3.3% clot retention rate. Even though TUR-P is efficient, there are developments of various alternative minimally invasive surgeries for BPH because of the morbidity rate of 18% in TUR-P procedures [8]. The administration of hematuria during and after operation is a threat and reducing blood loss is crucial. Treatment options for prostatic bleeding include tamponade of the prostate with a urethral catheter, endoscopic resection and fulguration of the prostate, hormonal ablation, use of antifibrinolytic agents, or careful observation with limiting of physical activity.

MVD is a histological measurement of angiogenesis and thus a surrogate marker of bleeding, as the prostates of men with BPH and haematuria have a significantly higher MVD in the suburethral portion than prostates of men with BPH alone [9]. Prostatic microvessel density is a histological and clinical indicator of angiogenesis in patients with BPH. Marshall and Narayan [6] concluded that prostatic hyperplasia with increased acinar and stromal cell proliferation stimulates increased angiogenesis, which can be easily disrupted, thereby providing the basis for recurrent bleeding.

Patients with clinical BPH and recurrent gross hematuria have a significantly higher suburethral prostatic microvessel density than patients with BPH alone [9]. BPH associated hematuria is probably related to the increased vascularity of the prostate [6, 10]. It has been accepted that this angiogenesis can be suppressed by androgen deprivation, which was shown in the prostates of dogs who demonstrated a distinct reduction in prostatic blood flow after being treated with finasteride [11]. 5α reductase inhibitors reduce blood loss during TURP via shrinking the prostate by decreasing the number of blood vessels in a way similar to the effect achieved with androgen ablation [6, 12]. Experimental studies with finasteride showed an inhibition in prostatic blood flow and vascular density, which is probably due to down-regulation of vascular endothelial growth factor (VEGF), and which may reduce the rate of haematuria associated with BPH. Taking finasteride before TURP was investigated in a randomized, placebo-controlled trial. Finasteride was given for 2 weeks before operation and the amount of Hb per gram of resected tissue and the amount of Hb in irrigation fluid reduced, but the blood concentration of Hb after surgery was higher in the group treated with finasteride [2]. Sandfeldt et al. [4] showed that 3 months of finasteride before TURP, especially in large prostates, decreased blood loss during surgery. In another study, giving finasteride for a mean of 2.7 months before surgery in patients with BPH, have reduced the blood loss [3]. For treating haematuria secondary to BPH, cyproterone acetate

and finasteride are reported effectively [13- 15].

The antiandrogen chlormadinone acetate given orally for 1 month before TURP did not reduce the crude blood loss during surgery, nor the blood loss corrected for operating time, compared with placebo, but did result in a significant difference in blood loss per gram of resected tissue. The MVD was lower in those who received chlormadinone acetate [4]. Recently, Tuncel et al. [16] reported that administration of dutasteride or Serenoa repens did not decrease perioperative blood loss and were not effective in suppression MVD in prostatic tissues.

In the present study we aimed to evaluate whether pretreatment with goserelin acetate reduces the degree of blood loss during TURP.

Goserelin is a synthetic decapeptide analogue of gonadotrophin-releasing hormone (GnRH) which stimulates gonadotrophin and sex hormone release in the short term, and then causes suppression with continued administration. Goserelin is given as a subcutaneous biodegradable depot incorporating 3.6 mg of the drug [17]. The goserelin 3.6 mg depot is registered worldwide for subcutaneous administration every 4 weeks for the treatment of patients with prostate cancer, breast cancer and various benign gynecological conditions (endometriosis, fibroids, endometrial thinning and assisted reproduction) [18]. After administration of 3.6 mg depot form, there were generally 2 peaks in the serum goserelin concentration; an initial transient peak within a few hours is followed by a greater second peak after 14 to 15 days. Therefore, goserelin reaches its average maximum concentration in serum after a 14-day period and declines within the next 14 days to the basal levels on 28 th day [19].

We evaluated the effect of one-dose 3.6 mg depot goserelin. The present study showed that one month administration of goserelin did not reduce blood loss, due to the drug's pharmacokinetics. Thus, we should think the use of long term therapy to obtain the optimum results. Zinner et al. [20] showed that in most (77.4%) patients receiving long-term therapy with 3.6 mg goserelin, the testosterone levels were consistently maintained within the castrate range.

The present study demonstrated that one-dose administration of goserelin 3.6 mg depot is not effective in reducing blood loss and did not have suppressive effects on MVD in prostatic tissues.

Conclusions

In conclusion, goserelin therapies were not superior to control in terms of not only the decrease in total blood loss during TUR-P, but also the level of MVD in goserelin group. Further clinical investigations are required to ascertain the exact dose and treatment period that would provide the maximum benefit.

Competing interests

The authors declare that they have no competing interests.

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