

Original Research Article

Effect of high-dose finasteride combined with trans-urethral plasmakinetic resection of prostate on prostate-specific antigen and inflammatory factors in patients with benign prostatic hyperplasia

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Abstract

Purpose: To ascertain the effect of perioperative application of high-dose of finasteride on prostate-specific antigen (PSA) in serum, tumor necrosis factor α (TNF- α) and interleukin-1 β (IL-1 β) in prostatic fluid of prostatic hyperplasia (BPH) patients with transurethral plasmakinetic resection of prostate (PKRP).

Methods: In total, 141 BPH patients treated with PKRP in Hunan Provincial People's Hospital, Changsha City, China from January 2015 to January 2017 were randomly divided into three groups of 47 cases each, viz, high-dose (10 mg of finasteride), low-dose (5 mg of finasteride), control (0 mg of finasteride). The levels of PSA in serum, as well as the levels of TNF- α and IL-1 β in prostatic fluid were evaluated 7 days before and after surgery. Re-bleeding within 3 months after surgery in the three groups were performed and the patients observed.

Results: Intra-operative bleeding volume, bleeding volume per unit resected tissue, and intra-operative volume of rinsing fluid were significantly less in high- and low-dose groups than those in the control group ($p < 0.05$); furthermore, the operation time was significantly shorter than that for the control group ($p < 0.05$). Seven days after surgery, international prostate symptom score (IPSS), serum PSA, and TNF- α and IL-1 β in prostatic fluid of the high- and low-dose groups were significantly lower than those of the control group ($p < 0.05$). Also, maximum urine flow rate was significantly higher than that of the control group. Serum PSA, and TNF- α and IL-1 β levels in prostatic fluid were significantly lower than those of low-dose group ($p < 0.05$). Serum PSA as well as TNF- α and IL-1 β levels in prostatic fluid were positively correlated with IPSS score ($r = 0.817, 0.838, 0.859, p < 0.001$). The admission rate due to re-bleeding was lowest in the high-dose group, followed by the low-dose group.

Conclusion: Finasteride combined with PKRP for BPH acts synergistically to reduce serum PSA levels and local inflammatory reaction. High-dose finasteride/PKRP combination is more efficacious than the low-dose combination, thereby improving short-term prognosis in patients.

Keywords: Finasteride, Transurethral plasmakinetic resection, Prostate, Prostate-specific antigen, Inflammatory factors

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INTRODUCTION

Benign prostate hyperplasia (BPH) is one of the common diseases in middle-aged males. The number of cases is increasing every year in tandem with rapid increase in number of aging people worldwide [1,2]. Transurethral plasmakinetic resection of prostate (PKRP) is a new surgical technique that has emerged in recent years [3]. Compared with the traditional transurethral resection of prostate, PKRP effectively reduces bleeding and transurethral resection syndrome [4], and so it is currently one of the reliable regimes for BPH.

Previous studies [5] considered the possibility that intraoperative and postoperative bleeding would occur easily in PKRP, which would affect the prognosis of patients, but finasteride was introduced to inhibit neovascularization and reduce blood flow in BPH, thereby preventing bleeding [6,7]. Thus, it was recommended that this drug should be used in the perioperative period. However, the effectiveness of finasteride in BPH treatment is associated with its inhibition of angiogenesis, and negative its effect on local anti-inflammatory agents [8,9]. However there are few reports on the impact of administration of finasteride in the perioperative period on the serum levels of inflammatory factors of patients.

Another impediment to the current use of finasteride is the issue of the dose regime of the drug in the perioperative period which has not been fully standardized. Furthermore, the best dose of the drug to be administered has not been made clear. On account of these shortcomings, a randomized controlled investigation was conducted in this study to unravel the curative effect of different doses of finasteride combined with PKRP in treating BPH, and its impact on prostate specific antigen (PSA) and serum inflammatory factors.

EXPERIMENTAL

General information

The study was conducted in 141 patients with BPH treated in Hunan Provincial People's Hospital from January 2015 to January 2017. The study was approved by the Ethics Committee of Hunan Provincial People's Hospital (approval no. 20141201), and followed the guidelines of Declaration of Helsinki [10]. The study randomly divided all the patients into three groups, each of 47 patients. The high dose group received high finasteride dose, while the low-dose group received a lower dose of finasteride.

The control group patients were not given finasteride.

Inclusion criteria

(1) Patients diagnosed as having BPH based on the standard "Guidelines for Diagnosis and Treatment of Urological Diseases of China (2014 version)" [11]; (2) Patient who presented evidence of PKRP, and agreed to be treated surgically; (3) Patients who did not receive anti-androgen drugs for the treatment of BPH within the previous 6 months; (4) Patients who had been informed of this study and had signed the "Informed Consent". All those who satisfied these criteria were accepted as subjects in this study.

Exclusion criteria

(1) Patients with uncorrected hypertension and diabetes; (2) Patients with abnormality in four blood coagulation indices; (3) Patients with unstable bladder; (4) Patients allergic to related drugs were excluded.

Therapeutic regimen

Patients in the two groups were operated by the same surgeon, and sustained epidural anesthesia was used. The Gyrus bipolar plasma continuous irrigation resectoscope with a cutting power of 200W and electrocoagulation power of 100W was used as the main equipment. Normal saline was used as irrigation fluid. The resectoscope was inserted into the urethra. The urethra, prostate and surrounding tissue morphology were first examined. The resection was carried out from the median lobe or the lateral lobe of the prostate, guided by the bladder neck and colliculus seminalis. The depth of the resection reached the circular fiber of the prostate capsule. Post-operative conventional indwelling catheter was used. The high-dose group received 10mg of finasteride (Liaoning Yuhuang Pharmaceutical Co., Ltd.; SFDA approval no: H20061299; 5 mg/tablet) twice daily continuously at 7 days before and 7 days post-surgery. The low-dose group received 5 mg finasteride daily continuously at 7 days before and 7 days after the surgery, while the control group did not receive finasteride.

Observation indices

Surgical results

These include operation time, intra-operative blood loss, weight of resected prostate, the amount of bleeding per unit of resected tissue, bleeding rate, amount of intraoperative rinsing

fluid (where the amount of bleeding per unit tissue = intraoperative blood loss/weight of resected prostate), and bleeding rate (intraoperative blood loss/operation time).

Clinical efficacy

The international prostate symptom score (IPSS) [12] and the maximum urinary flow rate of patients in the two groups were measured at 7 days before and after surgery.

Changes in PSA and inflammatory factors

The peripheral blood and prostatic fluid of the patients were collected before the first administration of finasteride, at 7 days before the surgery and after the last administration of the drug, and at 7 days after the surgery. The levels of serum PSA were measured by enzyme-linked immunosorbent assay (ELISA), using assay kits (American DPC (USA)). Radioimmunoassay was employed to determine levels of TNF- α and IL-1 β in prostatic fluid using an assay kit (Beijing North Institute of Biological Technology (China)). Re-bleeding situations after surgery were investigated within 3 months in the 2 groups.

Statistical methods

Data obtained were expressed as mean \pm standard deviation, and were tested for significance by paired t- test, one-way analysis of variance (ANOVA) and SNK- q test. The analyses

were done with SPSS 19.0 software. Constituent ratios were tested by chi-square test. Correlation analysis was performed by Pearson method. Differences between mean values were considered significant at $p < 0.05$.

RESULTS

Baseline data for the three groups

There were no significant differences in baseline data such as age, prostate volume, maximum urinary flow rate and underlying disease complications among the three groups ($p > 0.05$). These baseline data were comparable as shown in Table 1.

Surgical results

The weight of resected prostate and bleeding rate among the three groups showed no statistically significant differences ($p > 0.05$). Intraoperative blood loss, blood loss per unit resected tissue and the amount of intraoperative rinsing fluid were significantly lower in the high- and the low-dose group than those in the control group ($p < 0.05$). In addition, the operation time was significantly shorter in the high-dose group than that in the control group ($p < 0.05$), but there was no significant difference in these indices between the high- and the low-dose group ($p > 0.05$; Table 2).

Table 1: Baseline data for the three experimental groups (mean \pm SD)

Group	Age (year)	Prostate volume (ml)	Maximum urinary flow rate (ml/s)	Complicated with underlying diseases		
				Hypertension	Coronary heart disease	Diabetes
High-dose (47)	67.15 \pm 5.51	57.16 \pm 11.97	6.83 \pm 2.17	15 (31.91%)	8 (17.02%)	12 (25.53%)
Low-dose (47)	66.32 \pm 6.12	58.55 \pm 9.72	6.55 \pm 2.36	12 (25.53%)	10 (21.28%)	10 (21.28%)
Control (47)	68.68 \pm 5.86	56.23 \pm 9.54	7.11 \pm 1.95	16 (34.04%)	10 (21.28%)	12 (25.53%)
$F\chi^2$	1.980	0.586	0.783	0.870	0.357	0.310
P	0.142	0.558	0.459	0.647	0.837	0.856

Table 2: Surgical results for the three groups (mean \pm SD)

Group	Operation time (min)	Intraoperative blood loss (ml)	Weight of resected prostate (g)	Blood loss per unit resected tissue (ml/g)	Bleeding rate (ml/min)	Amount of intraoperative rinsing fluid (L)
High-dose (47)	52.19 \pm 14.49	99.38 \pm 12.30	28.19 \pm 4.34	3.00 \pm 1.74	1.86 \pm 0.74	17.11 \pm 4.96
Low-dose (47)	52.79 \pm 15.30	100.94 \pm 15.50	28.42 \pm 4.44	3.48 \pm 1.86	1.60 \pm 0.80	17.11 \pm 7.16
Control (47)	81.89 \pm 18.67	148.66 \pm 21.69	28.62 \pm 5.15	5.81 \pm 2.56	1.64 \pm 0.83	23.06 \pm 5.16
F	51.269	128.346	0.099	24.548	1.466	16.248
p	0.000	0.000	0.906	0.000	0.234	0.000

$p < 0.05$, compared with the control group

Clinical efficacy

The IPSS scores of all the patients at 7 days after surgery were significantly lower than those at 7 days before surgery, and the maximum flow rate at 7 days after the surgery was significantly higher than that at 7 days before the surgery; the inter-group difference was statistically significant ($p < 0.05$). The difference in IPSS scores and the maximum flow rate at 7 days before the surgery among three groups showed no statistical significance ($p > 0.05$). The IPSS scores of the high- and the low-dose group were significantly lower than those of the control group and the maximum flow rate was significantly higher than that of the control group at 7 days after the surgery ($p < 0.05$), but the difference between the high- and low-dose groups showed no statistical significance ($p > 0.05$; Table 3).

Changes in PSA, TNF- α and IL-1 β

The PSA in serum, and levels of TNF- α and IL-1 β in prostatic fluid were significantly decreased among three groups at 7 days after surgery ($p < 0.05$). The PSA in serum, and the levels of TNF- α and IL-1 β at 7 days before the surgery were not significantly different among the three groups ($p > 0.05$). The level of PSA in serum and TNF- α and IL-1 β at 7 days after the surgery in the high-dose group were the lowest, followed by the low-dose group, while the levels in the control group were the highest. The PSA values, and levels of TNF- α and IL-1 β in the high- and low-dose groups 7 days after surgery were statistically

significantly different from each other ($p < 0.05$, Table 4).

Correlation analysis of PSA in serum, TNF- α and IL-1 β in prostatic fluid and IPSS scores

Data obtained from 141 patients before and after surgery were included in this analysis. Pearson correlation analysis showed that PSA in serum, TNF- α and IL-1 β in prostatic fluid were significantly positively correlated with IPSS scores ($r = 0.817, 0.838, 0.859$; all $p < 0.001$). The scattergrams showing the lines of best fit are shown in Figure 1.

Admission rate due to re-bleeding within 3 months post-surgery

There were 2, 8 and 18 cases in the high-dose group, low-dose group and control group, respectively, due to re-bleeding within 3 months after surgery. The hospitalization rates were 4.26, 17.02 and 38.30 %, respectively. The rate of re-bleeding in the high-dose group was significantly lower than that of the other two groups ($\chi^2 = 4.100, 16.929$; $p < 0.05$), while the rate of re-bleeding in the low-dose group was significantly lower than that of the control group ($\chi^2 = 5.632$, all $p < 0.05$).

DISCUSSION

Hemorrhage is the main complication of PKRP [13,14]. The intraoperative blood loss of the three groups in this study were 99.38 ± 12.30 ml,

Table 3: Clinical efficacy of treatment in the three groups (mean \pm SD)

Group	IPSS score		Maximum flow rate (ml/s)	
	7 days before surgery	7 days after surgery	7 days before surgery	7 days after surgery
High-dose group (47)	24.23 \pm 6.59	6.68 \pm 1.49 [#]	6.59 \pm 1.75	28.47 \pm 4.78 [#]
Low-dose group (47)	23.96 \pm 4.56	6.26 \pm 1.86 [#]	6.05 \pm 1.57	29.14 \pm 4.94 [#]
Control group (47)	24.87 \pm 5.7	7.98 \pm 1.44 [#]	6.50 \pm 1.44	23.53 \pm 4.23 [#]
F	0.329	14.678	1.583	20.297
P	0.720	0.000	0.209	0.000

Note: Compared with the control group, $p < 0.05$; [#]compared with that at 7 days before surgery, $p < 0.05$

Table 4: Changes in PSA, TNF- α and IL-1 β for the three groups (mean \pm SD)

Group	PSA in serum (ng/ml)		TNF- α in prostate fluid (pg/ml)		IL-1 (pg/prostate fluid (pg/ml)	
	7 days before surgery	7 days after surgery	7 days before surgery	7 days after surgery	7 days before surgery	7 days after surgery
High-dose (47)	10.06 \pm 1.29	2.67 \pm 0.53 ^{#Δ}	66.05 \pm 17.26	3.24 \pm 0.50 ^{#Δ}	4.33 \pm 0.45	0.79 \pm 0.12 ^{#Δ}
Low-dose (47)	10.17 \pm 1.05	3.41 \pm 0.38 [#]	69.24 \pm 15.97	4.66 \pm 0.54 [#]	4.24 \pm 0.36	1.21 \pm 0.08 [#]
Control (47)	10.02 \pm 1.22	5.41 \pm 0.77 [#]	67.60 \pm 16.25	8.40 \pm 1.32 [#]	4.24 \pm 0.25	1.46 \pm 0.15 [#]
F	0.186	279.479	0.440	436.308	0.949	359.377
p	0.831	0.000	0.645	0.000	0.390	0.000

Compared with the control group, $p < 0.05$; ^{Δ} compared with low-dose group, $p < 0.05$; [#]compared with that at 7 days before surgery, $p < 0.05$

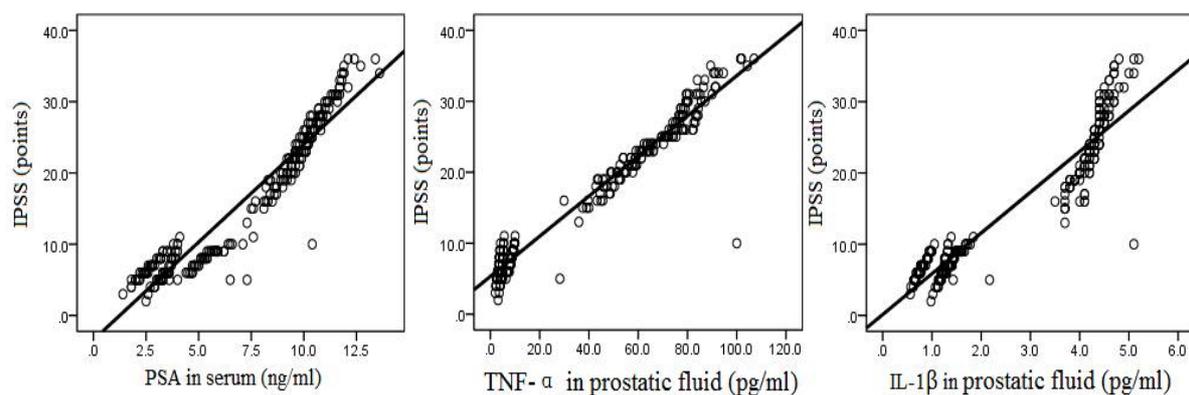


Figure 1: Scattergram of IPSS scores and PSA in serum, TNF- α and IL-1 β in prostatic fluid

100.94 \pm 15.50 ml, and 148.66 \pm 21.69 ml respectively, which are smaller in volume when compared to the intraoperative blood loss reported by Zhouliang *et al* [15] and Xiaowei *et al* [16].

The values they reported were 210.45 \pm 19.17 ml and 231.38 \pm 77.52 ml respectively. The causes of bleeding include bladder spasm, incomplete hemostasis and residual glands [17], which cannot be completely avoided even with improved surgical skills. Hence there is need to take auxiliary measures that will ensure that bleeding is prevented completely or in the event of re-bleeding, that it is reduced to the barest minimum.

Multiple studies [18,19] have revealed that treatment of patients with finasteride perioperatively helps to reduce intraoperative and post-operative blood losses. The results of this study were in accord with the earlier findings [18,19]. Finasteride at the doses used in the present study (5 mg/day or 10 mg/day) can reduce the intraoperative blood loss and blood loss due to tissue excision. Due to the low blood loss, the operative field was clearer, which accounted for the fact that the operation times in the high and high-dose groups were significantly shorter than that of the control group. This is consistent with the result obtained by Liuyu *et al* [20].

The protective effect of finasteride on intraoperative bleeding could be attributed to its inhibitory effect on the activity of vascular endothelial growth factor: androgens have stimulatory effect on vascular endothelial growth factor, and can increase prostate blood flow [21]. Finasteride can, by selectively and competitively inhibiting 5 α reductase type II, block testosterone conversion to dihydrotestosterone (DHT). This reduces the level of active androgen, and is accompanied by reduced prostate blood flow. A

previous report [22] also showed that finasteride can directly reduce the level of vascular endothelial growth factor (VEGF) in the kidney and the microvessel density.

However, finasteride has other mechanisms of action on BPH. For example, Wuchengzhang *et al* [23] found that finasteride when administered to elderly patients with BPH can reduce the levels of serum TNF- α and PSA, which explained the fact that treatment with finasteride can relieve systemic inflammation and overexpression of PSA. It further shows that treatment of patients with finasteride in perioperative period can also reduce the levels of PSA and inhibit inflammation. The present study found that the PSA in serum, TNF- α and IL-1 β in the high-dose groups were significantly lower than that of the control group, which gives credence to the foregoing hypothesis, and also lends weight to the view that finasteride when combined with PKRP can be the best and safest strategy for the management/ treatment of BPH.

Current studies on the use of finasteride in perioperative period for the reduction of bleeding in BPH surgery are yet to be conclusive. There are differences in the doses and duration of use in various reports. For example, Shenjun *et al* [24] holds the opinion that finasteride should be used for a long time before surgery while Dengguangpeng *et al* [25] believe that treatment with high-dose of finasteride at 7 days before surgery could improve the surgical outcome. On the basis of the foregoing opinions and the findings from this study it does appear that: (a) surgery may not produce complete curative effect on BPH, and (b) continuous application of finasteride after surgery may enhance the curative effect.

Thus, finasteride was applied 7 days before and after surgery, both in low and high-dose group in this study, and the results confirmed that the two

regimens improved the surgical outcome: the low levels of PSA and inflammatory factor observed in the high-dose group are remarkable, and suggest that this treatment strategy can bring about improved BPH prognosis. The low rate of re-bleeding admission after surgery as found in this study in the high-dose group is also indicative of better prognosis, which is consistent with previous reports [26,27].

Limitations of the study

The sample size in this study is limited. Furthermore, the effect of the specific mechanism action of different doses of finasteride on PSA, TNF- α and IL-1 β levels in BPH patients after PKRP is yet to be elucidated. Therefore, randomized trials based on a larger sample size are needed to further study.

CONCLUSION

Finasteride, when combined with PKRP in the treatment of BPH further reduces serum PSA and local inflammatory factors. The effect is more pronounced in patients treated with higher dose of finasteride. The combination therapy is thus a better management strategy for BPH.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. All the authors read and approved the manuscript for publication. Zhe Liu conceived and designed the study, Jia Chen collected and analysed the data, Qiang Lu wrote the manuscript.

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