Transurethral resection versus holmium laser enucleation of the prostate

A prospective randomized trial comparing perioperative thrombin generation and fibrinolysis

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Abstract

Objectives: The purpose of this study was to compare transurethral resection of the prostate (TURP) versus holmium laser enucleation of the prostate (HoLEP) in patients with benign prostatic hyperplasia (BPH) focusing on perioperative thrombin generation and fibrinolysis.

Methods: Sixty-five BPH patients were prospectively randomly assigned to undergo TURP (n = 32) or HoLEP (n = 33). The prothrombin fragment (PF) 1+2, thrombin-antithrombin complex (TAT), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor-1 (PAI-1) were measured preoperatively, at the 1st day and 3rd day after surgery.

Results: PF1+2, TAT, t-PA, and PAI-1 significantly elevated at day 1 and day 3 after surgery ($P < .05$) and remarkably decreased from the 1st day to the 3rd day ($P < .05$). The levels of PF1+2 and TAT were higher in TURP group postoperatively than that in HoLEP group ($P < .05$). There is no significant difference between 2 groups in regard of t-PA and PAI-1 ($P > .05$).

Conclusion: The activation of thrombin generation and fibrinolysis system were noticed in BPH patients after TURP or HoLEP. TURP may associate with a higher hypercoagulable thrombotic risk than HoLEP.

Abbreviations: BPH = benign prostatic hyperplasia, DM = diabetes mellitus, DVT = deep venous thrombosis, HoLEP = holmium laser enucleation of the prostate, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptoms, PAI-1 = plasminogen activator inhibitor-1, PE = pulmonary embolism, PF = prothrombin fragment, PVR = post void residual urine, Qmax = maximum urinary flow rate, QoL = quality of live, TAT = thrombin-antithrombin complex, t-PA = tissue plasminogen activator, TRUS = transrectal ultrasonography, TURP = transurethral resection of the prostate.

Keywords: benign prostatic hyperplasia, fibrinolysis, holmium laser enucleation of the prostate, thrombin generation, transurethral resection of the prostate

1. Introduction

Prostatectomy remains one of the most common procedures worldwide and majority of these are performed transurethrally.[1] Transurethral resection of the prostate (TURP) has

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historically been the standard surgical treatment for patients with benign prostatic hyperplasia (BPH).[2] But recently its position begins to be challenged and the transurethral holmium laser enucleation of the prostate (HoLEP) is a potential one of many outstanding challenges.[3]

Various risk factors such as aging, immobilization, surgical trauma, and comorbidities (e.g. hypertension and diabetes) make BPH patients vulnerable for thromboembolic events including deep venous thrombosis (DVT), pulmonary embolism (PE), and even myocardial or cerebral infarction.[4] Although the most common complication of TURP is bleeding, thromboembolic events are not uncommon. The reported incidence of DVT after TURP is 6.8–10%, while PE 0.2–2.2% before prophylaxis was commonly used.[5,6] There are few researches comparing the incidence of postoperative thromboembolic events between TURP and HoLEP. The reason may be that the incidence of thromboembolic events after TURP or HoLEP is much lower than that of open prostatectomy,[7] the misdiagnosis of postoperative DVT is high and most fatal PE can only be confirmed by autopsy.[8]

It is difficult to directly assess effects of two procedures on the incidence of postoperative thromboembolic events. The prothrombin fragment (PF) 1+2 and thrombin-antithrombin complex (TAT) have been described as reliable markers of thrombin generation meanwhile tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) are classic

indicators of fibrinolysis.[9–11] By assessing the perioperative activation of thrombin generation and fibrinolysis, it can reflect the risk of thromboembolic events.

2. Materials and methods

Between June 2015 and March 2017, 70 patients who underwent surgical treatment for BPH presenting to the Second Affiliated Hospital of Zhejiang University School of Medicine were recruited. The patients were randomized at a 1:1 ratio to undergo either TURP or HoLEP (Fig. 1). Inclusion criteria were listed as follows: severe lower urinary tract symptoms (LUTS), refractory to medical therapy with alpha-blockers and/or 5-alpha reductase inhibitors, post void residual urine (PVR) > 100 ml, and acute urinary retention. Exclusion criteria were neurogenic bladder, cardiovascular and/or cerebrovascular thromboembolic diseases, DVT, PE, malignancy, coagulopathy, and on antiplatelet or anticoagulant therapy. All patients gave their informed consent and the project was approved by the local ethics committee and performed in accordance with Declaration of Helsinki. All patients were investigated with medical history, physical examination, transrectal ultrasonography (TRUS), prostate volume, maximum urinary flow rate (Q_{max}), post void residual volume (PVR), International Prostate Symptom Score (IPSS), and quality of live (QoL) score.

All procedures were performed by a single surgeon with general anesthesia. A standard Wolf resectoscope (26.5F) and a standard loop using 160 W cutting power and 60 W coagulation power with 4% mannitol as irrigation fluid were adopted for TURP. Holmium:YAG laser (fiber size 550 μm; Versa Pulse Select, Coherent Corp., Palo Alto) with a power setting of 2 J/40–50 Hz and a 26F Olympus continuous fluid irrigation resectoscope with saline 0.9% as irrigation fluid were used for HoLEP. At the end of surgery, a 20F three-way catheter was inserted and retained in situ until the urine was clear. The surgery duration, weight of removed tissue, catheter time, and hospital time were recorded.

Blood samples were collected from the patients' antecubital fossa vein in 3 phases of period: Period 1 (in the morning, on the day of surgery), Period 2 (in the morning, on the first day after surgery) and Period 3 (in the morning, on the 3rd day after surgery) and placed into 10 ml tube containing sodium citrate. Within 30 min, the samples were centrifuged at 1400 g for 15 min and the resulting plasma was isolated and stored at −80°C for later batch analysis.

An overview of thrombin generation and fibrinolysis is shown in Figure 2. The assay used to measure the plasma concentrations of the various factors was enzyme linked immunosorbent assay (ELISA) (Human PF1+2, TAT, t-PA, PAI-1 ELISA Kit, Elabscience Biotechnology Co., Ltd, Wuhan, China).

2.1. Statistical analysis

As most of the studied variables did not follow normal distribution, the following nonparametric tests were used for the analysis. In order to verify the differences at various time points within the same patient group, the Wilcoxon signed rank test was used. In order to verify the differences between the patient groups, the Mann–Whitney U test was used. All analyses were carried out using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL). A P value of less than .05 was considered statistically significant and means ± standard deviation was used.

3. Results

In the TURP group, one patient was on antiplatelet, one had DVT, and one withdrew from this study due to the postoperative bleeding. In the HoLEP group, one patient had coronary heart disease and one failed to give the blood sample at the required time. They were all excluded. The remaining 65 patients were recruited, including 32 patients in the TURP group and 33 patients in the HoLEP group. In the TURP group, 5 patients had hypertension, 2 patients had diabetes mellitus (DM), and 1 patient had hypertension and DM. In the HoLEP group, 6 patients had hypertension, and 1 patient had DM.

The 32 BPH patients undergoing TURP did not differ from the 33 BPH patients undergoing HoLEP regarding age, TRUS volume, Q_{max}, PVR, IPSS, and QoL score (Table 1). The length of bed rest, catheterization, and hospitalization tended to be longer in the TURP group than that in the HoLEP group. The operative time was longer in the HoLEP group. The weight of the removed tissue was significantly heavier in the HoLEP group than that in the TURP group (Table 2).

PF1+2 and TAT, t-PA, and PAI-1 on Period 2 elevated significantly from Period 1 ($^{\#}P < .05$). PF1+2 and TAT, t-PA, and PAI-1 on Period 3 demonstrates a dramatic increase from Period 1, but with a fall subsequently after Period 2 ($^{\#}P < .05$). The levels of PF1+2 and TAT were higher in TURP group at Period 2 and Period 3 than that in HoLEP group ($^{*}P < .05$). There were no significant differences in the levels of t-PA and PAI-1 between two groups at Period 1, Period 2, or Period 3 ($\star P > .05$) (Fig. 3).

4. Discussion

TURP is a gold standard for transurethral prostatectomy, which is still widely applied among urologists, due to the short learning curve and the simple equipment. However, TURP is also associated with a high incidence of complications, like bleeding
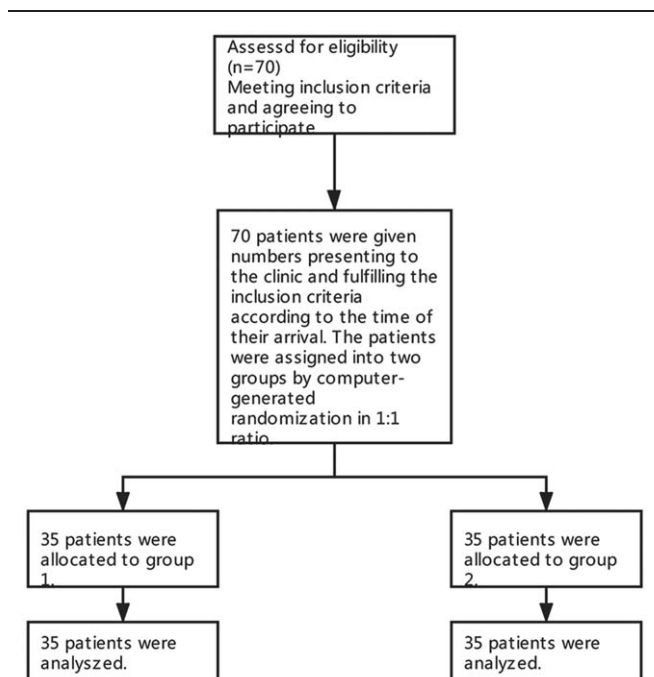

Figure 1. Flow of participants through the study.

Assessd for eligibility (n=70) Meeting inclusion criteria and agreeing to participate

70 patients were given numbers presenting to the clinic and fulfilling the inclusion criteria according to the time of their arrival. The patients were assigned into two groups by computer-generated randomization in 1:1 ratio.

35 patients were allocated to group 1.

35 patients were allocated to group 2.

35 patients were analyszed.
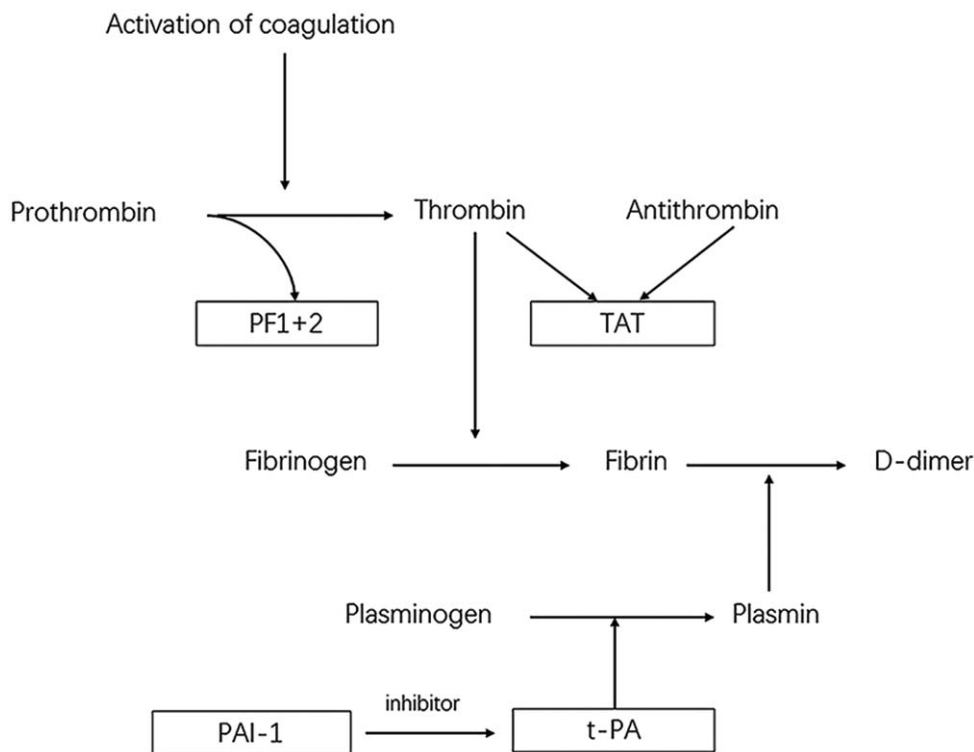
35 patients were analyzed.

Figure 2. Mechanism of the thrombin generation and fibrinolysis system. Tissue injury triggers the extrinsic coagulation cascade. This results in conversion of prothrombin into thrombin and prothrombin fragment (PF) 1+2. Thrombin is inactivated by antithrombin III, leading to formation of thrombin-antithrombin complex (TAT). Endothelial activation causes the release of tissue plasminogen activator (t-PA) antigen, which converts plasminogen into the active plasmin. This active enzyme leads to the breakdown of fibrin to D-dimer. Plasminogen activator inhibitor 1 (PAI-1) is released from the endothelium, hepatocytes, and platelets to inhibit t-PA.

or TUR syndrome and is unsuitable for extremely large prostates.[12] Relatively, HoLEP has the benefit of less blood loss, shorter catheter and hospital time and is suitable for almost all size of prostates.[13] Same as other surgical procedures, the presence of a hypercoagulable state after TURP or HoLEP is not surprising, which seems a physiological response to secure hemostasis.[14] Compared with TURP, HoLEP has a significantly less bleeding loss, which may be related to the coagulation effect of holmium laser.[15] Tuman et al found that there was a significant association between intraoperative bleeding loss and postoperative thrombin generation.[16] In our study, the postoperative levels of PF1+2 and TAT in TURP group are significantly higher than that in HoLEP group. However, the ratio of PF1+2 and TAT was maintained. The result may be due to different perioperative blood loss or operative trauma. Khaled

and his colleagues retrospectively analyzed the change of PSA in patients undergoing TURP and HoLEP, and found that the level of serum PSA dropped more in HoLEP group.[17] Nielsen et al found that PSA released after prostatectomy was associated with an increase in postoperative PF1+2 and TAT.[14] This may be due to the fact that the PSA is structurally and functionally very similar to the protein that activates the clotting reaction, since they all belong to the serine protease family,[18] although underlying mechanism is unclear. What's more, the variable in the duration of postoperative lower limb immobilization may also affect the risk of thrombo-embolic complications.

Mohamed et al reported that patients with abdominal aortic aneurysm had a prothrombotic, hypo-fibrinolytic diathesis indicated by elevated levels of PF1+2 and TAT, and normal levels of t-PA and PAI-1.[19] In our study, preoperative PF1+2, TAT, t-PA, and PAI-1 are all within normal range. The increase in postoperative t-PA and PAI-1 were evident and there was no significant imbalance in mean t-PA and PAI-1 levels after surgery.

Table 1

Baseline demographic data.

	TURP (n = 32)	HoLEP (n = 33)	P
Age (years)	69.24 ± 4.34	71.18 ± 6.04	0.189
TRUS prostate volume (ml)	82.85 ± 30.37	80.71 ± 26.39	0.646
Q_{max} (ml s^{-1})	5.64 ± 2.09	6.39 ± 1.99	0.358
PVR (ml)	124.88 ± 87.22	136.53 ± 73.36	0.270
IPSS	20.10 ± 6.21	21.42 ± 6.17	0.358
QoL	4.63 ± 1.17	4.41 ± 1.23	0.533

Statistically significant at $P < .05$. HoLEP = transurethral holmium laser enucleation of the prostate, IPSS = International Prostate Symptom Score, PVR = post void residual volume, Q_{max} = maximum urinary flow rate, QoL = quality of live, TRUS = transrectal ultrasonography, TURP = transurethral resection of the prostate.

Table 2

Perioperative comparative data.

	TURP	HoLEP	P
Operative time (min)	42.65 ± 11.33	60.69 ± 12.77	<0.001
Specimen weight (g)	28.38 ± 4.39	37.44 ± 6.35	<0.001
Bed rest (hour)	37 ± 10.3	32 ± 9.1	0.04
Catheterization (day)	2.76 ± 1.12	2.18 ± 1.01	0.031
Hospitalization (day)	4.54 ± 1.16	3.27 ± 1.18	<0.001

Statistically significant at $P < 0.05$. HoLEP = transurethral holmium laser enucleation of the prostate, TURP = transurethral resection of the prostate.
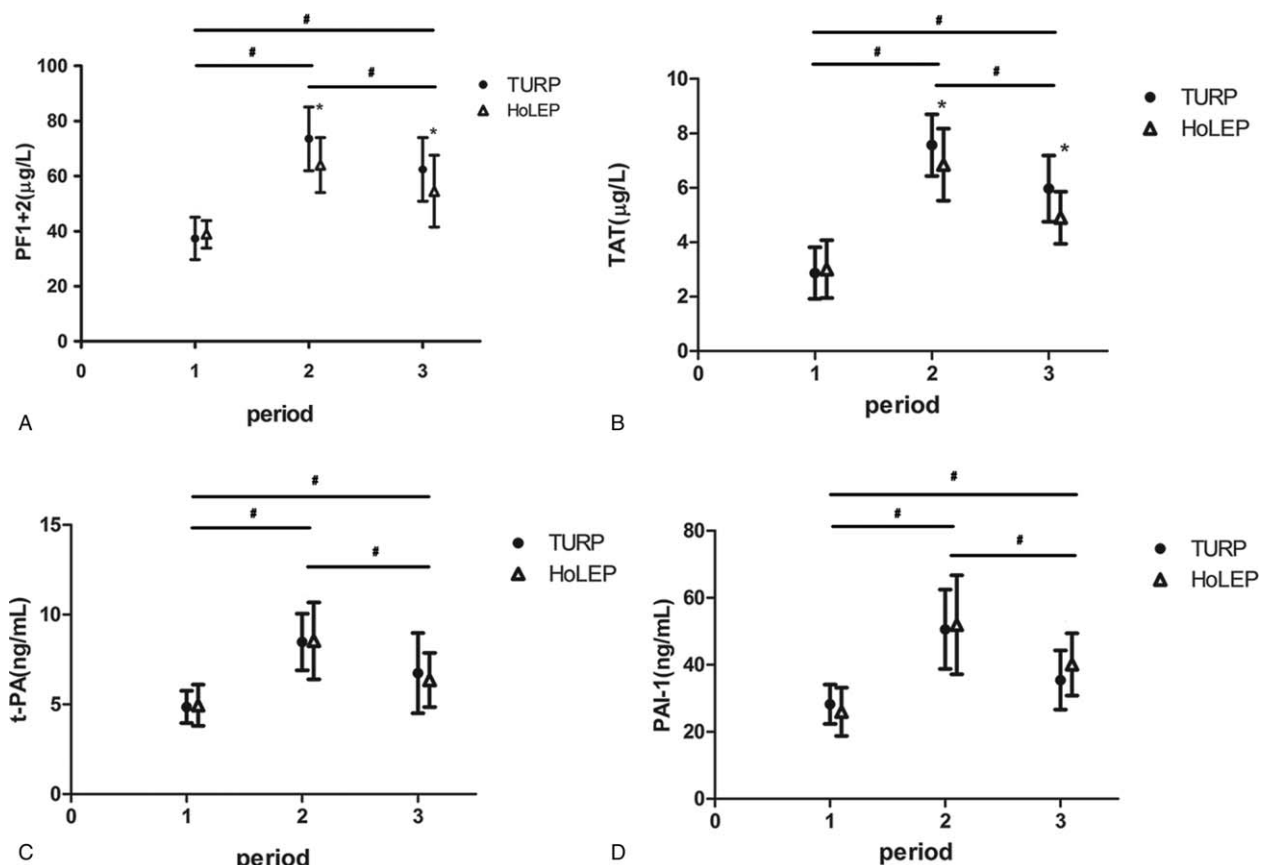
Figure 3. Changes of PF1+2, TAT, t-PA, and PAI-1 at different time points. (A) PF1+2: Prothrombin fragment 1+2. (B) TAT: thrombin-antithrombin complex. (C) t-PA: tissue plasminogen activator. (D) PAI-1: plasminogen activator inhibitor-1. *$P < .05$ compared between two group at the same period. #$P < .05$ compared between two group at the same period.

The prothrombotic state after surgery does not appear to be due to inhibition of fibrinolysis consequent upon an imbalance between t-PA and PAI-1, as reported in other forms of procedures.[20] Two different surgical modalities did not have a significant effect on the postoperative levels of t-PA or PAI-1.

As we know, TURP is verified to have a lower risk for postoperative thromboembolic events than open prostatectomy.[21] Although patients undergoing transurethral prostatectomy still should take some precautions against thromboembolic events, such as early mobilization, graduated compression stockings, or intermittent calf compression, especially to those who have thromboembolism history, DM, or malignancy, they are highly recommended to take low molecular heparin.[22] The limitation of this study are the small number of patients and the insufficient duration of postoperative observation. These limitations greatly affect the interpretation of our findings. A large pool of patients and a longer postoperative observation will provide a more accurate picture.

5. Conclusions

The study reveals a fact that TURP and HoLEP both will activate the thrombin generation and fibrinolysis system, nevertheless, the balance of coagulation and anti-coagulation, fibrinolysis and anti-fibrinolysis, coagulation and fibrinolysis appears to be maintained. However, we find significant differences between TURP and HoLEP with regard to thrombin generation, and TURP may be associated with a higher hypercoagulable thrombotic risk than HoLEP.

Author contributions

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