EFFECT OF LASER PROSTATECTOMY ON SERUM PROSTATE-SPECIFIC ANTIGEN LEVELS AND FREE/TOTAL PROSTATE-SPECIFIC ANTIGEN RATIO IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

Hakkı PERK, M.D., Köksal ÇELİK, M.D., T. Ahmet SEREL, M.D., Alim KOŞAR, M.D., Nuri DENİZ, M.D.

Süleyman Demirel University, Department of Urology, Isparta-Turkey
Gazi University, Faculty of Medicine, Department of Urology, Ankara-Turkey
Gazi Medical Journal 2001; 12: 183-187

ABSTRACT

Purpose: *To assess the effect of laser prostatectomy (LP) procedure on serum prostate-specific antigen (PSA) levels and free/total PSA (f/t). To our knowledge, this is the first study on this subject with respect to free/total PSA (f/t) levels.* ***Patients and Methods:*** *The serum PSA levels and f/t ratio were determined in 30 patients with benign prostatic hyperplasia (BPH) 1 day before and 1,7,30 days after LP. All patients underwent preoperative evaluation with routine blood tests, serum PSA levels (free and total), IPSS symptom questionnaire, intravenous pyelography (IVP), uroflowmetry, post void residual urine measurements, and transrectal ultrasonography (TRUS).* ***Results:*** *Total and free PSA levels showed a statistically significant ($p<0.001$) increase 24h after LP, then a slow decrease, and by 30 days the PSA levels had fallen to their initial levels. On the other hand, the difference between the preoperative and postoperative (1,7,30 days) f/t ratio was not found statistically significant ($p1=0.08$, $p7=0.90$ and $p30=0.40$). A statistically significant positive correlation was found between the PSA level 24h after LP and the amount of energy applied to the prostate during operation ($r=0,76$, $p<0.0001$). After 30 days, the mean PSA values were under the preprostatectomy concentration; the mean PSA values after 30 days were significantly lower than those measured before treatment ($p<0.001$). There was a statistically significant positive correlation between the PSA level one day after LP and the estimated prostatic weight by TRUS ($r=0.5$, $p<0.0001$).* ***Conclusions:*** *In our study, serum free and total PSA levels increased significantly without any meaningful change in the f/t PSA ratio on the first day after LP. These findings reveal that determination of the f/t ratio may be a more reliable parameter than serum total and free PSA values, especially 30 days after LP.*

Key Words: *Free/Total PSA Ratio, Laser Prostatectomy, Prostate, PSA.*

INTRODUCTION

Prostate-specific antigen (PSA) was first isolated in 1979 and is now recognized as the most useful marker available for prostate cancer (1-3). In early detection and screening of prostatic carcinoma, however, PSA level alone is considered not to be sufficiently sensitive, and especially not sufficiently specific (4). In an attempt to enhance the specificity and sensitivity of PSA for early prostate cancer detection, several forms of PSA have been demonstrated in the serum; the concentrations and ratios of those molecular forms are also used in clinical

practice.

It is well documented that serum total PSA levels may be increased in patients with benign prostatic hyperplasia (BPH) or prostatitis and after some interventions such as prostate biopsy,transurethral resection of the prostate and laser prostatectomy (LP) (5-8). However the effect of these procedures on free / total (f/t) PSA ratio is currently unknown. Moreover, the effect of laser prostatectomy on serum free/total PSA ratio in patients with BPH is still unknown .

The aim of this study was to investigate the effect of laser prostatectomy on serum PSA (free-total) levels and f/t PSA ratio in patients with BPH and to determine the reliability of f/t ratio after LP.

PATIENTS AND METHODS

The study included 30 patients with BPH. All patients were hospitalized and underwent Laser prostatectomy (LS). Before treatment, all patients underwent preoperative evaluation by digital rectal examination,routine blood tests,IPSS symptom questionnaire, total and free PSA in serum, intravenous pyelography (IVP), uroflowmetry, post void residual urine measurement, and prostate volume measurement using TRUS. The patients who had a f/t PSA ratio below 0.25 before the surgery underwent a TRUS-guided prostatic biopsy .

PSA Assay

All patient were examined between 8:00 and 10:00h in the morning. Blood samples for PSA (free and total PSA) determination were obtained 1 day prior to and 1,7 and 30 days after LP. The samples were analyzed on the same day. The serum total and free PSA was measured using direct chemiluminometric technology (ACS: 180 PSA / free PSA; Chiron diagnostics, Easts Walpole, Mass, USA). Normal serum PSA values for this assay are 0.0-4.0 ng/ml.

Transurethral LP

All patient were operated using the Nd-Yag laser system with a wave length of 1.060 ng,using a side firing ultraline laser fiber. The technique was visual side firing contact vaporization .All treatments were performed under sedoanalgesia, spinal or general anestesia, and were ended when minimal to no adenomatous tissue remained. Depending on the prostate volume, the duration of the operation varied from 15 to 75 (mean 38.33 ± 2.64) min and energy levels applied varied from 20,000 to 68,000J (mean 48300 ± 2488,2). All patients were managed postoperatively with an intraurethral catheter until hematuria was minimal (mean time 2.3 ± 0.9 days / range 1-5 days).

Statistics

Statistical analysis was done with the Graphpad instant Tm program on computer. Results of the free, total and free / total PSA levels were analyzed statistically with the non-parametric Wilcoxon signed rank test. Corelations among variables were determined calculating the Pearson correlation coefficient.

All tests were two-sided with p values of 0,05 or less being considered to be statistically significant.

RESULTS

The mean age of 30 patients was 62.60 ± 1.75 (range 40 to 80 years), as shown in Fig 1. Mean prostate volume was 40.3 ±1.05 ml (range 29 to 52), and mean operation time was 38.33 ±2.64 min (range 15 to 75). Twenty-eight patients prior to LP had PSA levels between 0 and 4 ng/mL while the f/t PSA ratio was below 25% in 2 patients. These patients were diagnosed as BPH histopathologically. The estimated prostatic weight measured by TRUS was 40 ± 1.05 g (range 29 to 52), and the mean amount of applied

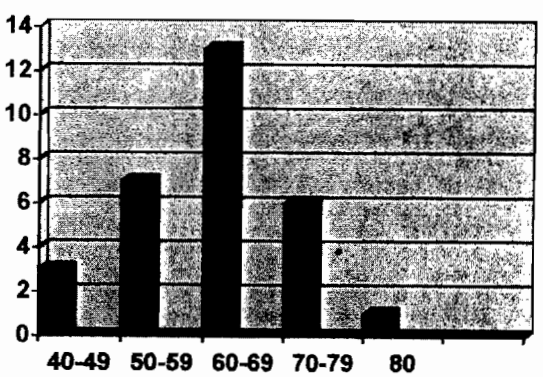

Fig. 1: Age distributions of the patients (n=30).

Table - 1: Mean (±SEM) serum PSA levels and free/total PSA ratios of patients with BPH before and after laser prostatectomy (N=30).

PSA(ng/ml)	Before LP	24h after LP	7days after LP	30days after LP
Total	2,37±0,35 0,29-8,30	7,42±1,79 0,33-43,94	3,24±0,54 0,67-11,32	2,07±0,30 0,15-6,20
Free	0,65±0,09 0,07-2,20	1,50±0,41 0,12-10,50	0,69±0,08 0,07-1,97	0,45±0,07 0,06-1,70
Free/Total (f/t)	0,31±0,03 0,07-0,72	0,22±0,02 0,02-0,75	0,32±0,04 0,04-0,82	0,28±0,03 0,02-0,77

The differences between preoperative and postoperative (1,7 and 30 days) PSA values were found statistically significant (all p<0,001), but preoperative and postoperative (1,7 and 30 days) free/total PSA values were not (p1=0,08,p7=0,90 and p30=0,40).

energy was 48300±2488.2 (range 20,000 to 68,000).

The results of the mean PSA levels (free and total), the f/t PSA values (preoperative and 1,7,30 days after transurethral LP) and statistical analysis are shown in table I.

Although the postoperative (1,7 days) total and free PSA increase was statistically significant compared with preoperative values ($p<0.0001$ and <0.001, respectively), after 30 days the mean PSA level of patients was under the initial levels and was statistically significant ($p<0.001$). On the other hand, the difference between the preoperative and postoperative (1,7 and 30 days) f/t PSA ratio was not found statistically significant (p1=0.08, P7=0.9 and P30=0.4).

There was a statistically significant positive correlation between the PSA level one day after LP and the amount of energy applied to the prostate during operation ($r=0.76$, $p<0.0001$), and the PSA level one day after the procedure and the estimated prostatic weight by TRUS ($r= 0.57$, $p< 0.0001$)

As shown in table 1, LP produced a variable rise in PSA, with a peak rise in PSA occurring 24h after the operation. Then the PSA level gradually decreased and after 30 days the mean PSA values (free and total PSA) were below the initial levels. The mean PSA values after 30 days were lower than the preoperative concentrations, these differences being statistically significant ($p<0.001$).

DISCUSSION

Study of the effects of LP on serum PSA (total and free) and f/t PSA ratio is necessary because this procedure has become a widely used treatment modality in the management of BPH (9,10). This treatment modality disturbs the prostatic architecture, causing protein denaturation, coagulative necrosis and vaporization (11-12). PSA is secreted by columnar prostatic epithelial cell into the lumina of the prostate ducts. The concentration of PSA in prostatic secretions is about 1 million -fold those in the serum (13). Elevated serum PSA concentrations are generally secondary to perturbation in the normal prostatic architecture. Normal prostatic epithelial cells are separated from the capillary and lymphatic system by an intact basal cell layer and basement membrane (14). When the basal membrane of the prostatic epithelium is disturbed by invasive treatments such as TURP, the serum PSA concentration increases rapidly (6,15) as PSA in the lumen leaks into the serum. Likewise, LP, which is also an invasive treatment modality, can probably raise the serum PSA level. Our results confirmed this increase in the serum PSA level after LP.

The serum PSA levels and f/t ratios are widely used in clinical practice to enhance the sensitivity of PSA in the diagnosis of localized prostate carcinoma. The determination of an appropriate reference range for percentage of free PSA is under investigation, and suggested cutoff values range from 15% to 25% according to different investigation (16-18). It is known that various conditions such as age, prostate volume, prostatic infection or invasive manipulation of the prostate can cause elevation of serum PSA, but the effect of these conditions, especially after

LP, on f/t ratio is not very clear and needs investigation. Oesterling et al. (19) concluded that the appropriate upper limit of the normal f/t PSA ratio is constant for men of all ages. In addition, Haese et al.(20) found no correlation between f/t PSA ratio and prostate volume. TURP causes significant PSA elevation in men with BPH, however, the f /t ratio does not change significantly. In our study, one day after LP in men with BPH, total PSA increased from 2,37 to 7,42 and free PSA was elevated from 0.65 to1.5 (Table 1), these elevations are statistically significant ($p<0.001$).

However, the f/t PSA ratio decreased, but the differences were not statistically significant ($p1=0.08$, $p7=0.9$ and $p30=0.4$; table 1). These findings reveal that the determination of the f/t PSA ratio may be a more reliable parameter than serum total and free PSA values after such interventions as LP.

The PSA levels of all patients rapidly increased to a maximum level one day after the LP and then slowly decreased, finally after 30 days the PSA levels were found to be normal (Table 1). A possible explanation for this situation can be that after LP much prostatic intracellular material, including PSA, enters the circulatory system as PSA is slowly eliminated from the serum. Marked elevations of PSA levels one day after LP can be explained by the fact that LP causes extensive damage to the prostate. There was a statistically significant positive correlation between the PSA level one day after operation and the amount of energy applied to the prostate during operation. This finding also shows the close relationship between the PSA level one day after LP and amount of damage to the prostate. A statistically significant positive correlation was found between the PSA level one day after operation and the estimated prostatic weight before operation. The close relationship between the PSA level 24h after LP and the prostatic weight can be explained by the fact that the larger the prostate, the more energy was applied to the prostate during operation. Van Iersel et al.(21) measured PSA levels after LP and found that at 24 h, the PSA value increased and reached a mean level 23 times higher than the PSA level before LP, and the rise in PSA one day after LP correlated positively with the prostatic size and energy applied.These results correlate with our results. The increased PSA levels of patients 24h after treatment gradually decreased during the follow-up one-month period. At the end of one month, PSA levels were below the initial levels. Van Iersel et.al. (21) and Kabalin (22) reported similar results. A possible explanation of this slow decrease in PSA after LP could be the altered architecture of the prostate with necrotic tissue remaining in situ for a long time after treatment. After 30 days the mean PSA levels of patients were below the initial levels ($p<0.001$). Similar results were observed in patients who underwent TURP in previous studies (6,15). In these studies, investigations showed correlations between the serum PSA concentration and the prostate volume determined postoperatively. On average, 1g of BPH tissue increases the serum PSA concentration by 0.2-0.3 ng/ml (23,24). This shows that PSA levels are closely related with the prostate volume in patients with BPH. A possible explanation for this low level of PSA 30 days after LP is that the procedure decreases the prostate volume.

In conclusion, we found that LP produced a variable rise in PSA, with a peak rise in PSA occurring 24h after the procedure. The rise in PSA was related to the amount of energy applied to the prostate. We recommend that blood should not be sampled for PSA for at least 30 days after LP. In our study serum-free PSA and total PSA levels increased significantly without any meaningful change in the f/t PSA ratio on the first day after LP. These findings reveal that the determination of the f/t ratio may be a more reliable parameter than serum total and free PSA values after interventions such as LP.

Correspondence to: Hakkı PERK, M.D.
Kurtuluş Mah. 1420 Sokak No: 22/3
32040 ISPARTA-TURKİYE
Phone: 246 237 17 47
Fax: 246 237 17 58
E-mail: haperk@med.sdu.edu.tr

REFERENCES

1. Oesterling JE. Prostate specific antigen: A critical assessment of the most useful tumor marker for adenocarcinoma of the prostate J Urol 1991; 145: 907-923.
2. Cooner WH, Mosley BR, Rutherford CL, Beard JH, Pond HS, Terry WJ, Igel TC, Kidd DD. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J Urol 1990; 143: 1146-1152.
3. Brawer MK, Chetner MP, Beatic J, Buchner DM, Vessela RL, Lange PH. Screening for prostatic carcinoma with prostate specific antigen. J Urol 1992; 147: 841-845.
4. Catolona WJ, Smith DS, Ratliff TL ,Dodds KM ,Yuan JJ, Petros JA, Andriole GL. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. J Urol 1991; 144: 1415-1419.
5. Hasui Y, Marutsuka K, Asada Y, Ide H, Nishi S, Osada Y. Relationship between serum prostate- specific antigen and histological prostatitis in patients with benign prostatic hyperplasia. Prostate 1994; 25: 91-96.
6. Oesterling JE, Rice DC, Glenski WJ, Bergstralh EJ. Effect of cystoscopy, prostate biopsy, and transurethral resection of prostate on serum prostate- specific antigen concentration. Urology 1993; 42: 276-282.
7. Sershon PD, Barry MJ and Oesterling JE. Serum PSA values in men with histologically confirmed BPH versus patients with organ - confined prostate cancer J .Urol 1993; 149: 421-425.
8. Koşar A, Sarıca K, Özdiler E, Budak M, Dinçel Ç, Göğüş O. Effect of laser prostatectomy on the serum prostate-specific antigen concentration:results of a prospective study. Eur Urol 1998; 34: 193-197.
9. Gerber GS. Lasers in the treatment of benign prostatic hyperplasia Urology 1995; 45: 193-199.
10. Costello AJ, Lusaya DG,Crowe HR. Noncontact sidefire laser ablation of the prostate. J Endourol 1995; 9: 107-111.
11. Milam DF, Smith JA. Laser prostatectomy devices and their tissue effects. J Endourol 1995; 9: 85-88.
12. Costello AJ, Bolton DM, Ellis D, Crowe H. Histopathological changes in human prostatic adenoma following neodymium: YAG laser ablation therapy .J Urol 1994; 152: 1526-1529.
13. Ellis WJ, Brawer MK. PSA in benign prostatic hyperplasia and prostatic intraepithelial neoplasia. Urol Clin North Am 1993; 20: 621-625.
14. Brawer MMK, Peehl DM, Stamey TA, Bostwick DG. Keratin immunoreactivity in the benign and neoplastic human prostate. Cancer Res 1985; 45: 3663-3667.
15. Vesey SG, Goble NM, Stower MJ, Hammonds JC, Smith PJB. The effects of transurethral prostatectomy on serum prostate- specific antigen. Br J Urol 1988; 62: 347-351.
16. Luderer AA, Chen YT, Soriano TF, Kramp WJ, Carlson G, Cuny C, Sharp T, Smith W, Petteway J, Brawer MK. Measurement of the proportion of free to total prostate-specific antigen improves diagnostic performance of prostate- specific antigen in the diagnostic gray zone of the total prostate- specific antigen. Urology 1995; 46: 187-194.
17. Kochanska-Dziurowicz AA, Mielniczuk MR, Stojko A, Kaletka J. The clinical utility of measuring free-to-total prostate-specific antigen (PSA) ratio and PSA density in differentiating between benign prostatic hyperplasia and prostate cancer. Br J Urol 1998; 81: 834-838.
18. Catalona WJ, Smith DS, Wolfert RL, Wang TJ, Rittenhouse HG, Ratliff TL, Nadler RB. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening .JAMA 1995; 274: 1214-1220.
19. Oesterling JE, Jacobsen SJ, Klee GG, Pettersson K, Piironen T, Abrahamsson PA, Stenman UH, Dowell B, Lovgren T, Lilja H. Free complexed, and total serum PSA: the establishment of appropriate reference ranges for concentrations and ratios . J Urol 1995; 154: 1090-1095.
20. Haese A, Graefen M, Noldus J, Hammerer P, Huland E, Huland H. Prostatic volume and ratio of free-to-total prostate specific antigen in patients with prostatic cancer or benign prostatic hyperplasia. J Urol 1997; 158: 2188-2192.
21. Van Iersel MP, Thomas CMG ,Witjes WPJ ,de Graaf R, de la Rosette JJMCH, Debruyne FMJ. Clinical implications of the rise and fall of prostate specific antigen after laser prostatectomy. Br J Urol 1996; 78: 742-746.
22. Kabalin NJ. Laser prostatectomy performed with a right angle firing neodymium :YAG Laser fiber at 40 watts power setting. J Urol 1993; 150: 95-99.
23. Lee F, Littrup PJ, Loft -Christensen L, Kelly BS Jr, McHugh TA, Siders DB, Mitchell AE, Newby JE. Predicted prostate - specific antigen results using transrectal ultrasound gland volume. Cancer 1992; 70: 211-220.
24. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987; 317: 909-916.