IMPORTANCE OF PROSTATIC SPECIFIC ANTIGEN (PSA) IN CLINICAL PRACTICE : OUR EXPERIENCE

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ABSTRACT

A total of 89 patients in the age group of 50-92 years having different histopathologically proven prostatic conditions were analysed with prostate specific antigen (PSA) and clinical co-relation undertaken. PSA levels were found to be significantly higher ($p < 0.05$) in 48 carcinoma prostate cases (mean 93.16 ± 50.75 ng/ml) as compared to 32 benign prostatic hyperplasia (mean 4.66 ± 3.85 ng/ml). Similarly, levels were considerably reduced in 15 post-operative adenocarcinoma cases (mean 10.77 ± 9.65 ng/ml) as compared to their pre-operative samples (mean 93.16 ± 60.75 ng/ml). PSA levels were moderately higher in 9 cases of prostatitis (mean 13.28 ± 4.53 ng/ml). A very high degree of sensitivity, specificity and positive predictive value of PSA e.g. 95.8%, 75.6% and 82.2% respectively was found in adenocarcinoma cases, when levels of PSA were > 10 ng/ml. Thus it necessitates a detailed and thorough examination in such cases to come to final conclusion and early management of the cases.

MJAFI 1998; 54 : 215-218

KEYWORDS : Prostatic Specific Antigen (PSA).

INTRODUCTION

Carcinoma of the prostate is the most common form of malignancy in men over fifty years of age followed closely by lung cancer and is the second leading cause of cancer deaths. It is currently estimated that approximately 2,00,000 new cases of carcinoma prostate are detected every year of which one fifth prove to be lethal [1]. In addition to these neoplasm, there is an even more frequent anatomic form of prostatic carcinoma in which cancer is discovered as an incidental finding, either at autopsy or in a surgical specimen removed for other reasons e.g. nodular hyperplasia. With increase in life expectancy in recent years, the incidence of prostatic carcinoma is likely to rise further.

Early diagnosis of the disease is very essential so that number of potentially curable patients is increased. Thus clinical evaluation including digital rectal examination (DRE), ultrasound examination and finally histopathological check up are the common modalities to come to a reasonable conclusion about the prostatic pathology. However, there are chances that a final diagnosis may not be achieved due to initial stage of the disease or due to concealment of malignancy by superadded inflammation. Prostatic specific antigen (PSA) has achieved a wide spread clinical use as a

tumour marker in the field of prostatic pathology. It is an organ specific marker and is being used as a serological and immuno-histochemical marker. Most of the studies on assaying of PSA have been conducted abroad where the immunological state of the patient, his genetic character, dietary and exercise habits are different [2-3] and very little data is available in India, more so in the Armed Forces. Keeping these points in mind a prospective study was carried out in 1995-96 at Army Hospital (Research and Referral), Delhi Cantt to evaluate the clinical application of PSA in different prostatic pathological situations.

MATERIAL AND METHODS

The study included a total of 89 patients in the age group of 50-92 yrs (mean 70.09 ± 7.42). Most of these patients were initially diagnosed clinically as carcinoma prostate cases. However, few clinical cases of benign prostatic hypertrophy and prostatitis were also studied. Out of the total 89 cases, 48 cases were ultimately diagnosed histopathologically as carcinoma prostate. Their age ranged from 50-92 years (mean 70.47 ± 8.87). Other 32 patients were proven as benign prostatic hyperplasia (BPH) with age ranging from 52 to 90 years (mean 70.65 ± 7.42) (Fig 1). Nine other cases were diagnosed as prostatitis with or without BPH findings with age range of 55-75 yrs (63.77 ± 7.06) (Fig 1).

Out of a total of 48 cases of carcinoma prostate 15 cases underwent bilateral orchidectomy and were followed up clinically and then PSA level were also monitored post-operatively. First post operative sample in such cases was taken at least 4-6 weeks after the operation and then at 2-3 monthly intervals.

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Fig. 1 : Age distribution of 89 cases of Prostatic lesions.

For PSA estimation serum samples of all the patients were taken prior to any manipulative procedure of the prostate or the samples were collected at least one week after the initial manipulative procedure. Five ml of blood was collected aseptically and serum was separated, aliquoted and frozen at -20°C for further PSA estimation. Briefly, 100ul of serum samples were reacted with an ELISA plate already coated with polyclonal antibody against PSA. The wells were washed 5 times with washing buffer after an incubation for 45 minutes and further incubated with Monoclonal antibody-Horse raddish peroxidase conjugate. This resulted in the PSA molecule being sandwiched between the solid phase antibody and enzyme conjugate antibody. A substrate solution was added in the wells after 45 min of further incubation and washing. Finally PSA estimation was done with the help of known standard concentrations and by using a computerized laboratory data system on ANTHOS HT-II ELISA reader.

In few patients of carcinoma prostate, serum samples were collected 4-6 weeks after the bilateral orchidectomy and/or prostatectomy and at 2-3 months interval thereafter.

Mean and standard deviation of all patients age and PSA levels in different groups, were calculated by standard statistical methods. Sensitivity, specificity and predictive value of serum PSA from various diagnostic group was calculated as per Kochhar et al [4]. To find the significance of difference between each of the groups, non parametric multiple range test [5] was applied and a p value of < 0.05 was considered significant.

The diagnosis was confirmed histopathologically either on Tru-cut needle biopsy specimen or on TUR prostate specimen.

Tru-cut needle biopsy was carried out by Bard Biopsy^T instrument (Biopsy gun) and 18G (1.2mm) biopsy needle. These biopsy samples were collected in 10% buffered formalin solution for histopathological examination. All these biopsy samples were given a coded number. They were processed in the routine manner, and reported upon independently and separately without the knowledge of the particulars of the patient to the reporting pathologist. The pathologist was also not provided with the PSA levels before the reporting was carried out by him. In few patients TUR prostate samples were received which were also treated in a similar manner as tru-cut biopsy and were reported upon. Carcinoma of prostate patients were further classified as moderately or poorly differentiated adenocarcinoma based on WHO criteria for typing of tumour [6].

RESULTS

In case of carcinoma patients ($n=48$), PSA was found to be significantly higher ($p < 0.005$) and in the range of 8.4 ng/ml to

Fig. 2 : Distribution of serum PSA values in various prostatic conditions (ng/ml).

260 ng/ml with a mean of 74.75 ± 59.39 ng/ml) than in 32 cases of benign prostatic hyperplasia, where serum PSA levels were in the range of 0.2 to 14.5 ng/ml (mean 4.66 ± 3.85). While in nine cases of prostatitis serum PSA were in the range of 6.91 to 20.75 ng/ml with a mean of 13.28 ± 4.53 (Fig.2) (Table 1).

TABLE I

Serum PSA levels in carcinoma prostate, BPH and prostatitis cases

Serum PSA level (ng/ml)	Carcinoma (No. of pts)	BPH (No. of pts)	Prostatitis (No. of pts)
< 4	Nil	19	Nil
4.1 - 10	2	10	2
10.1 - 20	6	3	6
20.1 - 50	15	—	1
> 50	25	—	—
Total	48	32	9

PSA estimation was also done in 15 patients of adenocarcinoma after the operation and thereafter regularly at 2-3 monthly interval. Serum PSA values of first post-operative assay were found to be significantly lower ($P < 0.005$) than the pre-operative values (Fig 3) and ranged from 1.23 ng/ml to 27.42 ng/ml, with a mean of 10.77 ± 9.64 . The pre-operative values for the same patients were in the range of 38.2 to 250.4 ng/ml with a mean 93.16 ± 60.75 ng/ml. These patient's age ranged from 60 to 82 yrs (mean 71.64 ± 5.86 years)

Fig. 3 : Pre and post operative serum PSA levels in 15 patients.

Sensitivity, specificity and positive predictive values for serum PSA level at cut off levels of 4 ng/ml and 10 ng/ml were calculated (4). With a cut off limit of 4 ng/ml of PSA values, sensitivity was found to be 100% but specificity and positive predictive value were low at 46.3% and 68.5%. These figures were found to be 95.8%, 75.6% and 82.1% respectively with a cut off limit of 10 ng/ml PSA values (Table 2).

TABLE 2

Sensitivity, specificity and positive predictive value of PSA

	Cut off level 4 ng/ml		Cut off level 10 ng/ml	
	<4.0 ng/ml	>4.0 ng/ml	<10 ng/ml	>10 ng/ml
Carcinoma prostate	Nil (FN)	48 (TP)	2 (FN)	46 (TP)
BPH	19 + Nil = 19	13 + 9 = 22	29 + 2 = 31	3 + 7 = 10
Prostatitis	(TN)	(FP)	(TP)	(FP)
Sensitivity	100%		95.8%	
Specificity	46.3%		75.6%	
Positive predictive value	68.3%		82.1%	

FN - False negative, TP - True positive,
TN - True negative, FP - False positive

DISCUSSION

PSA was first identified in seminal plasma by Hara et al [7] in Japan in 1971 and was termed as gamma seminoprotein and in 1973 [8], the protein was isolated and purified. In 1979 Wang et al [9] isolated a tissue specific antigen from prostate and termed it as prostate specific antigen (PSA), which was later found to be immunologically identical to that originally found in seminal plasma. In 1980, a serological test to measure PSA in human serum was developed [10].

It is a single chain glycoprotein of 240 aminoacid residue and a 4 carbohydrate side chain. It is homologous with protease of the kallikrein family, and has 34 KD molecular wt. It is organ specific produced only by prostate epithelial cells and results in liquification of the seminal coagulum. Half life of PSA is found to be 2.2 ± 0.8 days and because of this long half life, a

minimum of 3-4 weeks is required for the serum PSA concentration to reach its nadir after prostate biopsy or surgery on prostate [11]. There is no diurnal variation of serum PSA and this marker remains stable in frozen serum for a long period [12].

PSA concentration can be affected by any type of prostatic manipulation which includes per rectal examination, prostate biopsy, prostatectomy and prostatitis. Prostate biopsy results in significant elevation of PSA and levels do not reach a baseline till the end of 4 weeks. So PSA estimation should not be done within one month of prostatic biopsy. Other factors which may increase serum PSA levels includes strenuous exercise, acute retention of urine and prostatic ischemia [12].

In our preliminary study, serum PSA levels in 48 cases of carcinoma prostate ranged from 8.4 to 260 ng/ml with mean 74.75 ± 59.39 ng/ml. In case of BPH, PSA levels ranged from 0.2 to 14.5 ng/ml (mean 4.66 ± 3.85), while in case of prostatitis, PSA ranged from 6.91 to 20.75 (mean 13.28 ± 4.53 ng/ml).

The sensitivity, specificity and positive predictive value of PSA with cut off level of 4 ng/ml and 10 ng/ml were found to be 100%, 46.3% 68.3% and 95.8%, 75.6% and 82.1% respectively (Table 2).

Thus it was found in our study, that serum PSA levels of 10 ng/ml and above were good indicator to detect carcinoma of prostate with a high level of positive predictive value. However, with low cut off point, sensitivity was increased but predictive value and specificity suffered, thereby getting a large number of false positive cases.

PSA in BPH is generally < 4.0 ng/ml and in our study 19 out of 32 (59.1%) cases had levels less than 4 ng/ml. A total of 10 patients (31.2%) had a serum PSA levels between 4 and 10 ng/ml, and 3 patients (9.4%) had a serum PSA of greater than 10 ng/ml. Ereole et al 1980 [13], had 18% and 3% of BPH cases with serum PSA levels of 4-10 ng/ml and > 10ng/ml respectively. In another study [14] it was 43% and 10% of BPH cases in the same range, where as Armitage et al [15] had 35% and 12% cases in the same range of PSA. In our series the figures comparatively match with those found in other international studies.

In the study conducted by Stamey et al 1987 [16], the mean PSA levels in cases of carcinoma patients has been detected to be 5-16 times higher than the normal BPH levels. In our study, the PSA levels, were also found to be very high in few cases and touching upto 260 ng/ml. However in most of the cases, the levels were in the range of 10-70 ng/ml (Fig.2).

Thus it was found that PSA is a very reliable indicator in diagnosing carcinoma prostate with cut off levels of 10 ng/ml or above. Above this the chances of a lesion being benign become lesser and lesser.

Finally, it is concluded that PSA estimation should be conducted in all clinical cases of prostate enlargement before any prostatic manipulation is carried out. The levels may be clinically co-related and future therapeutic approach accordingly adopted. PSA levels are also of much help in the post-operative follow-up of prostate cases more so in malignant conditions.

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