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ROLE OF ANTIBIOTICS IN RAISED SERUM PROSTATE SPECIFIC ANTIGEN (PSA)

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ABSTRACT

Background: The prostate-specific antigen (PSA) level is considered an essential diagnostic tool for detecting prostate cancer. The abnormal digital rectal examination (DRE) has been obviously reduced and biochemical result (elevated PSA) have augmented the indication of prostate biopsy over the past.
Objective: The objective of this study is the comparison of PSA level in patients before and after four weeks antibiotics therapy.
Material and Methods: Patients were evaluated with history, physical examination and urine C/S after prostatic massage and serum PSA through ELISA method. If PSA level was raised ≥ 4ng/dl then antibiotic therapy was given on the basis of urine culture sensitivity. Patients with negative urine cuture tablet Ciprofloxacin 500mg BD was started for a period of four weeks. Serum PSA level repeated after completion of therapy, trans-rectal ultrasound (TRUS) guided biopsy was performed if serum PSA remained above 4ng/dl (ELISA method).
Results: In present study, mean patient age was 64.0±10.1 year. (ranged, 45-85 year). Distribution of patients by urine C/S was as follows: No growth in 26 (65.0%) of patients, sensitivity to augmentin (Amoxicillin+Clavulinic acid) in 5 (12.5%),

ciprofloxacin and levofloxacin 2 (5.0%) each, mixed growth 3 (7.5%), enoxabid and nitrofuratoin 1 (2.5%) respectively. Table-3 reveals the types of antibiotics given, majority of the patients i.e 31 (77.5%) received ciprofloxacin, followed by levofloxacin given in 2 patients (5.0%), augmentin (Amoxicillin+Clavulinic acid) in 6 patients (15.0%) and nitrofuration in 1 patient (2.5%) (Table-3). Out of 40 patients, PSA level became normal in 21 patients (52.4%). Outcome of biopsy was as follows: focal chronic prostatitis 14 (70.0%), chronic prostatitis 4 (20.0%) and moderately differentiated adenocarcinoma 2 (10.0%). Before treatment mean serum PSA was 10.45±5.38 ng/ml and after treatment mean serum PSA decreased to 5.47±4.49 ng/ml.

Conclusion: Antibiotics treatment for 4 weeks in patients with PSA level ≥ 4 ng/dl, may decrease serum PSA significantly. This may help us in avoiding un-necessary prostatic biopsies and its complications.

Introduction: Acute and chronic prostatitis, is a common disease in men of all age groups and demographics [1,2] even then some controversy exists regarding the role that bacteria may have in causing symptoms which bacteria are responsible for the pathologic condition. A definitive diagnosis of lower urinary tracts infection is by culture of specific organism. Patients with lower urinary tract infection are commonly treated with antibiotics as first line therapy. Due to wide range of pathogens that may cause UTI and recently observed trend of increased gram-positive pathogens, an antibiotics with culture specific would be ideal [3,4]. Prostate specific antigen (PSA) is a serine protease produced by prostate tissue. It is prostate specific but not cancer specific. Normal PSA values are less than 4ng/ml. As PSA exhibit sub-optimal specificity different strategies have been proposed to decrease the number of negative biopsies. Some authors advocate a repeat PSA test as an appropriate initial approach in asymptomatic patients with a raised PSA and a normal DRE [5] (Digital Rectal Examination). Although more controversial, it has also been suggested that antibiotic treatment could be an appropriate initial regimen in these patients [6]. An empirical course of antibiotics has been proposed as a cost-saving strategy to differentiate patients with benign and malignant conditions as it could avoid unnecessary biopsies [7,8].

Numerous studies have been linked with lower urinary tract infection with an increase in serum prostate specific antigen (PSA) [9-11]. PSA has become an important tool in prostate cancer screening and men with serum PSA greater than 4 ng/ml are at higher risk for prostate cancer. These patients are usually referred for a biopsy procedure. However, increased PSA is also associated with conditions other than cancer, such as prostatatic inflammation, benign prostatic hypertrophy and prostatitis. Treatment with antibiotics (culture specific) has been shown to decrease PSA significantly of such patients. The treatment of UTI or prostatitis with an antibiotic may provide cost-effective approach to decrease the number of negative biopsies [12-13].

The initial UTI treatment may also provide a more acceptable alternative in patients who are apprehensive about undergoing transrectal ultrasound guided biopsy.

REVIEW OF LITERATURE:

Researchers credit Ablin, Soanes, Bronson, and Witebsky (1970a; 1970b) [14] as the earliest known researchers investigating antigens specific to human prostate tissue [15]. Ablin et al [14] demonstrated the presence of three prostatic antigens; they isolated two from prostate tissue extract and one from prostatic fluid. Researchers, however, cannot confirm that the identified antigens were what we currently know as prostate-specific antigen (PSA) [16]. Other researchers examined antigens from human seminal plasma. Hara, et al [17] described what they labeled as y-seminoprotein while Li and Beling [18] described what they labeled as E1 antigen; these investigators independently isolated the same protein [16]. Sensabaugh and Crim [19] described what they labeled as p30 and demonstrated that p30 and the E1 antigen were identical. While Li and Beling [18] concluded the E1 antigen was "probably not prostatic in origin", Sensabaugh and Crim [19] demonstrated that sthe prostate was the tissue of origin. Wang et al [20] purified an antigen from normal, benign hypertrophic, and malignant prostatic tissue while demonstrating the absence in other human tissues; they accordingly labeled this as a prostate-specific antigen. Researchers later demonstrated the proteins identified by these researchers (i.e., y-seminoprotein, E1, and p30) were identical, prostate-specific antigen [16]. Papsidero et al. [21] subsequently examined and identified that prostate-specific antigen was detectable in the sera of prostate cancer patients. This apparent correlation with prostate cancer promptly led to the suggestion of PSA's potential candidacy as a tumor marker [22]. Subsequently, the U.S. Food and Drug Administration (FDA) approved the use of PSA to monitor prostate cancer in 1986 and later approved the use of PSA for the early detection of prostate cancer in 1994 [23]. The American Cancer Society formally endorsed utilization of the PSA test to screen for prostate cancer in 1992 [24]. Medicare began covering annual PSA screening in 2000 [25].

Historical perspective of prostatitis

The prostate gland was described in the anatomical studies of Herophilus about 350 BC and was rediscovered in the 16th century by the Venetian physician Nicola Massa. At the same time the physician Riolanus noted that bladder obstruction can be caused by swelling of the prostate gland. Prostatitis as a clinical entity/syndrome was first described in 1815 by Legneau, who noted that inflammation of the prostate gland could be a complication of urethritis [26]. The time between the 1880 and 1928 was a period of searching for bacteria and confirming the postulates of Koch and Wirchow related to the mechanisms of bacterial infections acting in the human body [26].

Between 1900 and 1930, the basic chemistry of prostatic fluid was studied and the role of possible pathogen bacteria cultured from the prostate gland and from prostate secretion was defined and von Lackum´s theory of possible retrograde secondary infection ascending from the urethra to the prostatic ducts was clinically demonstrated by several physicians [27].

The period between 1930 and 1960 was marked by an active search for etiological factors related to prostatitis syndrome, factors that could be responsible for its chronicity and the histological changes that take place, fibrosis and scarring together with late functional disorders of the prostate gland. Despite of all these new findings, there were many internists

and psychoanalysists who denied the existence of chronic prostatitis processes, and the latter group termed such symptoms ”anal/rectal psychoses” [28].

In the late 1950s it was recognized and noted, especially by Campbell (1957), that chronic prostatitis may be present in the prostate gland without any clinical symptoms, and it was also realized that a disease such as prostatitis can be congestive and nonbacterial [29]. The active clinical research period of the 1970s and 1980s, was motivated by the findings of Meares and Stamey (1968), [30] From the 1990s onwards a young generation of disappointed urologists who did not accept all the written data from past concerning prostatitis as a forgotten”light urological ambulatory pathology” and”not needing special urological care” started a new era in prostatitis research [32].

Objective

The objective of this study is: The comparison of PSA level in patients before and after four weeks antibiotics therapy.

MATERIALS AND METHODS

STUDY DESIGN: Cross-sectional analytical study.

SETTING: Department of Urology Sandaman Provincial Hospital SPH Quetta.

DURATION OF STUDY: Study was carried out over a period of six months from April 2024 to October 2024.

SAMPLE SIZE: The sample size of 40 patients was estimated by using 5% level of significance and 80% power of test with expected PSA level of 8.33±4.46 and 5.36±3.82 ng/ml for before and after antibiotics therapy respectively.

SAMPLING TECHNIQUE: Consecutive Sampling.

Inclusion Criteria

- Patients with high serum PSA level (>4ng/ml) with UTI or without UTI.

Exclusion Criteria:

Patients with positive TRUS-guided biopsy.

Patients with retention of urine

DATA COLLECTION: Forty cases suspected of having raised PSA > 4 ng/ml were included in study. Patient with or without lower urinary tract symptoms (LUTS) like urgency, frequency, nocturia and sense of incomplete emptying of bladder etc. Patients were collected from Indoor and OPD clinic of Urology Department, Sandaman Provincial Hospital SPH Quetta. After taking informed consent, patients were evaluated with history, physical examination and urine C/S after prostatic massage and serum PSA by ELISA method. If PSA level was raised ≥4 ng/ml then antibiotic therapy was given on the basis of urine culture sensitivity. Those with –ve urine C/S were given Tab. Ciprofloxacin 500 mg BD PO (Ciprofloxacin 12-17 mg/kg) for four weeks. Then serum PSA level repeated after completion of therapy and for diagnosis confirmation trans-rectal ultrasound (TRUS) guided biopsy was done in those patients with serum PSA remained elevated ≥ 4ng/ml even after the antibiotic therapy. Data was collected through Proforma (attached).

DATA ANALYSIS PROCEDURE: The data was entered and analyzed by using SPSS version 15.0. Age and PSA level was reported by using mean ± S.D. Urine C/S results was reported by using frequencies. Comparison of PSA levels before and after therapy was performed by using paired t-test. Change in PSA levels was described by using percentage and number of patients attained normal PSA level after therapies were reported by percentage. P-value ≤0.05 was considered significant.

RESULTS

A total of 40 patients were included in this study over a period of six months from April 2012 to October 2012 in the Department of Urology Shaikh Zayed Hospital, Lahore. In present study, mean patient age was 64.0±10.1 year. (ranged, 45-85 year) (Table-1). Out of forty patients, no organism was detected in 26 patients (65%). In 14 patients (35%) organism was detected on C/S of urine. Sensitivity to augmentin (Amoxicillin + Clavulinic acid) was found in 5 patients (12.5%), while sensitivity to ciprofloxacin and levofloxacin was detected 2 patients (5%) each, mixed growth, enoxabin and nitrofuratoin was detected in 3 (7.5%), 1 (2.5%) and 1 (2.5%), respectively (Table-2).

Table-3 reveals the types of antibiotics given, majority of the patients i.e 31 (77.5%) received ciprofloxacin, followed by levofloxacin given in 2 patients (5.0%), augmentin (Amoxicillin + Clavulinic acid) in 6 patients (15.0%) and nitrofuratoin in 1 patient (2.5%) (Table-3). Out of 40 patients, PSA level became normal in 21 patients (52.4%). Outcome of biopsy as follows: focal chronic prostatitis 14 (70.0%), chronic prostatitis 4 (20.0%) and moderately differentiated adenocarcinoma 2 (10.0%). Before treatment mean serum PSA was 10.45±5.38 ng/ml and after treatment mean serum PSA decreased to 5.47±4.49 ng/ml (Table 4-6).

Table-1: Distribution of patients by age

Age (Year)	Number	Percentage
45-55	08	20.0
56-65	14	35.0
66-75	14	35.0
76-85	04	10.0
Total	**40**	**100.0**
Mean±SD	**64.0±10.1**	

Table-2: Distribution of patients by urine C/S

Urine C/S	Number	Percentage
No growth	26	65.0
Amoxicillin + Clavulinic acid)	5	12.5
Ciprofloxacin	2	05.0
Levofloxacin	2	05.0
Mixed growth	3	7.5
Enoxabid	1	2.5
Nitrofuratoin	1	2.5
Total	**40**	**100.0**

Table-3: Types of antibiotics given

Types of antibiotics	Number	Percentage
Ciprofloxacin	31	77.5
Levofloxacin	02	05.0
Amoxicillin + Clavulinic acid)	06	15.0

Nitrofuratoin	01	02.5
Total	**40**	**100.0**

Table-4: Change in PSA level

Change in PSA	Number	Percentage
Abnormal (≥ 4ng/ml)	21	52.4
Normal (< 4ng/ml)	19	47.6
Total	**40**	**100.0**

Table-5: Outcome of biopsy
n=20

Outcome of biopsy	Number	Percentage
Focal chronic prostatitis	14	70.0
Chronic prostatitis	04	20.0
Moderately differentiated Adenocarcinoma	02	10.0
Total	**20**	**100.0**

Table-6: Comparison of serum PSA (before treatment and after treatment)

Serum PSA	Mean	Standard deviation	P value
Before treatment	10.45	5.38	< 0.001
After treatment	05.47	4.49	

DISCUSSION

Prostatitis is defined as "inflammation of prostate gland". In clinical practice, the prostatitis is combination of multiple disorders that cause symptoms related to prostate gland. Stamey describes prostate as "a wastebasket of clinical ignorance" because a lot of poorly characterized syndromes are taken as prostatitis. The prostatitis ranges from simple acute bacterial prostatitis to so much complicated condition that may not involve the prostate gland inflammation. These situations may confer the patients as well as clinician [27]. Hara et al, identified the PSA as gamma-semino protein from the seminal plasma [17], Wang et al. reported that the PSA might be tumour marker for the prostate cancer [20], while Papsidero et al. reported PSA as an important diagnostic tool for the early diagnosis follow-up for prostate cancer patient [21]. Some authors have taken PSA as non-specific diagnostic parameter for the prostate cancer because PSA may be raised in so many other conditions and different prostatic manipulation, PSA is a serine protease which is secreted by the prostatic epithelial cell [22], from primary gastric cell, mammary glands and also from breast cancer tissue [28]. PSA level may be raised in the prostate cancer, also in BPH, prostatitis, in certain other situation such as after prostatic biopsies, DRE, in acute urinary retention even after the cystoscopy [29]. PSA velocity has been promoted as a marker to aid in the detection of prostate cancer [17]. Previous studies have shown that PSA velocity is strongly associated with risk of cancer on biopsy [10-09]. Perhaps as a result, NCCN

guidelines now state that men with a PSA velocity greater than 0.35ng/ml/year should consider a prostate biopsy, even with a PSA levels below the current biopsy thresholds [23]. Despite a plausible biological association between PSA velocity and risk of prostate cancer, a systematic review found little direct evidence that PSA velocity helps to predict the outcome of a prostate biopsy [24]. In a cohort of 2742 men undergoing biopsy as part of the European Randomized Screening study of Prostate Cancer (ERSPC), we found little support for any clinically useful role for PSA velocity for helping to determine an initial biopsy. The predictive accuracy of a statistical model including PSA and age was improved slightly by the addition of PSA velocity, but there was little value for detection of high grade cancers, or when we excluded a small number of men with very high PSA velocity, which was associated with a reduced risk of prostate cancer [25]. Prostate specific antigen density (PSAD) is defined as the ratio of serum PSA to the volume of the prostate [11]. The concept of PSAD is based on the fact that benign prostatic hypertrophy increases serum PSA through hypertrophy of the glandular tissue. While in prostate cancer the increase in serum PSA results from disruption of the vascular architecture, without significant increase in volume of the prostate gland. For a given serum PSA value, the prostate volume will be greater. PSA density is less in patients with benign prostatic hypertrophy (BPH), compared with patients with prostate cancer. BPH and carcinoma of the prostate frequently co-exist. By calculating PSAD, theoretically, one can minimize the influence of BPH on serum PSA. In this article Benson MC, Whang IS, Pantuck A describe their findings related to the association of PSAD with biochemical disease-free survival (BDFS) in patients with prostate cancer treated with external beam radiotherapy [08]. Study by Dalton et al revealed that raise PSA level in acute bacterial prostatitis and normalized after antibiotic therapy [31]. Neal et al also reported the rise in PSA level in chronic bacterial prostatitis [32]. In another study prostate volume and the inflammation of the prostate gland was taken as the most important factor for the rise in PSA level without the evidence of prostate cancer [10]. Ozden et al [20] and Cho et al [29] reported that the prostatitis must be considered while taking PSA as a tumour marker because they reported normalization or decrease in PSA level after effective antibiotic therapy in patients with bacterial prostatitis. In present study, we treated for 4 weeks based on the fact that in chronic bacterial prostatitis and inflammatory CPPS, a total treatment period of 4 to 6 weeks has been recommended by Grabe M, Bishop MC. [02]. Mean age of the patients in current study was observed 64.0±10.1 years. In a study carried out by Schaeffer et al [303] demonstrated mean age of the patients 63.0±10.2 years, which is close to mean age of our study. In current study, mean serum PSA level before treatment was 10.45±5.38 ng/ml and after treatment it decreased to 5.47±4.49 ng/ml. PSA level decreased in 47.6% of patients. Cho et al in their study reported that after antibiotics treatment serum PSA values decreased to the normal range in 56.4% of the patients [299]. This is also similar like previous two studies showed that treatment of chronic prostatitis with antibiotics can decrease serum PSA to within the normal range in a significant percent of men [13,304]. However, in a recent study, there was no significant difference in the PSA levels of men with

and without prostate inflammation [300]. Baltacı et al. reported that although antibiotics therapy will decrease serum total PSA, it will not decrease the risk of prostate cancer even if the PSA decreases to less than 4 ng/ml therefore, prescribing antibiotics for asymptomatic men with a newly increased PSA may not be an appropriate method of management [301]. His study contradicts our results, but most of studies are in favor of treating chronic bacterial prostatitis with antibiotics.

CONCLUSION

Antibiotics treatment for 4 weeks in patients with increased PSA level > 4 ng/ml, may decrease serum PSA significantly. However, because the PSA level was not decreased to the normal range (less than 4 ng/ml) in all patients, it seems that antibiotics therapy before prostatic biopsy is not necessary.

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