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Study of evidence of inflammation in pathogenesis of BPH

Dr. Sarvesh kumar dubey [1], Dr. Jitendra kumar chaudhary [2], Dr. Subham Anand[3], Dr.prof. D.K.Sinha [4]
1&3-Junior Resident, RIMS; 2-Senior Resident, RIMS; 4- Professor, RIMS.
DEPARTMENT OF GENERAL SURGERY, RIMS,Ranchi.

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I. Introduction

Structurally, prostate is a chest nut shaped organ around proximal urethra. Histologically BPH can be defined as an overgrowth of the epithelial and stromal cells from transitional zone and periurethral area (hyperplasia of stromal and epithelial cells).[1] Benign prostatic hyperplasia is the most frequent neoplasm in aging men mostly after age of fifty.[2] Incidence of histological BPH could be over 70% at 60 years old and over 90% at 70 years old.[3]

BPH does not always lead to clinical manifestations. It is a progressive disease and it requires a long period to evolve from earlier tissue alterations to clinical onset with LUTS (lower urinary tract symptoms). The diagnosis of benign prostatic hyperplasia is often in response to the development of lower urinary tract symptoms (LUTS), including urinary hesitancy, urgency, and frequency. These symptoms are among the most common comorbidities associated with aging in men.[1,4,5]

Till date, we still have no precise knowledge of the cellular and molecular processes underlying the pathogenesis of BPH and leading to a symptomatic disease.[6] Although the influence of androgens and estrogens has been demonstrated, hormonal factors alone may not fully explain BPH development.

Prostatic inflammation could be a key component in prostatic enlargement and benign prostatic hyperplasia progression. Region of chronic inflammation are common across the stroma and glandular epithelium of human prostate tissue[7], with the potential to drive cell proliferation and angiogenesis.

Analysis of data and biospecimens from MTOPS study found inflammatory infiltrates associated with large prostate volume and LUTS progression.[8,9,10] Similarly, chronic inflammation was associated with LUTS severity in REDUCE trial[11] i.e. two of the major clinical studies on BPH i.e. MTOPS (Medical Therapies of Prostatic Symptoms) and REDUCE (Reduction by DUtasteride of prostate Cancer Event) studies, recently demonstrated a link between histological prostatic inflammation and prostatic enlargement or symptoms scores.[1]

Numerous of the major key players in chronic inflammation have been studied in BPH: varieties of growth factors and cytokines have been shown to be involved both in the inflammatory process and in the epithelial/stromal prostatic cells interactions.[13] These mediators are released in the prostatic gland by inflammatory cells that can be found on most of the surgery derived BPH specimens.[4]

BPH can be seen as a form of asymptomatic inflammatory prostatitis, whose pathogenesis may be triggered by infection. The release of prostatic self antigens following tissue damage may sensitize the immune system and start autoimmune response. Among proinflammatory cytokines and chemokines produced by the prostatic microenvironment, stromal derived IL-8 may be considered a key link between chronic inflammation and stromal cell proliferation. We know that chronic inflammatory infiltrates mainly composed of chronically activated T cells and macrophages frequently associated with BPH Nodules.[5,6] These infiltrating cells are responsible for the production of cytokines (IL-2 and INF gamma) which may support fibromuscular growth in BPH. Immigration of T cells into the area is attracted by increase production of pro inflammatory cytokines such as IL-6,IL-8,IL-15.[6]

Although the histological examination of prostatic tissue remains the only available method to diagnose chronic inflammation, different parameters, such as prostatic calcifications, prostatic volume, LUTS severity, storage and prostatitis-like symptoms, poor response to medical therapies and urinary biomarkers, have been shown to be correlated with chronic inflammation. If inflammation is indeed associated with BPH symptoms, anti-inflammatory agent should be investigated as a new target for the pharmacological treatment of BPH.

As we know the role of COX-2 and prostaglandins in bladder function, Anti-inflammatory agents like NSAIDS, 5ARI, COX-2 inhibitors, Phytotherapy should have the role in treatments of BPH symptoms. As prostatic inflammation is associated to prostatic volume, it might be a therapeutic target in BPH. Di Silverio et al studied the effects of 5-ARI and COX-2 inhibitors combination therapy. Patients taking the combination therapyhad a significant increase in the apoptotic index compared to the patients treated with 5-ARI alone.[9] In

the MTOPS study, the use of 5-ARI was found to be more efficient in patients with prostatic inflammation. Vela Navarette et al studied the effects of serenoarepens phytotherapy on postatic inflammatory status. They found a significant reduction in the numbers of lymphocytes B and other inflammatory markers (TNF and IL-1) after treatment.

This study was a humble attempt to understand the role of inflammation in BPH and clinical detection of this inflammation will expand our understanding of BPH pathogenesis, its histological progression, allows risk stratification for patients presenting with BPH related LUTS and suggest novel treatment strategies.

II. Aims And Objective

To study the role of inflammation in pathogenesis of BPH and hence to find out the role of nsaids in treatment.

III. Materials And Methods

Study design

This is hospital based prospective observational study.

Sample size

Number of patients included in this study – 50

Duration of study:

October 2019 to September 2021.

Study population:

Patients undergoing prostatectomy (OPEN/TURP) for Benign Prostatic Enlargement admitted in RIMS, Ranchi.

Place of study:

Department of Surgery and Department of Urology, RIMS, Ranchi.

Selection of study subjects and technique:

Study subject was 50 cases requiring prostatectomy (OPEN/TURP) admitted in RIMS, Ranchi were selected.

Inclusion criteria:

1. Patients age >18 yrs.
2. Patients requiring prostatectomy.
3. Patients giving consent to participate in the study.

Exclusion criteria:

1. Patients age <18yrs.
2. Biopsy proven prostatic carcinoma patients.
3. Immuno-compromised patients.
4. HIV positive patients.

OUR STUDY WAS BASED ON

A. IPSS SCORE

B. PROSTATE VOLUME

C. INFLAMMATION SCORES[7,8] :- It combines

1. Cytological parameters.

2. Immunohistochemistry(IHC)markers.

Cytological parameters[9] :

There were total six cytological parameters:

1. Lymphocytes
2. Macrophages
3. Polynuclear leukocytes infiltrates

Three glandular aspect modifications:

4. Glandular atrophy
5. Glandular destruction
6. Tissue fibrosis

Immunohistochemistry markers[10] :

There were 5 IHC markers:

1) CD3
2) CD4
3) CD8 decorating T-lymphocytes
4) CD20 decorating B-lymphocytes
5) CD163 decorating macrophages

For cytological and immunohistochemical inflammation scoring, presence or absence of macrophage, polynuclear leucocytes, atrophy, destruction and fibrosis was quoted using binary score (0/1) and for lymphocytes and other IHC markers like CD3, CD4, CD8, CD20 and CD163 was quoted as absent, low or high (0/1/2).

IV. Results

TABLE-1
AGE WISE DISTRIBUTION OF THE PATIENTS WITH PROSTATIC ENLARGEMENT

Age group (years)	No. of Patients	Percentage of cases (%)
51-60	13	26
61-70	24	48
71-80	10	20
81 & above	3	6

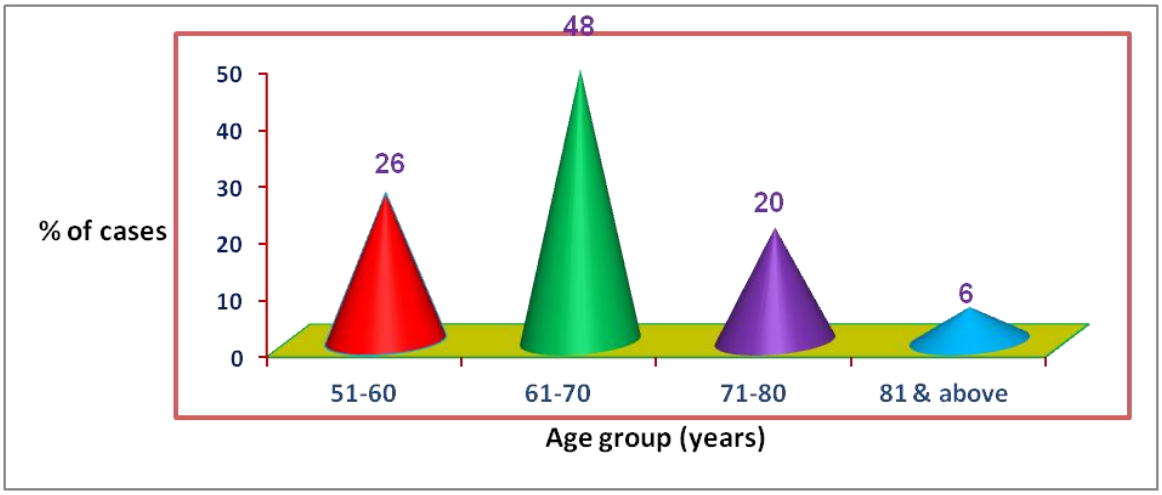


TABLE-2

PROSTATE VOLUME AMONG BPH PATIENTS OF DIFFERENT AGE GROUPS

Age group (years)	Mean Age±SD	No. of cases	Prostate volume (cc)	
			Mean ±SD	Range
51–60	57±2.0	13	36±8.0	24–46
61 –70	65.5±4.5	24	44±8.8	24–83
71 –80	74.6±3.2	10	60±15.1	26–121
>80	84.6±3.5	3	38±5.0	29–44
Total	70.4	50	44.5	

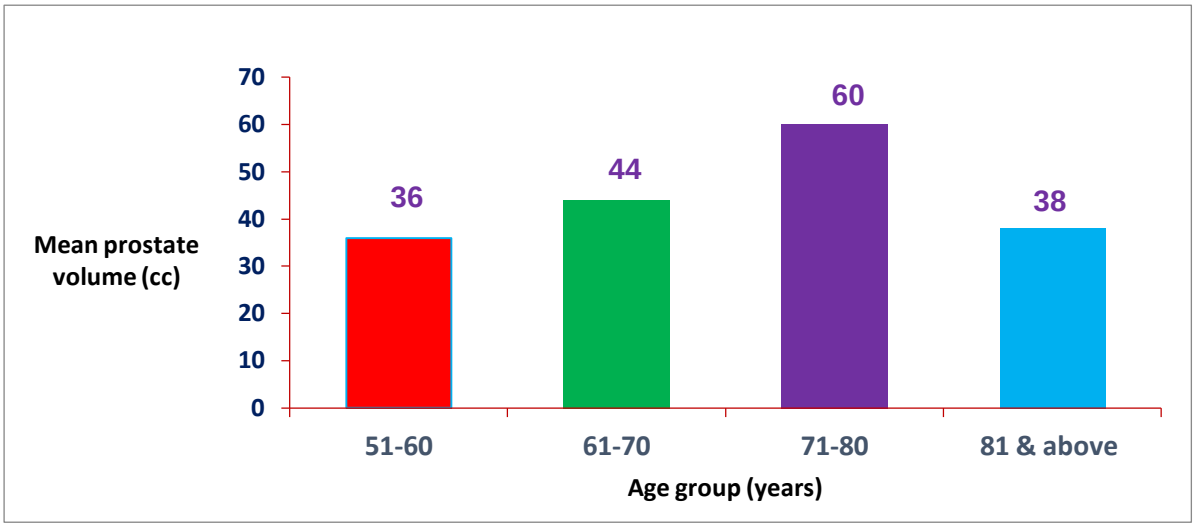


TABLE- 3

PRESENTING SYMPTOMS IN CASE OF PROSTATE ENLARGEMENT

Symptoms	No. of cases	Percentage of cases (%)
Incomplete emptying	42	84
Frequency	44	88
Intermittency	25	50
Urgency	12	24
Weak Stream	40	80
Straining	16	32
Nocturia	42	84
Terminal dribbling	32	64
Hesitancy	43	86

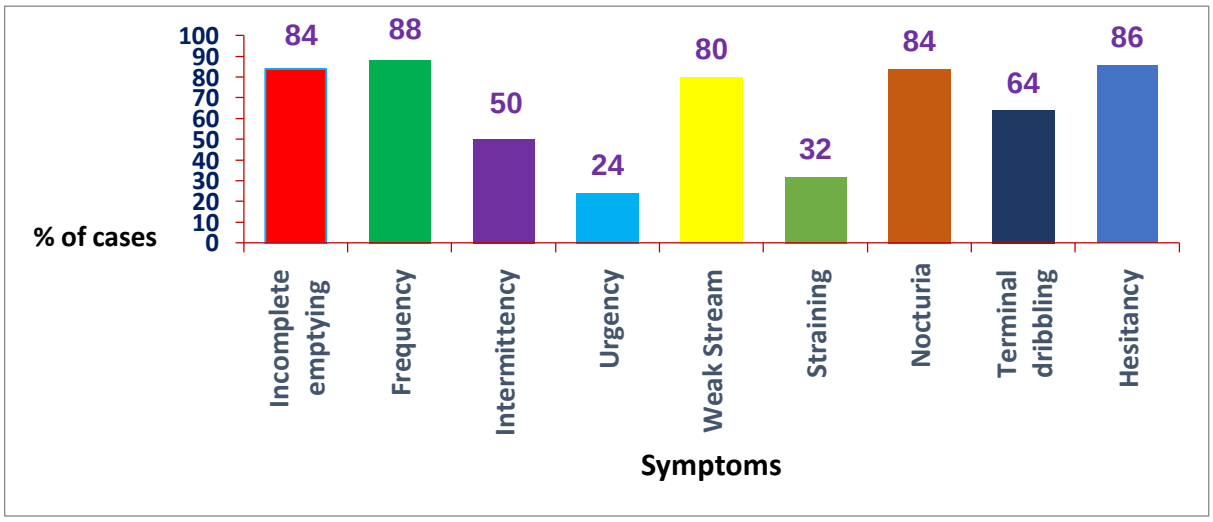


TABLE- 4

DESCRIPTION OF INFLAMMATORY CELLS INFILTRATE IN 50 PATIENTS USING CYTOLOGICAL GRADING

Cytological inflammation grading			
	Grade	n	Percentage (%)
Lymphocytes	0 1 2	11 23 16	78
Macrophage	0 1	28 22	44
Polynuclear	0 1	47 3	6
Atrophy	0 1	40 10	20
Destruction	0 1	46 4	8
Fibrosis	0 1	42 8	16

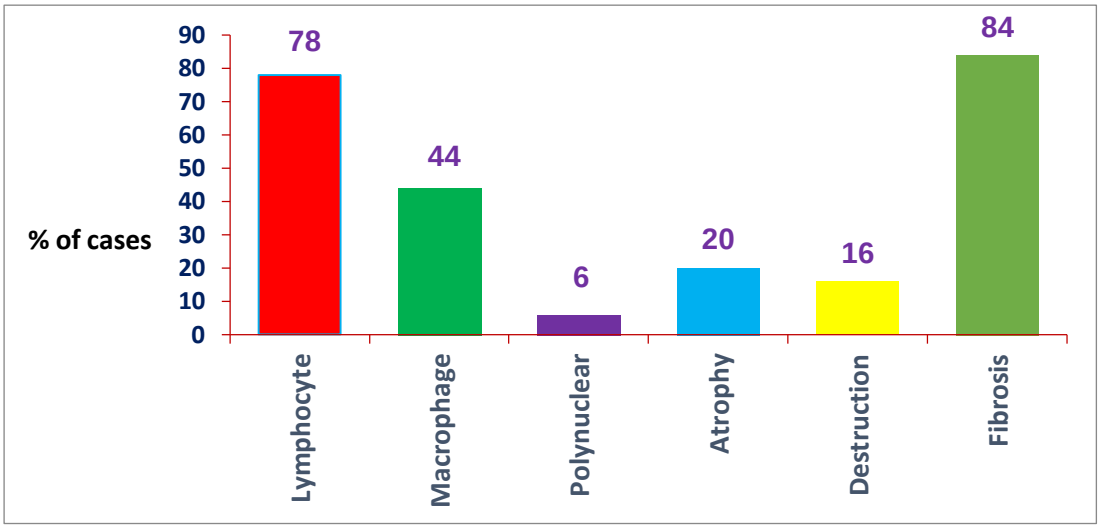


TABLE- 5
DESCRIPTION OF INFLAMMATORY CELLS INFILTRATE IN 50 PATIENTS USING IHC GRADING

IHC inflammation grading			Percentage (%)
IHC marker	Grade	N	
CD3	0 1 2	10 22 18	80
CD4	0 1 2	31 17 2	38
CD8	0 1 2	10 25 15	80
CD20	0 1 2	24 15 11	52
CD163	0 1 2	9 28 13	82

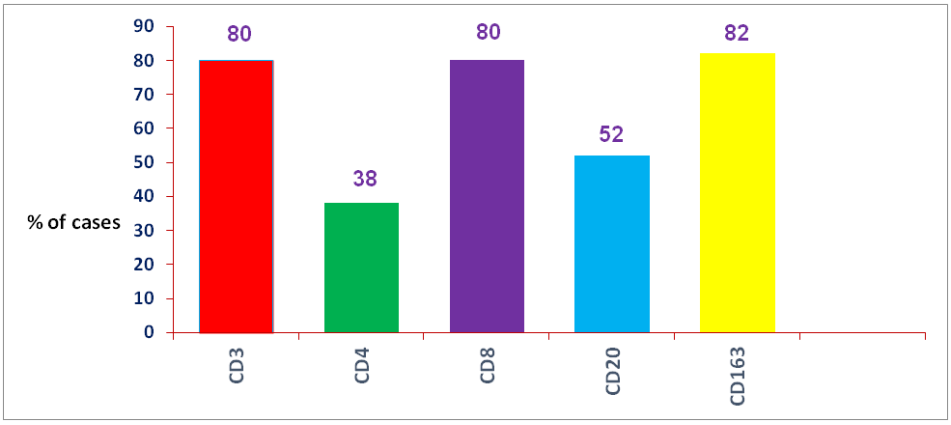
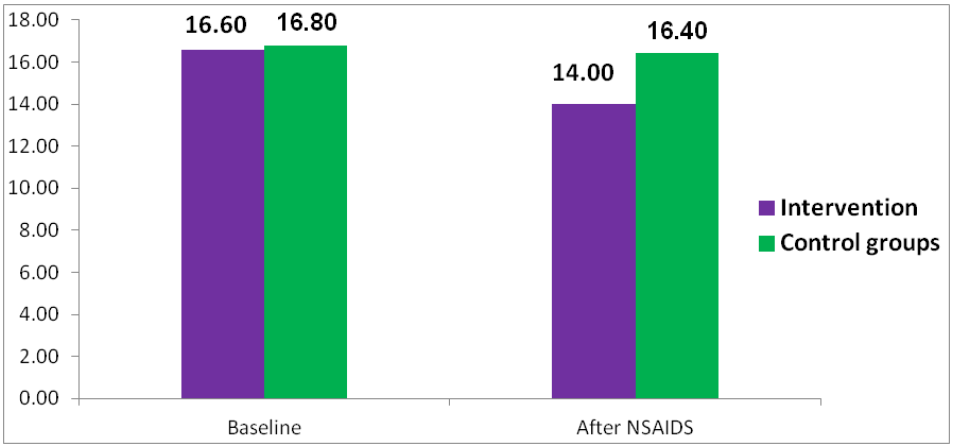


TABLE- 6

AVERAGE IPSS SCORE BEFORE AND AFTER 4–6 WEEK OF NSAIDS TREATMENT

	Baseline (Intervention/Control groups)	**After NSAIDS (Intervention/Control groups)**
IPSS Score	16.6/16.8	14.0/16.4



V. DISCUSSION

1. We observed that majority of patients 24(48%) were in age group 61-70 year.There was no patient in age group less than 51 years.
2. Mean age of presentation was 70.4 years. Mean prostatic volume was 44.5 cc however it was higher (60 cc) in age group 71-80 years.
3. Most common and earliest presenting symptom was frequency; it is seen in 44(88%) patients. Frequency, hesitancy, nocturia, sense of incomplete emptying and weak stream were observed in >80% of cases.
4. Most commonly observed infiltrating cell was lymphocyte. It was observed in 39 patients(78%) on cytological examination. Atrophy was most frequent glandular modification and it was observed in 10 cases(20%).
5. On immunohistochemistry analysis T-lymphocytes (80%) and macrophage (82%) were the most frequently observed inflammatory cells. CD3 40(80%), CD8 40(80%) and CD163 41(82%) were most common IHC markers.
6. There was significant reduction in IPSS score in low inflammation group after 4-6 weeks of NSAIDS treatment as compared to high grade inflammation group.

VI. Conclusion

Therefore it may be concluded that chronic inflammation plays major role in pathogenesis of Benign Prostatic Enlargement in term of cytological and immunohistochemical examination of specimens derived after TURP and open prostatectomy. There was significant reduction in IPSS score and prostate volume after treatment with NSAIDS indicating the role of anti-inflammatory agents in benign prostatic enlargement patients.

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