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Does asymptomatic prostatic inflammation alter the outcome of transurethral resection of prostate?

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Introduction There is contradictory evidence in literature with respect to the association of asymptomatic prostatic inflammation on biopsy with complications of Transurethral Resection of Prostate. The aim of the present study was to evaluate the association of prostatitis in biopsy specimens of patients undergoing transurethral resection of prostate with bladder neck contracture (the primary end point) and other complications.

Material and methods Patients who had undergone transurethral resection at a single centre between 2005 and 2010, with a minimum of 3 months follow-up were included. The study population was divided into two cohorts: those with inflammation on prostatic biopsy (Group A) and those without (Group B). These two groups were compared with respect to demographic data and pre-operative and intraoperative confounding factors. Immediate complications were documented using the modified Clavien-Dindo system and compared. Long term complications like bladder neck contracture, meatal stenosis, urethral stricture, and recurrent adenoma were also compared.

Results Both groups were comparable except for Group A patients having a higher median resected weight (20 vs. 14 gms, p = 0.009). There was no significant difference between the groups with respect to the rate of bladder neck contracture and other long-term and short term complications on univariate and multivariate analysis. Larger resected weight of gland was associated with lower rate of bladder neck contracture on multivariate analysis (p = 0.019, Odds ratio: 0.937).

Conclusions Presence of histologically confirmed prostatic inflammation is not associated with bladder neck contracture or other complications following transurethral resection. Smaller resected prostatic weight was associated with higher incidence of bladder neck contracture.

Key Words: bladder neck contracture ‹› complications ‹› prostatic inflammation ‹› transurethral

INTRODUCTION

The co-existence of inflammation and benign prostatic hyperplasia (BPH) in the prostate is well-known, although the significance of histologically proven prostatic inflammation and its relationship with BPH is not well understood [1]. Prostatic inflammation may play a role as an inciting event in the development of BPH nodules. Its association with higher symptom scores and suboptimal outcome of medical management have been suggested [2, 3]. The presence of chronic inflammation has also been associated with progression of disease and acute urinary retention [4]. These observations indicate a broad consensus among experts that the presence of an active inflammatory reaction leads to excessive cellular proliferation, larger prostatic adenomas, recurrent adenomas, resistance to medical therapy and increased early development of complications like retention of urine. Studies testing the hypothesis

that inflammation related excessive cellular proliferation results in an increased incidence of bladder neck contracture following transurethral resection of prostate (TURP) have had varied outcomes.
Few studies have looked into the association of asymptomatic histopathological prostatitis with the complications following TURP, especially with respect to bladder neck contracture. Bucuras et. al did not find any association of histological prostatitis with intra-operative and post-operative complications following TURP [5], whereas Doluoglu et al., found that prostatic inflammation was associated with a higher number of re-interventions for urethral stricture and bladder neck contracture after TURP [6].
The primary aim of the study was to see if there is a significant difference in the rate of bladder neck contracture between patients with and without prostatic inflammation on biopsy. The secondary aims were to see if there was a difference in the rates of other complications between the two groups, and if any other pre-operative factor was associated with bladder neck contracture.

MATERIAL AND METHODS

This is a single centre hospital based retrospective cohort study. All patients who underwent TURP between 2005 and 2010, and satisfied the following inclusion and exclusion criteria were recruited.
Inclusion criteria:
1. Patients with a minimum follow-up of 3 months following TURP.
2. Patients whose biopsy showed BPH and lymphocytic/ neutrophilic infiltrate in contact with the glandular epithelium in the prostatitis group (group A) and without any inflammatory cells in the control arm (group B).
3. Absence of chronic perineal/pelvic pain (i.e. patients classified to have asymptomatic inflammatory prostatitis – Category IV of the NIH Classification of Prostatitis [7])

Exclusion criteria:
1. Patients undergoing TURP with a concomitant procedure (e.g. hernioplasty/circumcision/cystolitholapexy/internal urethrotomy).
2. Patients who had a histological diagnosis of carcinoma prostate.
3. Prior history of urethral instrumentation (internal urethrotomy /urethral dilatation)
4. Biopsy patterns showing diffuse /focal pure stromal lymphocytic infiltrate without any acinar/ peri-glandular involvement or granulomatous inflammation.

Data of the selected patients were retrieved retrospectively. Institutional Research Board and Ethics Committee clearance was obtained (Institutional approval number IRB (EC)-ER-5-21-3-2012). TURP was performed using the same technique in all cases: using a 26F continuous irrigation resectoscope with a bipolar or monopolar energy source. In small prostates (defined as <30 grams on preoperative digital assessment), bladder neck incision (BNI) after resection was added to standard TURP. Foley's catheter was removed after 48 hours. Patients were asked to follow up at 3 months or earlier if symptomatic, and thereafter, yearly. At each follow up visit patients underwent clinical assessment and uroflowmetry. An arbitrary cut-off for follow up of at least three months was chosen, as some patients who go on to develop bladder neck contracture present as early as three months after surgery [8].
Baseline parameters that were recorded included age, indication for TURP, use of preoperative 5-alpha reductase inhibitors, presence or absence of pre-operative Foley's catheter, approximate preoperative digital assessment of gland size, co-morbidities like diabetes mellitus, hypertension, ischaemic heart disease, chronic obstructive pulmonary disease, anticoagulant use, anti-platelet use and chronic renal failure.
The type of energy source (monopolar or bipolar) was documented and compared. The actual weight of the resected prostatic tissue (in grams) along with the presence of inflammatory infiltrate and its location was noted from histopathology reports. Patients with inflammatory cells in the stroma alone were excluded, as pathological consensus dictates that inflammatory cells (lymphocytes or neutrophils) must typically infiltrate the prostate in a peri- or intra-glandular distribution, to be considered prostatitis. Diffuse stromal infiltrates or focal lymphoid aggregates in the stroma may be seen ubiquitously, are considered to be of little clinical significance, and graded to have least histological aggressiveness [9, 10].
Pre- and post-operative urine cultures were also documented. Colony counts of >100,000 colony forming units were considered significant. Those with positive cultures were treated before TURP.
Immediate complications (within 30 days of surgery) were graded from Clavien grade 1 through grade 5, using the modified Clavien-Dindo system for TURP proposed by Mamoulakis et al. [11]. Long term complications (any time after 30 days of surgery) such as bladder neck contracture, meatal stenosis, urethral stricture, or recurrent adenoma requiring intervention were noted on follow-up. Re-interventions for complications were performed if the patient presented with poor flow and uroflowmetry showing a maximum flow rate of less than 10 ml/second on follow up.

Sample size calculation

Based on studies in contemporary literature, the expected mean difference in bladder neck contracture between those with (8%) and without (2%) prostatic inflammation was kept at 6% [8, 12]. The number needed to detect a significant difference, keeping the power at 80%, was calculated to be a minimum of 140 in each arm. We finally included 422 subjects (220 and 222 in each arm respectively) in the study.

Definition of Cohorts and statistical analysis

Patients were divided into two groups based on the presence of inflammatory infiltrates in the biopsy specimen obtained from TURP. Group A included patients with glandular/peri-glandular inflammatory infiltrates, while Group B included patients without any inflammatory infiltrates in the biopsy specimen. Student's t-test was used to compare quantitative normally distributed variables and the Pearson's Chi-squared test was used for non-normally distributed data and data in the form of proportions. Mean ±standard deviation were used for normally distributed data and median & range (min–max) was used for skewed data to avoid the outlier effect. Logistic regression was used for univariate and multivariate analysis. A p value of <0.05 was taken as significant. Statistical Package for Social Sciences version 16.0 was used for statistical analysis.

RESULTS

The study flow (patients excluded and their details) is shown in Figure 1.

Study group profile

The study group comprising 442 patients had a mean age of 63.5 years. Median hospital stay was 5 days, including the dates of admission and discharge. The median resected weight was 15 grams (ranging from 1–125 grams). Median duration of follow up was 18.5 months, ranging from 3–96 months. Around 9.5% of patients underwent resection with a bipolar energy source. The most common indication for offering TURP was failure of medical management (42.8%), followed by urinary retention. Out of 42.8% of patients in whom the indication for TURP was failure of medical management, 15.8% of patients were on 5 alpha reductase inhibitors. The baseline demographic data (Tables 1 and 2) and intraoperative parameters in Group A and B were similar except for higher median resected weights of prostate gland in group A as compared to group B (20 g vs. 14 g).

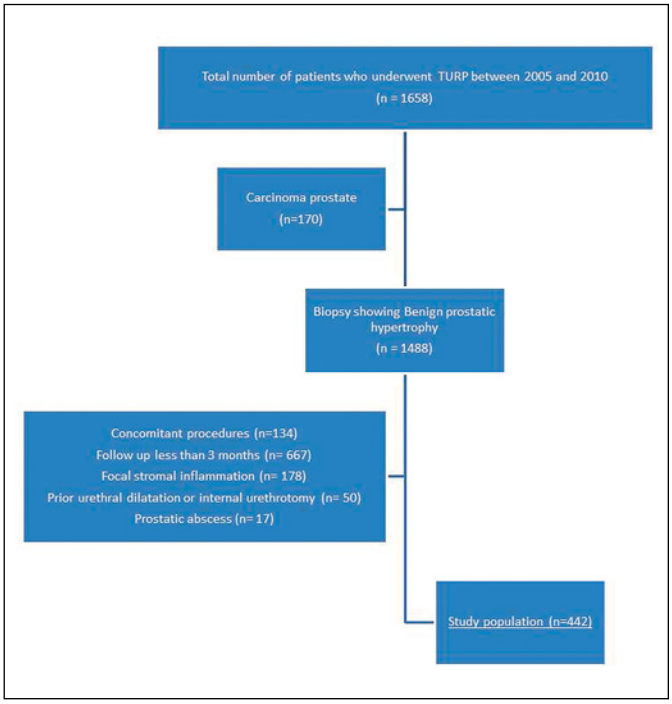

Figure 1. *Study flow showing selection of study population (patients excluded and their details).*

Table 1. *Distribution of preoperative and intraoperative parameters in group A and B*

Baseline and intra-operative variables	Group A (Pi+) N = 222	Group B (Pi-) N = 220	p value
Age in years [mean ±SD]	63.65 ±8.21	63.34 ±8.08	0.692
DRE gland size in grams [median (range)]	30 (15–70)	30 (15–70)	0.302
Resected weight in grams [median (range)]	20 (1–70)	14 (1–125)	0.009
Hospital stay in days [median (range)]	5 (3–18)	5 (4–19)	0.296
Follow-up in months [median (range)]	15 (3–96)	23.5 (3–83)	0.224
Comorbidities present	79.7%	83.6%	0.228
Preoperative ARI used	15.8%	15.9%	0.967
Preoperative urethral catheter	44.6%	45%	0.932
Bipolar energy source	9.9%	9.1%	0.769
Intra operative blood transfusion	5%	5.5%	0.593
TURP + BNI	9.5%	10.9%	0.614

DRE gland size: Approximate assessment of gland size on digital rectal examination; TURP + BNI, Addition of Bladder neck incision on the standard transurethral resection of prostate if resected prostatic gland was smaller than 30 gm; (Pi-), absence of prostatic inflammation; (Pi+), presence of prostatic inflammation; ARI, Alpha reductase inhibitor.
Normally distributed data is presented as mean ±SD and skewed data as Median (range).

This difference was statistically significant, indicating the potential confounding effect of this parameter on the outcomes.

Primary outcome

In group A, 5% of patients had bladder neck contracture as compared to 2.8% in group B. This difference failed to reach statistical significance (p = 0.223). On multivariate analysis, taking into account the difference in the weight of gland resected in the two groups and type of surgery performed (TURP vs. TURP+BNI), the risk of bladder neck contracture in those with prostatitis was reduced by 54%(odds ratio of 0.459) though it failed to reach statistical significance (p = 0.139, Tables 3 and 4). Hence on accounting for potential confounders, we observed no association of prostatic inflammation with bladder neck contracture.

Secondary outcomes

Short term complication

The short term complications as recorded by the Clavien-Dindo system were similar in the two groups (Table 5).

Other Long term complications

Urethral stricture, submeatal stenosis and regrowth of adenoma were numerically more in group A; however differences were not statistically significant (Table 3).

Other pre-operative factors associated with bladder neck contracture

On univariate analysis, weight of resected prostatic tissue was not significantly associated with bladder neck contracture (p = 0.066). On multivariate analysis, (Table 4) with inclusion of presence of prostatitis and type of surgery (TURP + BNI vs. TURP) in the model, with each additional gram of tissue resected, odds of developing bladder neck contracture was 0.937 (i.e. there was a 6% reduction in incidence with each additional gram of tissue resected) which was statistically significant (p = 0.019). For every 10 grams of additional resection there was a 48% reduction in the incidence of bladder neck contracture (odds ratio of 0.521). Resection of a larger gland was found to be associated with adenoma regrowth (odds ratio of 1.033, p value = 0.011) on univariate analysis. For every 10 grams of additional resection there was a 38% additional risk of adenoma regrowth.

Table 2. *Indications for TURP in group A and B*

Indication for TURP	Group A (Pi+) n = 222 %	Group B (Pi-) n = 220 %	p value
Chronic retention	13.5%	10%	0.374
Acute retention	18.9%	19.2%	
Acute on chronic retention retention	14.9%	16.4%	
Failure of medical management	38.9%	46.6%	
Obstructive nephropathy	0.5%	0%	
Recurrent UTI	3.2%	1.4%	
Recurrent hematuria	1.8%	0.9%	
Bothersome LUTS	8.6%	5.5%	

Acute on chronic retention, retention volume >1 litre; LUTS, lower urinary tract symptoms;
(Pi-), absence of prostatic inflammation; (Pi+), presence of prostatic inflammation; UTI, Urinary tract infection.

Table 3. *Long term complications in Group A and B (univariate analysis)*

Long term complications	Group A (Pi+) n = 220 %	Group B (Pi-) n = 220 %	p value
Stricture urethra and meatal stenosis	5.9%	3.2%	0.18
Bladder neck contracture	5%	2.8%	0.223
Recurrent adenoma	3.2%	2.3%	0.56

(Pi-) absence of prostatic inflammation; (Pi+) Presence of prostatic inflammation

Table 4. *Multivariate analysis of factors associated with bladder neck contracture*

Variables	Odds Ratio	95% Confidence Interval		P Value
		Lower	Upper	
Gland resected (gms)	0.937	0.887	0.989	0.019
Prostatitis (Group B vs. A)	0.459	0.164	1.288	0.139
Surgery performed (TURP+BNI vs. TURP)	1.401E8	0.000	–	0.997

Group A, those with prostatitis; Group B, those without prostatitis; TURP+BNI, In addition to standard transurethral resection of prostate these patients underwent bladder neck incision; TURP, patient undergoing standard Transurethral resection of prostate.
Logistic model was tested for Significance (by log likelihood method) p ≤0.005
Goodness of fit was checked by Hosmer-Lemeshow method p = 0.522

Subgroup analysis

There were 45 patients in the study population who underwent TURP + BNI, 21 of them were in Group A and 24 in group B. None of these patients developed

Table 5. *Immediate complications in two groups recorded as per Clavien System*

	Complications	Group A (Pi+)	Group B (Pi-)	p value
Clavien Grade 1	Hematuria	3.2%	1.8%	
	Clot retention	1.8%	1.8%	
	Blocked catheter	0.5%	0%	
	Bedside failed TWOC	3.2%	1.4%	0.93
	Transient rise of creatinine	0%	1.4%	
	Post-operative UTI requiring antibiotics	15.3%	9.2%	
Clavien Grade 2	Hemorrhage requiring blood transfusion	2.3%	0.9%	
	UTI with septicemia	1.8%	2.3%	0.334
	Supraventricular tachycardia	0%	0.9%	
Clavien Grade 3	Re-exploration with anesthesia	0.9%	2.3%	0.248
Clavien Grade 4	TUR Syndrome requiring ICU admission	1.4%	2.7%	0.306

TWOC, Trial Void without catheter; UTI, Urinary tract infection; TUR, Transurethral resection; (Pi-), Absence of prostatic inflammation; (Pi+),Presence of prostatic inflammation, ICU: Intensive care unit

bladder neck contracture. Therefore, the addition of BNI to TURP had a protective effect on the incidence of bladder neck contracture, however this was not statistically significant on univariate ($p = 0.517$) or multivariate analysis ($p = 0.997$, Table 4).

DISCUSSION

The significance of finding asymptomatic histopathological prostatic inflammation in the biopsy specimens of patients undergoing TURP has been debated. While some authors reported an association with outcomes [6], other researchers failed to demonstrate a definite association between this pathological entity and clinical outcomes after TURP [5].

The present study was an attempt to see if there is an association between asymptomatic prostatitis found incidentally on TURP specimens with either long term or short term outcomes. Our baseline demographic data showed that both groups had a similar clinical profile, except with respect to the resected weight of the gland, which was significantly more in Group A. The immediate short term complications were stratified into five Clavien-Dindo Grades, and these failed to show any association with the presence or absence of asymptomatic prostatitis. Finally, the presence of histological inflammation was not found to be associated with the occurrence of long term complications (urethral stricture, bladder neck contracture or recurrent adenoma) even after taking into account variation in the sizes of gland resected; rather, on multivariate analysis, presence of prostatic inflammation showed a trend towards a protective effect on incidence of bladder neck contracture (though not statistically significant). This trend suggests two possibilities: one, that the presence of inflammatory cells in prostatic tissue promotes better healing in the bladder neck area, which is difficult to explain biologically; or the fact that there are other (chiefly surgical and hence difficult to quantify) factors which have been unaccounted for in this analysis e.g. bladder neck over-resection, which have a much greater influence on bladder neck contracture rate. Hence, it is unlikely that prostatic inflammation in itself has any effect on the incidence of bladder neck contracture.

In a similar study, the duration of the surgery and presence of prostatic inflammation showed a statistically significant association with re-interventions done for urethral stricture and bladder neck contracture [6]. However, there were major differences between this study and ours. Re-intervention for bladder neck contracture and urethral stricture was the final outcome and association of various factors with this outcome were studied [6]. This approach assumes that both urethral stricture and bladder neck contracture have a similar pathophysiology and the same factors account for both. In the present study, the association of various factors with bladder neck contracture alone were studied.

In the study mentioned above, the prostatic inflammation group included those patients who had presence of any inflammatory cells in the histopathology specimen[6]. In the present study, patients with pure stromal inflammation of any degree were excluded, and only those who had glandular and periglandular inflammation (suggesting a higher grade of histological aggressiveness) were included in the prostatic inflammation group, so as to clearly bring out any differences. Moreover, groups with and without inflammation were not equal in the above mentioned study, while in the present study both groups included a similar number of patients.

On multivariate analysis, a clinically relevant and statistically significant association was seen between the weight of gland resected and the development of bladder neck contracture, with smaller resections more likely to have bladder neck contracture even after taking into account prophylactic bladder neck incision in smaller glands and presence or absence of prostatitis. The association of smaller gland

resections with bladder neck contracture, has also been suggested by other retrospective studies [8, 13]. The present study did not show any bladder neck contracture in the subgroup of patients who underwent TURP + BNI. This protective effect of the addition of BNI did not reach statistical significance in our study probably because this study was neither designed nor powered to answer this question. In another retrospective analysis of factors (other than inflammation) associated with the occurrence of bladder neck contracture, the addition of BNI to TURP reduced the incidence of bladder neck contracture [8].

The overall incidence of long term complications in our study (0.5%, 4.1%, 3.8% and 2.7% for meatal stenosis, urethral stricture, bladder neck contracture and recurrent adenoma respectively) is comparable to that found in a contemporary series on TURP complication rates [12]. This fact is an indirect indicator that the selected sample is representative of the larger population it represents.

Limitations of this study include its retrospective nature and inherent selection bias such as inclusion of patients with at least 3 months of follow up. To assess the impact of loss to follow up bias, we calculated the percentage of patients with histopathological asymptomatic prostatic inflammation in the loss to follow up group and the group which followed up, and found it to be 41.1% and 35.8% respectively ($p = 0.051$). It is therefore unlikely that differential loss to follow up significantly impacted the results of the present study. We were unable to include data regarding serum prostate specific antigen (PSA) and transrectal ultrasound (TRUS) volume of the prostate as it is not an institutional policy to screen patients undergoing TURP with PSA or to routinely do TRUS. We did not use any of the proposed grading systems for histological aggressiveness, as none of them have been validated yet, and their use would have converted the prostatitis group into further subgroups, making analysis more complicated. On the other hand, our approach of using groups at the extreme ends of the pathological spectrum would have clearly brought out any differences in the outcomes, if they existed. Another significant limitation that deserves mentioning is the fact that studies on the topic (association of prostatic inflammation and bladder neck contracture following TURP), including the present study, consider histological presence of infiltrates in periacinar and periductal prostatic glands as markers of inflammation, without evaluating known specific inflammatory pathways of prostatic inflammation e.g. oxidative stress, vitamin D pathways [14]. Prospective evaluation of the role of these pathways would be the way forward in understanding the factors responsible for the development of post TURP bladder neck contracture.

The strengths of this study include its methodology and focussed primary objective, as it was designed and powered to study the association of asymptomatic histological prostatitis and bladder neck contracture. The study population was followed up long enough (median duration of follow up 18.5 months) to capture the primary outcome, as literature suggests that the median and mean follow up at which bladder contracture presents is 8.5 and 9 months respectively [8, 15].

CONCLUSIONS

Presence of histological asymptomatic prostatic inflammation is not associated with bladder neck contracture following TURP. Other complications (both short term and long term) were not affected by the presence of inflammation. A smaller resected weight of prostatic gland was associated with higher incidence of bladder neck contracture and the addition of prophylactic bladder neck incision in smaller glands undergoing TURP may prevent bladder neck contracture.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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