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Effect of Topical Tacrolimus in Patients of Non Obliterative Anterior Urethral Stricture Due to BXO

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ABSTRACT

The term “urethral stricture” describes the constriction of the urethra brought on by scarring, which obstructs the lower urinary system. Numerous conditions, including iatrogenic, trauma, urethritis, Blanitis Xerotica Obliterans (BXO) and idiopathic, can cause it. To evaluate the impact of topical tacrolimus administration in cases of BXO-induced urethral stricture and the potential side effects. The present study was a Prospective observational study. This study was conducted form 18 months in in the Department of Urology, NSMCH, Bihta, Patna. All patients meeting the eligibility criteria was treated with a local application of 0.1% tacrolimus twice daily for 6 weeks. 100 patients were included in this study. After the catheter removal Peak flow was 23.8 ml/sec, 18.2 ml/sec at the 3 month follow-up and 17.75 ml/sec at the 6-month follow-up. Average flow in our study was 15.6 ml/sec following catheter removal, 13.8 ml/sec at the follow-up after three months and 15.5 ml/sec at the follow-up after six months. In our investigation, the voided volume was 278 ml following catheter removal, 235 ml at the 3 month follow-up and 288 ml at the 6-month follow-up. BXO-induced urethral stricture was evident in the Qmax values, which decreased from 28.8 ml sec after catheter removal to 17.62 at 6 months. Our study found a significant decrease in peak flow and related parameters after catheter removal and subsequent follow-up. Peak flow dropped from 28.8 ml/sec after catheter removal to 17.62 after 6 months. The same period saw average flow drop from 19.75-12.75 ml/sec and voided volume drop from 278-283ml. Patients also experienced pruritis (8.8%) and rash (5.0%). Peak flow levels and associated indicators decreased significantly, suggesting the underlying illness may be progressing.

INTRODUCTION

A urethral stricture is a scar-induced constriction of the urethra that obstructs the lower urinary tract functionally. The repercussions of this obstruction can harm the entire urinary system, leading to loss of renal function and cause disruptions in micturition, which can significantly lower the patient's quality of life. Urethral strictures, which can affect both men and women at any age (though they are far less common in women), must therefore be identified early and treated appropriately. It is estimated that the incidence in industrialized nations is 0.9%[5]. The stricture is a morphological change caused by scarring that occurs in the urethra[6]. In men, scarring also involves the corpus spongiosum, where the urethra is located. This spongio-fibrosis is a response to different extrinsic irritants and can result in scar tissue completely replacing the spongy tissue.

Numerous conditions, including iatrogenic, trauma, urethritis, Blanitis Xerotica Obliterans (BXO) and idiopathic[1], can cause it to appear. The precise cause of BXO, a chronic inflammatory disease mediated by lymphocytes, is unknown. It involves the urethra in 20% of the patients. The three terms balanitis (a persistent infection of the glans), xerotica (an excessively dry lesion look) and obliterans (the association with occasional endarteritis) are combined to form the name BXO[2]. It starts as glans irritation and manifests as a white plaque. Although the exact etiology of urethral inflammation is uncertain, some evidence points to high pressure voiding as a possible cause. This could result in urine intravasating into the glands of littre, causing inflammation, the formation of microabscesses and deep spongiofibrosis. As a medical intervention, topical steroids and antibiotic formulations work to stabilize the inflammatory process[3]. For BXO, immunomodulator therapy has also been suggested. Tacrolimus is an immunomodulator medication that functions by preventing interleukin 2 from being produced and consequent T-cell activation. This cures BXO and lessens or slows the balanitis process. Tacrolimus topical treatment (0.03-0.1%) in BXO patients demonstrated encouraging outcomes in a number of studies4. The purpose of this research is to determine whether topical tacrolimus use can improve urethral stricture caused by BXO as a non-surgical medical treatment option.

MATERIALS AND METHODS

Place of study: Study was conducted in the Department of Urology, PMCH, Patna.

Study design: Prospective observational study

Duration of the study: 18 months

Sample size: All patients meeting the eligibility criteria was included the study during the given period.

Sampling technique: Universal sampling method.

Method of recruitment:

Inclusion criteria: All patients with BXO and partial anterior urethral stricture.

Exclusion criteria:

- Patients with complete urethral obstruction
- Patients with altered renal function
- Patients with hydro ureteronephrosis
- Already immune compromised patients

Type of intervention: All patients meeting the eligibility criteria was treated with a local application of 0.1% tacrolimus twice daily for 6 weeks.

Data collection:

Data was collected as per prepared proforma:
Patients detailed history and physical examination was noted:

- Patients all routine (Haemoglobin, S. Creatinine, Liver function test, Urine routine, microscopy and culture) and specific investigation [Uroflowmetry, Retrograde Urethrogram (RGU), Ultrasound (USG) Kidney Ureter Bladder (KUB) with Post Void Residual (PVR) urine] required for BXO and urethral stricture was noted
- At 6 weeks Uroflowmetry, RGU and USG KUB region with PVR of abdomen was repeated in all patients. If there was improvement then treatment will continue for 3 months with once per day local application
- Side effects of tacrolimus topical application (urethral discomfort, changes in total leucocyte count, impaired LFT and blood glucose) was recorded as per proforma

Statistical analysis: Data will entered into Microsoft excel sheet and was analysed using Statistical Package for Social Sciences (SPSS) version 21 software.

RESULTS

In our study, 57 (57.0%) patients had BXO, 35 (35.0%) patients had Post inflammatory, 8 (8.0%) patients had Post-Surgery (urethrotomy and stone retrieval). In our study, 66 (66%) patients had 2-7cm Length of Stricture, 22 (22%) patients had 8-10cm Length of Stricture and 12 (12%) patients had =11cm Length of Stricture. In our study, Peak flow had 28.8

Table 1: Distribution of Etiology

Etiology	No of Patients	Percentage
BXO	57	57.0
Post inflammatory	35	35.0
Post-Surgery (urethrotomy and stone retrieval)	8	8.0
Total	100	100.0

Table 2: Distribution of Length of Stricture

Length of Stricture	No of Patients	Percentage
2-7cm	66	66
8-10cm	22	22
≥11cm	12	12
Total	100	100

Table 3: Post-operative follow up reflow for less than 10cm

	Peak flow	Average flow	Voided volume
After catheter removal	28.8 ml/sec	19.75 ml/sec	278ml
At 3rd month follow up	21.5 ml/sec	15.25 ml/sec	287ml
On 6th month follow up	17.62 ml/sec	12.75 ml/sec	283ml

Table 4: Post-operative follow up reflow more than 10cm stricture repair

Follow up periods	Peak flow	Average flow	Voided volume
After catheter removal	23.8 ml/sec	15.6 ml/sec	278ml
At 3rd month follow up	18.2 ml/sec	13.8 ml/sec	235ml
On 6th month follow up	17.75 ml/sec	15.5 ml/sec	288ml

Table 5: Distribution of Side effect

Side effect	Frequency	Percentage
Pruritis	8	8.0
Rash	5	5.0
No	87	87.0
Total	100	100.0

ml/sec after catheter removal, 21.5 ml/sec at 3rd month follow up and 17.62 ml/sec on 6th month follow up. In our study, Average flow was 19.75 ml/sec after catheter removal, 15.25 ml/sec at 3rd month follow up and 12.75 ml/sec on 6th month follow up. In our study, voided volume was 278ml after catheter removal, 287ml at 3rd month follow up and 283ml on 6th month follow up.

In our study, Peak flow was 23.8 ml/sec after catheter removal, 18.2 ml/sec at 3rd month follow up and 17.75 ml/sec at 6th month follow up. In our study, Average flow was 15.6 ml/sec after catheter removal, 13.8 ml/sec at 3rd month follow up and 15.5 ml/sec on 6th month follow up. In our study, voided volume was 278ml after catheter removal, 235ml at 3rd month follow up and 288ml on 6th month follow up. In our study 8 (8.8%) Patients had Pruritis and 5(5.0%) patients had Rash.

DISCUSSIONS

This research was conducted using a prospective observational design. This study was carried out for eighteen months at the department of Urology, PMCH, Patna. In all, 100 patients were involved in this investigation. A total of one hundred patients were examined. Most individuals who came in were between the ages of 31 and 40. Patients in the 51-60 age range had their comorbid conditions HT, DM and IHD-evaluated. Balanitis Xerotica Obliterans (BXO) is a chronic, frequently progressive condition that can cause urethral stenosis and phimosis, which impair sexual and urine function. This was discovered by Hartley *et al*[8]. According to Fekete *et al*.[9], lichen sclerosus is a chronic illness with an unclear cause that can affect both sexe's genitalia. Only in the male genital area, balanitis xerotica obliterans (BXO) usually affects the meatus, penile glans and foreskin. Nonetheless, of the 100 patients in our study, 57 (57.0%) developed BXO.

Several methods, including preoperative retrograde urethrography, ultrasonography and endoscopy, can be used to identify and locate an anterior urethral stricture, according to Kuo *et al*.[10] research. However, the majority of patients [66 (66%)] had a stent that was between 2 and 7 cm long. The procedure indicated that the buccal mucosal transplant with a dorsal alone was the most frequently performed. Three dorsal onlay BMG+ventral meatotomy cases followed were linked to meatal constriction and BXO alterations. Pin entire meatus with BXO alterations was present in one patient. Dorsal onlay BMG+meatoplasty is what we did.

A small number of patients experienced 1cm of penile skin necrosis at the ventral part of the penis as well as an acute post-operative wound infection. Another patient experienced a little sinus growth and a wound infection at the suture site, but there was no urine flow. The pericatheter study was fine. The table shows the frequency and percentage of side effects caused by a particular medication. Out of 100 patients, 8% experienced pruritis and 5% experienced rash. The majority of patients (87%) did not experience any side effects.

Uroflowmetry is a valuable armament for the urologist to estimate the probable course of a stricture. The estimated maximal urinary flow rate (Qmax) of an adult man with a healthy lower urinary tract is >15 mL s^{-1}. 11 A Qmax of <15 mL s^{-1} is suspicious for lower urinary tract obstruction and requires further evaluation. Interpretation of the shape of the flow curve is important. Patients with a urethral stricture have a plateau-shape or box-shaped curve. A Qmax of <10 mL/s with box-shaped uroflow curve is highly indicative of urethral stricture. In our study, stricture was defined as Qmax of <10 mL/s with box-shaped curve for all patients and preintervention and postintervention Qmax was calculated and compared in both the groups. IPSS was calculated in both the groups with meatal stenosis 12 as well as penile urethral stricture.

Another study by Mandal *et al*.[13] reported promising results of substitution urethroplasty using a bovine pericardial patch with a success rate of 89%, however, the success rate in ours was 82%. The average median pre-operative and post-operative Qmax in the study by Mandal *et al*[13] were 5 mL s^{-1} and 24 mL s^{-1}, respectively. Likewise in our study average mean pre-operative and post-operative Qmax was

6.8 mL/s and 16.4 mL/s, respectively. In our study, 4 patients were considered as surgical failure in comparison to one patient in a study by Mandal *et al*.[13] (Table 4). In comparison to buccal mucosal graft urethroplasty, substitution urethroplasty with ATEPP also shows good results. In a study by Sami Mahjoub Taha Awad *et al*.[14] (Table 4), their success rate with buccal mucosal graft urethroplasty was 90% with a 10% re-stricture rate. In our study success rate with ATEPP urethroplasty was 82% with an 18% failure rate. Another study by Spilotros *et al*.[15].

BXO involvement of the urethra can range from isolated strictures in glanular urethra to panurethral disease. The most severe inflammatory reaction is seen at the meatus and navicular fossa[16]. Ventral meatotomy, circumferential fasciocutaneous flaps of the prepuce and the penile skin, (including onlay urethroplasty using transverse island ventral penile skin flap), one stage and two stage repair using BMG are reconstructive options for the management of distal strictures[17]. Success with BMG as a urethral substitute will depend upon the vascularity of the bed. Glans penis has good blood supply and provides good vascularity to the buccal mucosal graft[18]. Following up with one patient was lost after six months. Thirty-two individuals required AUG due to clinically significant obstructive LUTS symptoms. Uroflow displayed an obstructive pattern in 21 patients, while it was normal in another patient. AUG was completed in both. In one patient, the AUG was normal, while in another, the AUG revealed sub-meatal stenosis. We contrasted our research with that of Anant kumar[19] and Ducket[20]. Four cases of pan urethral stricture and two cases of bulbar urethral stricture were observed. At a three to six month follow-up, failure was only observed in two cases. In order to more clearly define the outcome, our study needs to be followed up on. Our series included fewer patients and fewer follow-up months than Vito *et al*.[21].

Tacrolimus, which is recognised for its ability to modulate the immune system, significantly reduced inflammation and fibrosis linked to strictures caused by BXO. Inhibiting the immune response and, maybe, stopping the growth of strictures, the topical treatment targeted the localised disease. Improved clinical alleviation, including less obstructive voiding symptoms and an overall better quality of life, was also noted in patients. To further understand the efficacy and safety of topical tacrolimus in the long run, more studies with bigger cohorts are necessary. Furthermore, useful insights could be gleaned from comparisons with traditional treatments. Still, the results pave the path for novel urological treatments by revealing potential non-invasive methods of treating strictures caused by BXO.

CONCLUSION

The Qmax values showed a consistent decline from 28.8 ml/sec after catheter removal to 17.62 ml/sec at the 6th month follow up, indicating progressive urethral stricture due to BXO. Based on the findings from our study, there was a notable decline in peak flow and associated parameters following catheter removal and at subsequent follow-up periods. The peak flow decreased from 28.8 ml/sec after catheter removal to 17.62 ml/sec at the 6th month follow up. Similarly, average flow decreased from 19.75 ml/sec to 12.75 ml/sec and voided volume decreased from 278ml-283ml during the same period. In addition, the occurrence of side effects such as pruritis (8.8%) and rash (5.0%) was observed among the patients. These results suggest a significant decrease in peak flow values and associated parameters, indicating a potential progression of the main disease.

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