

# Comparative effect of intraurethral clobetasol and tacrolimus in lichen sclerosus-associated urethral stricture disease

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## Abstract

**Background:** Management of urethral stricture related to lichen sclerosus (LS) is now gradually changing from surgical to nonsurgical due to availability of anti-inflammatory agents such as corticosteroids and calcineurin inhibitors. We determined the clinical impact of these agents in such patients on outpatient department basis in terms of improvement in symptoms on International Prostate Symptom Score (IPSS), external skin appearance, and maximum urinary flow rate (Qmax).

**Materials and Methods:** Eighty patients of meatal stenosis and penile urethral stricture with histopathologically proven LS were divided into two groups, and clinical and predetermined parameters such as Qmax, IPSS, and changes in external appearance were compared between these groups after 3 months of topical and intraurethral application of clobetasol and tacrolimus with self-calibration.

**Results:** A significant intragroup difference was noted in IPSS ( $P < 0.001$ ) as well as Qmax ( $P < 0.001$ ); postintervention intergroup difference in IPSS was not significant ( $P = 0.94$ ) and however postintervention intergroup difference in Qmax was significant in favor of clobetasol ( $P = 0.007$ ). A significantly increased number of additional procedures were done in the group receiving intraurethral tacrolimus ( $P = 0.0473$ ) with significantly less number of skin complication in the group with topically applied clobetasol ( $P = 0.003$ ).

**Conclusion:** Though both clobetasol and tacrolimus, improved symptom score, Qmax and local external appearance yet topical and intra-urethral clobetasol application via urethral self calibration seems to be better option for lichen sclerosus related urethral stricture in terms cost and local complications.

**Keywords:** Clobetasol, International Prostate Symptom Score, lichen sclerosus, tacrolimus, urethral stricture, uroflowmetry

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## INTRODUCTION

Lichen sclerosus (LS) et Atrophicus or balanitis xerotica obliterans is one of the most important causes of urethral stricture. Genital LS has wide spectrum

of clinical presentation from insidious and chronic course with few early symptoms to aggressive form. Urethral involvement usually starts at the meatus and with progression may involve proximal urethra due to

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spongiofibrosis. The etiology of LS stricture disease is debatable.<sup>[1,2]</sup> In our study, the most common presenting complaint was decreased urinary flow and thin stream of urine. Symptom score was calculated for all patients using International Prostate Symptom Score (IPSS) to grade severity. Differential diagnosis of LS includes lichen planus, localized scleroderma, leukoplakia, vitiligo, and the cutaneous rash of Lyme disease.<sup>[3]</sup> The diagnosis of LS is usually clinical. When the clinical features are typical, histologic examination is not always essential.<sup>[3]</sup> Surgery (urethroplasty) is the main stay of treatment, but as every surgery, urethroplasty has its own associated complications. Many studies are evaluating the role of medical management of urethral stricture disease associated with LS with anti-inflammatory agents such as corticosteroid and calcineurin inhibitors; calcineurin inhibitors have less systemic immunosuppressive property but costlier than corticosteroid in long-term course.<sup>[3]</sup> There are many studies available in literature like Potts *et al.*<sup>[4]</sup> who described the benefit of intraurethral steroid with self-calibration twice a day for LS-related urethral stricture and Kim *et al.*<sup>[5]</sup> who described the benefit of topical tacrolimus for genital LS, but none is available comparing efficacy of both these agents. A large number of patients with urethral stricture follow-up on outpatient department (OPD) basis in our institution and available literature suggested the beneficial effect of intraurethral application of both clobetasol and tacrolimus. In view of this, we compared the efficacy of both these agents on OPD basis in terms of local appearance, symptomatic relief, improvement in urine flow pattern (by uroflowmetry), and improvement in IPSS.

## MATERIALS AND METHODS

This OPD-based prospective observational study was done for a period of 1 year from June 2020 to May 2021 in a tertiary health care center of India after obtaining institutional ethics clearance with null hypothesis that topical and intraurethral clobetasol is not effective as topical and intraurethral tacrolimus for LS-associated meatal stenosis and urethral stricture and alternate hypothesis that topical and intraurethral clobetasol is as effective as topical and intraurethral tacrolimus for for LS-associated meatal stenosis and urethral stricture. Total sample size was 80. Inclusion criteria were only male patients, age more than 18 years, patients with clinically and biopsy proven LS and with complaints of lower urinary tract symptoms and decreased flow on uroflowmetry (maximum flow rate <10 mL/s) and thin stream of urine, meatal stenosis, and

penile urethral strictures of variable length. Exclusion criteria were patients having urethral stricture without histopathologically proven LS, LS but no urethral stricture or meatal stenosis, upper tract changes and decreased renal functions, patients with penile growth, neurogenic bladder, bladder outlet obstruction secondary to prostatomegaly, and bladder neck stenosis.

After taking informed consent and applying inclusion and exclusion criteria, 80 patients were considered for the study. Of these 80 patients, 22 had diabetes mellitus, 15 were hypertensives, 44 were smokers, 6 patients were of rheumatoid arthritis, and 3 patients had connective tissue disorder. Of these, patients presenting with phimosis underwent circumcision before intervention and were included in the study. Patients were selected on chit basis with ratio 1:1 and were divided into two groups with 40 in Group I and 40 in Group II, respectively. Intervention done was topical application of clobetasol and tacrolimus as well as via self-calibration, respectively, in each group. Self-calibration (patients were advised to pass a 12/14 Fr Foley's catheter through external urethral meatus into penile urethra) was done for adequate drug application at stricture segment as well as to dilate the strictured segment and as a tool for follow-up evaluation. Group I received Ointment Clobetasol (0.05%) which was applied topically as well as with self-calibration twice daily for 12 weeks and Group II received Ointment Tacrolimus (0.03%) which was applied topical as well as with self-calibration twice daily for 12 weeks. Preintervention measures included detailed history, general examination and local examination of penis, IPSS, uroflowmetry with maximum flow rate (Qmax), and retrograde urethrogram (RGU). Urethroscopy was done in selected patients for definitive diagnosis of urethral stricture. Severity of stricture was assessed on the basis of IPSS, maximum flow rate, and stricture length >2 cm on preintervention RGU. All patients were followed up after 3 months and those who were not benefitted or symptoms remained same or deteriorated were subjected to surgical intervention depending on the length and nature of urethral stricture. The patient outcome was evaluated in terms of improvement in IPSS, local skin changes at glans and prepuce, change in uroflow pattern, and maximum urine flow rate and complications (if any). During the course of the study, five patients from Group I and eight patients from Group II lost to follow-up and so were excluded while analyzing the outcome. Final assessment was done for 35 patients in Group I and 32 patients in Group II. Elective suprapubic cystostomy was done in 21 patients with preintervention poor IPSS, i.e. 11 patients in Group I and ten patients in Group II.

All data of patients were entered into Microsoft Excel spreadsheet. The data were analyzed using IBM-SPSS software (IBM Corp, Armonk, NY, USA version 26, 2019). Numerical variables were summarized as mean and standard deviation and compared between the two groups with unpaired *t*-test. Categorical variables were summarized as counts and compared between the two groups by Pearson's Chi-square test. For these comparisons,  $P < 0.05$  was considered statistically significant.

## RESULTS

The most common age group affected was 41–50 years, followed by 31–40 and 51–60 years age groups, respectively. The mean age in both the groups was similar,  $44.4571 \pm 10.3337$  years in Group I and  $44.2813 \pm 10.8427$  years in Group II. Pre- and postintervention intragroup change in Qmax in both the groups was significant ( $P < 0.001$ ) [Table 1]. Pre- and postintervention intragroup change in IPSS in both the groups was significant ( $P < 0.001$ ) [Table 2]. Postintervention intergroup change in Qmax ( $P = 0.007$ ) was significant [Table 3] in favor of clobetasol, whereas postintervention intergroup change in IPSS ( $P = 0.94$ ) score was not significant [Table 3]. The need for additional procedure like meatal dilatation and urethral endodilatation was more in Group II ( $P = 0.047$ ) [Table 4]. The only complications encountered during the study were local skin irritation, itching, and redness of skin. No systemic and major adverse reactions were noted. In Group I, two patients had itching and skin irritation and two patients had redness of the skin. In Group II, ten patients had skin itching as complication, while three patients had redness of skin and one patient had mild headache. Thus, there were more complications in Group II as compared to Group I and it was significant ( $P = 0.003$ ). Both the groups had improvement in local skin changes after intervention. Twelve patients (five in Group I and seven in Group II) had recurrent urethral stricture (on RGU) after 3 months and were subjected to surgical treatment. Out of these 12 patients with recurrent urethral stricture, six were diabetic patients and two patients had rheumatoid arthritis and the rest four had no associated comorbidity.

## DISCUSSION

Genital LS being a chronic progressive inflammatory process leads to stricture disease which impairs urinary flow, affects psychosexual function, and sometimes leads to social detachment. Although it can affect any age group, it is more common in the third to fifth decade. Similarly, in

**Table 1: Intragroup change in maximum flow rate at 3 months**

Group	Qmax	n	Mean±SD	P
I	Preintervention	35	7.51±1.52	<0.001
	Postintervention	35	12.57±2.98	
II	Preintervention	32	8.68±2.09	<0.001
	Postintervention	32	12.61±2.14	

Qmax: Maximum flow rate, SD: Standard deviation

**Table 2: Intragroup change in International Prostate Symptom Score at 3 months**

Group	IPSS	n	Mean±SD	P
I	Preintervention	35	19.28±6.02	<0.001
	Postintervention	35	11.94±6.58	
II	Preintervention	32	17.50±5.29	<0.001
	Postintervention	32	12.06±6.18	

IPSS: International Prostate Symptom Score, SD: Standard deviation

**Table 3: Postintervention intergroup change in maximum flow rate and International Prostate Symptom Score**

Parameter	Group	Number of patients (n)	Mean±SD	P
Postintervention change in Qmax	I	35	5.06±1.86	0.007
	II	32	3.93±1.42	
Postintervention change in IPSS	I	35	11.94±6.58	0.94
	II	32	12.06±6.18	

IPSS: International Prostate Symptom Score, SD: Standard deviation, Qmax: Maximum flow rate

**Table 4: Distribution of additional procedures in both groups during study period**

Additional procedures	Group I	Group II	P
Urethral endodilatation	0	4	0.047
Meatal dilatation	1	2	
Meatotomy	0	2	
No procedure	34	24	

our study, the majority of patients were in the age group of 30–50 years.

Biopsy can be done to rule out squamous cell carcinoma (SCC) in male patients with LS associated urethral stricture, however progression to SCC is definitely proven in female patients with genital LS.<sup>[6]</sup> In our study, genital skin biopsy was done in all cases to prove LS.

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.<sup>[7]</sup> A Qmax of <15 mL/s 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.<sup>[8]</sup> 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<sup>[9]</sup> as well as penile urethral stricture.

The treatment objectives in male patients with genital LS include unobstructed voiding, painless intercourse, and adequate external appearance. Most patients are satisfied with unobstructed voiding and painless intercourse.

Management for LS ranges from medical to surgical, depending on severity and location of disease, patient factors, and response of previous treatments. Surgery is preferred in long segment urethral stricture with varying degree of urethral involvement. In urethral stricture due to LS, surgeries like single stage or staged urethroplasty<sup>[10]</sup> are often required. Though surgery provides the best results in strictures associated to LS, surgical complications do occur like harvesting site complications,<sup>[11]</sup> erectile dysfunction,<sup>[12,13]</sup> decreased penile length and chordee. Recurrences after surgery are also common in LS associated stricture, even with buccal mucosal grafts<sup>[14,15]</sup> and/or with local flaps.<sup>[16,17]</sup> Urethroplasty has preoperative limiting factors too, like age related co-morbidities, health status and anatomical factors like inability to achieve lithotomy position, rendering urethroplasty unamenable in such patients.

Self-calibration is one of the most commonly suggested conservative treatments for stricture disease.<sup>[18]</sup> The frequency of self-calibration in this study was twice a day for 3 months.

LS being an inflammatory condition can be treated with anti-inflammatory agents like corticosteroids.<sup>[19,20]</sup> Topical corticosteroids in various preparations like clobetasol propionate (0.05%), betamethasone (0.05%), mometasone (0.1%), and hydrocortisone (2.5%–10%) improve symptoms and external appearance of disease<sup>[21]</sup> as well as histological feature.<sup>[22]</sup>

In our study, clobetasol propionate 0.05% was used. Potential side effects of corticosteroids include skin atrophy, adrenal suppression, and skin irritation.<sup>[23]</sup> However, in our study, four patients were noted to have local skin complications, namely skin irritation, redness of skin, and itching with majority with improved external appearance [Figure 1a and b].

LS of glans has also been successfully managed with topical calcineurin inhibitors (TCIs) like tacrolimus<sup>[24]</sup> which have



**Figure 1:** (a) Glans external appearance before application of topical clobetasol in a 34 years male. (b) improved glans external appearance after topical clobetasol in a 34 years male

significant anti-inflammatory activity, immunomodulatory effects, and a low systemic immunosuppressive potential. TCIs are considerably more costly than topical corticosteroids when considering for chronic course of LS. Increased risk of malignant transformation of genital LS by long-term use of TCIs is still a significant concern.<sup>[25,26]</sup>

Various studies on male genital LS have shown positive impact of topical corticosteroids and TCIs individually; however, ours is the first such study comparing both the agents in male genital LS patients.

Potts *et al.*<sup>[4]</sup> in their study on self-calibration using clobetasol in 28 patients of LS with urethral stricture, with the most common age affected being patients in their fifties, showed improvement in 25 patients in terms of decreased need for urethroplasty and decreased frequency of self-calibration. Similarly, in our study, 35 patients of LS with anterior urethral stricture treated with topical clobetasol via self-calibration showed decreased need for additional procedure (one patient underwent meatal dilatation) during the study and only five patients of these underwent urethroplasty after 3 months because of patients difficulty to continue self-calibration [Table 4].

Hayden *et al.*<sup>[27]</sup> in their study on 42 patients with LS-related urethral stricture disease treated with topical corticosteroid showed a significant improvement in the median IPSS from 12 to 8 during median follow-up of 8.4 months. In our study, on 35 patients receiving topical clobetasol as well as via self-calibration, IPSS significantly improved from 19 to 12 during 3 months of follow-up [Tables 2 and 3].

Majority of patients had symptomatic relief and improved urinary flow rate, in study by Mallick *et al.*<sup>[28]</sup> when treated with topical Tacrolimus. Similarly, in our study too, on 32 subjects with LS with anterior urethral stricture,

majority of patients had improved IPSS [Tables 2 and 3] with improved Qmax [Tables 1 and 3] after application of topical and intraurethral tacrolimus after 3 months of follow-up. However, seven patients (out of 32) had recurrent urethral stricture on RGU and were subjected to surgical intervention.

A study on 20 male patients of LS with anterior urethral strictures by Dey *et al.*<sup>[29]</sup> explained the positive effect of tacrolimus 0.03% on urethral strictures. In our study, tacrolimus 0.03% was used. Our study also showed positive results in terms of improvement in IPSS [Tables 2 and 3] and Qmax [Tables 1 and 3] and external appearance [Figure 2a and b].

Improvement in IPSS as well as in external appearance was more with topical clobetasol as compared to topical tacrolimus [Figures 1a, b and 2a, b] as per our study [Tables 2 and 3]. Our study showed that less number of minor procedures (endodilatation, meatal dilatation, and meatotomy) were required in patients using intraurethral clobetasol in comparison to those using tacrolimus [Table 4]. Although literature suggest less skin-related complications when using TCIs, we found more skin-related complications when using topical tacrolimus (14 patients out of 32) as compared to topical clobetasol (four patients out of 35) in our study. There were no major complications during the usage of both these agents; this however might be due to short duration of usage of these agents for 3 months. Recurrent urethral strictures were more common in patients with diabetes mellitus (six patients out of 12).

## CONCLUSION

We found intraurethral instillation of Clobetasol or Tacrolimus via self calibration improve skin appearance, symptoms and urinary flow in LS related urethral strictures. Topical Clobetasol being less costly and with fewer local



**Figure 2:** (a) Glans and prepuce external appearance before application of topical Tacrolimus in a 53 years male. (b) improved glans and prepuce external appearance after application of topical Tacrolimus in a 53 years male

complications seems to be better option for LS induced stricture than topical Tacrolimus.

Observational nature, less number of patients, and limited duration of study were limitations of this study.

## Main Points

According to our study:

- Both intraurethral clobetasol and tacrolimus improve IPSS and urinary flow rate in patients with LS-associated urethral stricture
- Both clobetasol and tacrolimus when topically applied improved external appearance of glans and prepuce in patients with LS
- Intraurethral clobetasol is better than intraurethral tacrolimus in improving IPSS and urinary flow rate in patients with LS-associated urethral stricture
- Although both intraurethral clobetasol and tacrolimus had minor complications, intraurethral tacrolimus had more complications than intraurethral clobetasol.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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