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# Role of Phosphodiesterase Inhibitors in Improving Urodynamic Parameters in Patients with Spinal Cord Injury: A Preliminary Report

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## Abstract

**Objective** To analyze role of phosphodiesterase 5 (PDE5) inhibitors on urodynamic parameters in patients with suprasacral spinal cord injury.

**Materials and Methods** This was a prospective observational hospital-based study conducted on a cohort of patients, aged between 18 and 65 years with suprasacral spinal cord injury, who were registered in Department of Neurosurgery/Urology. Cutoff period since injury was 2 years. After taking consent, baseline urodynamic study was performed, which was repeated 2 hours after taking single oral dose of 20 mg tadalafil. Urodynamic parameters such as maximum detrusor filling/voiding pressures, maximum bladder capacity, and bladder compliance before and after taking drug were compared for final results and conclusion.

**Results** Following administration of 20 mg of tadalafil, maximum bladder capacity in mL showed statistically significant improvement from 268.39 ± 130.0 to 298.55 ± 112.0.($p < 0.05$). Bladder compliance improved from 18.68 ± 6.4 to 20.25 ± 7.5 mL/cm $H_2O$ ($p > 0.05$). Maximum detrusor filling pressure improved from 36.03 ± 20.54 to 32.90 ± 16.47 cm $H_2O$ ($p > 0.05$). Maximum detrusor voiding pressure improved from 64.65 ± 33.19 to 58.13 ± 20.7 cm $H_2O$ (0 > 0.05). In patients with injury above D6 spinal cord level, statistically significant improvement was seen in maximum bladder capacity and bladder compliance after 2 hours of single oral dose of tadalafil ($p < 0.05$).

**Conclusion** Our study suggests a positive role of PDE inhibitors in improving urodynamic parameters in patients with suprasacral spinal cord injury with improvement in parameters such as bladder capacity, detrusor pressures, and bladder compliance. Because this is a small study group, more studies such as this are required to reach to final conclusion.

**Keywords**
- suprasacral spinal cord injury
- phosphodiesterase 5 inhibitors
- lower urinary tract symptoms
- urodynamic parameters

## Introduction

Spinal cord injury (SCI) is one of the most debilitating and devastating injuries to humans. It occurs throughout the world with an annual incidence of 15 to 40 cases per million.[1] The occurrence of SCI is highest among young persons in the 16 to 30 age group.[2] The most common mode of injury is road traffic accidents. In the Indian subcontinent, every year there are approximately 20,000 new cases of SCI in trauma victims,[3] with main mode of injury being fall from height.

The sacral spinal cord begins at about spinal column level T12 to L1. Injury above T12 to L1 qualifies as suprasacral SCI

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(SSSCI). The patients with SSSCI often develop lower urinary tract symptoms (LUTS). Failure to properly address the LUTS associated with SSSCI can lead to significant morbidity and mortality.[4] In the past few decades, survival rates have considerably improved in SCI patients,[5] and hence it has become increasingly important to give these patients better quality of life.

Urodynamic study is gold standard for evaluation of urinary tract dysfunction in SCI patients as well as to establish effectiveness of new drugs.[6] Efficacy of phosphodiesterase 5 (PDE5) inhibitors in amelioration of LUTS has gained attention in recent years. In our knowledge, few studies[7,8] done till date have shown that PDE5 inhibitors positively affect urodynamic parameters in SCI men. These studies included only subjects of the male sex, but in our study we included patients from both sexes as we assumed that PDE5 receptors would be present on detrusor muscles and on bladder outflow area equally in both sexes, so females should also be evaluated for the actions of PDE5 inhibitors.

## Materials and Methods

This was a prospective observational hospital-based study carried on a cohort of 31 patients suffering from SSSCI with LUTS in the age group 18 to 65 years who came for follow-up in the Department of Neurosurgery/Urology from November 2012 to October 2014 in SKIMS, Soura, Srinagar. Institutional ethical clearance was sought before undertaking the study. After taking proper consent, urodynamic study was performed in these patients and repeated 2 hours after taking single oral dose of 20 mg tadalafil. Urodynamics were performed on patient in sitting position, zeroing of device done every time at the start of procedure. We used normal saline at the rate of 15 mL/s at temperature of 25°C as filling fluid. Urodynamic parameters such as maximum detrusor filling pressure (DFP) in cm $H_2O$, maximum detrusor voiding pressure (DVP) in cm $H_2O$, maximum bladder capacity in mL, and bladder compliance in mL/cm $H_2O$ before and after tadalafil administration were specifically recorded and analyzed. Patients with chronic renal and liver disease, diabetes mellitus, proven urinary tract infection, history of pelvic surgery, and absolute contraindications to tadalafil were excluded from the study.

In patients with a history of autonomic dysreflexia or whose neurologic level of injury was D6 or above, blood pressure was monitored during testing. We used Netherlands-made medication measurement systems (MMS) (medication measurement systems) LIBRA+ 3T urodynamic system for urodynamic study. Data were analyzed by MMS software ver.7.3t. Data before and after taking the drug were compared for final results and conclusion. *p*-Value of < 0.05 was considered statistically significant.

## Results

Thirty-one patients were included in our study. Mean age of the study group was 34.5 ± 12.6 years, with the youngest patient being 18 years old and oldest patient being 62 years old. Twenty-five patients were males and six were females. Twelve patients suffered injury at and above D6 spinal cord level and 19 below D6 spinal cord level. Out of 31 patients, 10 had complete injury and 21 had incomplete injury. Severity of injury was calculated according to ASIA (American Spinal Injury Association) scale. Type A was labeled as complete injury and types B and C as incomplete injury, as shown in ►**Table 1**.

Maximum filling detrusor pressure in cm $H_2O$ before administration of drug was 36.03 ± 20.54. It improved after taking drug to 32.90 ±16.47, although results were not statistically significant ($p > 0.05$).

Maximum voiding detrusor pressure in cm $H_2O$ before taking drug was 64.65 ± 33.19. It improved to 58.13± 20.7; however, *p*-value in this case was > 0.05.

Maximum bladder capacity in mL showed a statistically significant improvement after single 20-mg dose of tadalafil ($p < 0.05$) as shown in ►**Table 2**. The results for males and females are shown in ►**Tables 3** and **4**, respectively. In males,

**Table 1** Demographic profile of patients

| | |
|---|---|
| Number of patients | 31 |
| Mean age | 34.52 y |
| Sex distribution | |
| Male | 25 |
| Female | 6 |
| Level of injury | |
| At or above D6 | 12 |
| Below D6 | 19 |
| Severity of injury | |
| Complete | 10 |
| Incomplete | 12 |

**Table 2** Pre- and post-tadalafil values in whole study group

| Variable | Pre-tadalafil (mean ± SD) | Post-tadalafil (mean ± SD) | *p*-Value |
|---|---|---|---|
| DFP | 36.03 ± 20.547 | 32.90 ± 16.477 | 0.289 |
| DVP | 64.65 ± 33.199 | 58.13 ± 20.760 | 0.416 |
| CAPACITY | 268.39 ± 130.036 | 298.55 ± 112.027 | 0.049* |
| COMPLIANCE | 18.68 ± 6.414 | 20.35 ± 7.50 | 0.189 |

Abbreviation: SD, standard deviation.
Note: DFP = maximum detrusor filling pressure (cm $H_2O$); DVP = maximum detrusor voiding pressure (cm $H_2O$); CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (mL/cm $H_2O$).
*Statistically significant value.

**Table 3** Pre- and post-tadalafil values in males

| Variable | Pre-tadalafil (mean ± SD) | Post-tadalafil (mean ± SD) | *p*-Value |
|---|---|---|---|
| DFP | 38.32 ± 21.311 | 33.56 ± 17.054 | 0.112 |
| DVP | 66.76 ± 35.226 | 55.84 ± 21.33 | 0.143 |
| CAPACITY | 246.32 ± 120.123 | 286.36 ± 107.06 | 0.020* |
| COMPLIANCE | 18.69 ± 6.02 | 22.833 ± 11.01 | 0.243 |

Abbreviation: SD, standard deviation.
Note: DFP = maximum detrusor filling pressure (cm $H_2O$); DVP = maximum detrusor voiding pressure (cm $H_2O$); CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (mL/cm $H_2O$).
*Statistically significant value.

**Table 4** Pre- and post-tadalafil values in females

| Variable | Pre-tadalafil (mean ± SD) | Post-tadalafil (mean ± SD) | *p*-Value |
|---|---|---|---|
| DFP | 26.50 ± 14.76 | 30.17 ± 14.892 | 0.273 |
| DVP | 55.83 ± 23.267 | 67.67 ± 16.281 | 0.058 |
| CAPACITY | 360.33 ± 140.05 | 349.33 ± 128.20 | 0.752 |
| COMPLIANCE | 18.66 ± 8.45 | 22.83 ± 11.01 | 0.136 |

Abbreviation: SD, standard deviation.
Note: DFP = maximum detrusor filling pressure (cm $H_2O$); DVP = maximum detrusor voiding pressure (cm $H_2O$); CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (mL/cm $H_2O$).

**Table 5** Pre- and post-tadalafil values in patients with injury above D6

| Variable | Pre-tadalafil (mean ± SD) | Post-tadalafil (mean ± SD) | *p*-Value |
|---|---|---|---|
| DFP | 33.92 ± 17.85 | 34.50 ± 16.98 | 0.683 |
| DVP | 58.92 ± 25.86 | 59.08 ± 26.548 | 0.969 |
| CAPACITY | 263.33 ± 123.79 | 302.67 ± 123.445 | 0.015* |
| COMPLIANCE | 17.01 ± 5.63 | 21.733 ± 6.73 | 0.017* |

Abbreviation: SD, standard deviation.
Note: DFP = maximum detrusor filling pressure (cm $H_2O$); DVP = maximum detrusor voiding pressure (cm $H_2O$); CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (mL/cm $H_2O$).
*Statistically significant value.

maximum bladder capacity in mL showed a statistically significant improvement after single 20-mg dose of tadalafil, but in female patients we did not observe any statistically significant improvement in any of these parameters.

On stratification of data, we observed that patients with injury above D6 level showed a statistically significant improvement in bladder compliance from 17.01 ± 5.63 to 21.73 ± 6.7 ($p < 0.05$) and bladder capacity from 263.33 ±123.7 to 302.67 ± 123.44 ($p < 0.05$), as shown in ►**Table 5**.

## Discussion

Urogenital diseases have been reported as one of the primary causes of death in SCI patients.[9-12] The low compliance neurogenic bladder due to SCI clinically receives special attention as it causes deterioration of renal function.[13,14] SSSCI patients often develop LUTS that manifests as detrusor areflexia and urine retention initially followed by overactive detrusor and detrusor-sphincter dyssynergia (DSD). The recovery of lower urinary tract function occurs weeks later, but the voiding function deteriorates and manifests by hyperreflexia and incomplete voiding secondary to DSD during voiding[15] and consequent renal damage, if untreated. Urodynamic study is an important part of the evaluation in SCI patients with LUTS and can provide useful clinical information about the function of the urinary bladder, sphincteric mechanism, and voiding pattern.[16]

Overactive bladder is the underlying cause of LUTS in SSSCI patients, the impact of PDE5 inhibitors on improving of SCI-induced LUTS seems valid.[17] PDE5 receptors are normally present in the detrusor muscles, bladder neck, and urethra. Human bladder expresses the *PDE5* gene on quantitative reverse transcriptase-polymerase chain reaction and protein on immunohistochemistry and Western blot as well as PDE5 enzymatic activity.[18,19] The cyclic guanosine monophosphate (cGMP) represents an important mediator in the control of the outflow region (bladder, urethra). Use of PDE inhibitors such as sildenafil, tadalafil, vardenafil, avanafil, or udenafil known to restrain the degradation of the second messenger cGMP can produce significant relaxation of the aforementioned tissues offering great opportunities in the treatment of lower urinary tract dysfunction.[20] Major mechanisms in SCI patients that contribute to LUTS include reduced nitric oxide/cGMP signaling, increased RhoA kinase pathway activity, autonomic over activity, increased bladder afferent activity, and pelvic ischemia.[21] The probable mechanism

by which PDE5 inhibitors decrease these LUTS is that nitric oxide enters the smooth muscles and stimulates guanosinecyclase that converts cyclic guanosine three phosphate to cGMP, which in turn decreases intracellular calcium concentration and consequently causes muscle relaxation.[21,22] Latest evidence on pathophysiology of LUTS has provided the rationale for use of PDE5 for (1) improvement of lower urinary tract oxygenation, (2) negative regulation of proliferation and trans-differentiation of lower urinary tract stroma,(3) reduction in bladder afferent nerve activity, and (4) downregulation of prostate inflammation

Tadalafil and other PDE5 inhibitors have demonstrated beneficial effects on smooth muscle relaxation, endothelial cell proliferation, nerve activity, and tissue perfusion that may impact LUTS in men.[21] A 20-mg once-daily dose of PDE5 inhibitor such as tadalafil is well tolerated and has shown clinically meaningful and statistically significant efficacy in men with benign prostatic hyperplasia (BPH) and LUTS. Tadalafil, the drug we used in our study, has half-life of 17.5 hours. Peak plasma concentration is reached within 2 hours, with steady-state plasma concentrations achieved after 5 days of once-daily dosing.[23] Tadalafil 20 mg is an effective and well-tolerated treatment for erectile dysfunction that has a period of responsiveness of up to 36 hours.[24]

Few studies have been conducted so far that have demonstrated the effect of PDE5 inhibitors on SCI patients. One study[8] demonstrated that a single 20 mg vardenafil administration allows significant improvement in urodynamic parameters, including maximum detrusor pressure (MDP), maximum cystometric capacity (MCC), and detrusor over activity volume (DVO) in 25 male patients. Placebo administration did not affect urodynamic parameters in these patients. In seven SCI patients above D6, they observed the most significant improvement in the evaluated urodynamic items, including MDP ($p = 0.039$), MCC ($p = 0.004$), and DVO ($p = 0.003$). Another study[7] conducted on 20 male patients showed that following administration of 20 mg oral tadalafil, there was an increase in the bladder compliance, bladder capacity, maximum voiding detrusor pressure, and maximum detrusor filling pressure.

We conducted our study on 31 patients and included both sexes unlike the previous studies,[7,8] which were confined only to male patients. In our study, mean bladder capacity in mL showed a statistically significant improvement after single 20-mg dose of tadalafil, especially in male patients. This is an important finding and suggests a positive role of PDE inhibitors in improving bladder capacity in SCI patients. This increase in maximum bladder capacity will decrease daily urinary frequency and incontinence, leading to an extra period of urinary storage. This may increase the quality of life in these patients. Our assumption was that because PDE5 receptors are present on smooth muscles of the bladder neck, it should be equally effective in both sexes. However, our results failed to demonstrate any positive effect in female patients. Because of the small sample size of female patients in our study, we suggest further work be done in this population group with larger sample size to draw final conclusions.

We observed that the patients with injury above D6 level showed statistically significant improvement in bladder compliance and bladder capacity ($p < 0.05$). Increase in bladder compliance will help patients in accommodating more urine at same detrusor pressures, which will lead to a lessening of urinary leakage leading to physical and social well-being. In patients with injury below D6, no statistically significant change in urodynamic parameters could be established. This observation points out the further need of research in this field.

Limitation of our study includes limited sample size in women population and relatively old urodynamic machine. However, to the best of our knowledge, very limited literature is available on the topic and there is need to research in this field to explore new possibilities and use of these drugs in SCI patients.

## Conclusion

Our study has been an important step forward in finding the role of PDE inhibitors in SCI patients. Improvement in bladder capacity and compliance will allow patients to store more urine at same pressures, decreasing daily urinary frequency and avoiding leakage and hence providing a better quality of life. However, we recommend further work should be done on the role of PDE inhibitors in improvement of urodynamic parameters in SCI patients so that these drugs can become a future treatment modality in these patients.

**Source(s) of Support**
None.

**Conflicts of Interests**
None.

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