

## TO STUDY THE EFFECT OF TADALAFIL IN IMPROVING URODYNAMIC PARAMETERS IN SPINAL CORD INJURY PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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### ABSTRACT

**Objectives:** The aim of the study was to compare the effect of single dose Tadalafil 20 mg 2 h after administration on Urodynamic study (UDS) parameters and comparison with calcium+vit-D3 (control) in spinal cord injury (SCI).

**Methods:** Sixty-six SCI individuals with lower urinary tract symptoms (LUTS) and upper motor neuron bladder were randomized into Tadalafil group (n=33) and calcium+vitD3 group (n=33). UDS was done and parameters (maximum detrusor filling pressure [MDFP], maximum bladder capacity, and bladder compliance) were recorded at baseline and 2 h after administration of respective drugs in both groups and comparison was done.

**Results:** Statistically significant improvement in mean MDFP from 24.42±6.75 to 21.12±5.72 cm H<sub>2</sub>O (p < 0.001), mean maximum bladder capacity from 263.94±108.48 to 287.67±112.71 mL (p<0.001), and mean bladder compliance from 11.07±4.31 to 13.94±5.13 mL/cm H<sub>2</sub>O (p<0.001) was observed in Tadalafil group whereas in calcium+vit-D3 group, no significant improvement was observed. When we compared difference of mean of MDFP, bladder capacity, and bladder compliance between Tadalafil and calcium+vitD3 group, significant improvement (p<0.001) in Tadalafil group was noted as compared to calcium+vitD3 group.

**Conclusions:** Single dose of oral Tadalafil 20 mg has shown significant improvement in MDFP, bladder capacity, and bladder compliance in SCI individuals with LUTS as compared to control.

**Keywords:** Urodynamics, Tadalafil, Spinal cord injury.

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### INTRODUCTION

Neurogenic bladder dysfunction is one of the well-known complications following spinal cord injury (SCI) and seen in 80% of individuals [1]. It will lead to urinary tract infection, incontinence, nephrolithiasis, renal failure and bladder cancer, and poor quality of life [2]. It is the most common cause of hospitalization as well as morbidity and mortality in acute as well as in chronic SCI.

Urological evaluation in SCI includes history, voiding diary, physical and neurological examination, microscopic urine analysis and culture and antibiotic sensitivity, creatinine clearance, urodynamic study (UDS), and radiography of urinary tract. UDS with pressure flow studies diagnose underlying causes of lower urinary tract dysfunction and information acquired can be used to formulate treatment strategies.

Management of bladder dysfunction depends on UDS finding along with neurologic examination. Main goal for bladder management includes preserving upper urinary tracts, minimizing lower urinary tract complication and using appropriate methods for emptying bladder thus achieving dryness. Conservative management is routinely advocated which includes clean intermittent catheterization, indwelling urinary catheter, suprapubic catheterization, and various drugs to improve bladder and sphincter functions like antimuscarinic drugs, beta-3 agonists, alpha-blockers, imipramine, botulinum toxin, and phosphodiesterase 5 (PDE5) inhibitors.

Tadalafil increases blood perfusion to the pelvic area, causes smooth muscle relaxation, and contributes to the improvement of lower urinary tract symptoms (LUTS) [3]. Tadalafil is a potent PDE5I and attained peak concentration in about 2 h, and it has a long elimination half-life of approx 18 h [4,5].

To the best of our knowledge, only a few studies have been done till date and shown PDE5 inhibitors have positive influence on UDS parameters in SCI individuals. The objective of present study was to observe the effect of single dose Tadalafil 20 mg on UDS parameters in SCI after 2 h of administration compared to calcium+vitD3 (control).

### METHODS

The SCI individuals with supra sacral lesion and LUTS between age group of 18–65 years, in the indoor patient department of physical medicine and rehabilitation department of Sawai Man Singh Hospital, Jaipur, giving written and informed consent were taken between December 2022 and March 2023.

Persons with diagnosed renal, liver, cardiovascular diseases, diabetes mellitus, urinary tract infection, any anatomical abnormalities, history of major pelvic surgery, for example, prostatectomy, augmentation cystoplasty or colectomy, people with spinal shock, lower motor neuron type and continent bladder, history of allergy to Tadalafil and calcium+vitD3 and usage of drugs that have contraindication for PDE5 inhibitors administration were considered as exclusion criteria.

The present study was approved by ethics committee of SMS hospital with reference number 981/MC/EC/2021 dated October 30, 2021, which is in accordance with the declaration of HELINSKI.

This was an interventional comparative randomized control trial. All the individuals were explained about the nature and purpose of the study, written informed consent was obtained, all required demographic data was recorded. A detailed history was obtained from the individuals followed by complete neurological and urological examination was done.

Sample size was calculated at 80% study power and alpha error of 0.05 assuming standard deviation of 122.027 cc in post-treatment group and mean difference of 80 cc in bladder capacity between the groups, 30 patients in each group were required as sample size which was further rounded off to 33 patients in each group as final sample size for the present study expecting 10% dropouts/loss to follow up/attrition. Sixty-six individuals of SCI with LUTS who satisfied study inclusion criteria were recruited and randomized by computer-generated randomization table equally in two groups, Tadalafil group (n=33) and calcium+vitD3 group (n=33). The random allocation sequence was concealed from the person who recruited and enrolled participants.

UDS was performed at SMS Medical College using Laborie UDS -94-bt machine with person in lithotomy position in a room with controlled temperature under proper antimicrobial prophylaxis. The device was calibrated at zero every time before starting the procedure. First, individual bladder was emptied by a K-91 catheter along with lignocaine jelly (2%); then, a double lumen 7Fr catheter was inserted into bladder through urethra to measure intravesical pressure and 10Fr rectal catheter was inserted through anus for intra-abdominal pressure. EMG electrodes were placed in a proper position and all the channels were connected to the UDS machine. Person's vitals were monitored by multipara monitor to avoid untoward conditions such as autonomic dysreflexia. Normal saline was instilled into the bladder via double lumen 7Fr catheter at the rate of 20–30 mL/min. UDS parameters: MDFP in cm H<sub>2</sub>O, maximum bladder capacity in mL, and bladder compliance in mL/cm H<sub>2</sub>O were recorded at first sensation, first desire, strong desire, capacity/leaking, cough, and permission to void as per individual medical condition. After baseline UDS assessment, 20 mg Tadalafil in case group and 500 mg calcium + 250 I.U Vitamin D3 was given in control group and repeat UDS assessment was done.

#### Outcome measures

The following UDS parameters were evaluated at baseline and 2 h later drug administration for both Tadalafil and control group.

1. Maximum detrusor filling pressure (MDFP)
2. Maximum bladder capacity
3. Bladder compliance.

#### Statistical analysis

Statistical analysis was performed; categorical variables were expressed as frequency and percentage and analyzed using a Chi-square test for comparison between the two groups. Continuous variables were expressed as mean and standard deviation and analyzed using independent sample t-test for comparison between the two groups. Paired t-test was used for before and after comparison.  $p < 0.05$  was taken as statistically significant.

#### Statement of ethics

We certify that all applicable institutional and government regulations concerning the ethical use of human volunteers were followed during this research. Trial was registered Prospectively at Clinical Trials Registry India CTRI/2022/12/047913 on December 06, 2022.

## RESULTS AND DISCUSSION

A total of 112 patients with SCI having LUTS were screened and out of them 46 were excluded as they did not meet inclusion criteria or declined to participate and remaining 66 eligible participants were assigned either to control group or to intervention group according to computer randomization schedule (Fig. 1). Both the groups were comparable at baseline.

In this study, mean age of Tadalafil group was  $36.48 \pm 12.36$  years and in Calcium+vitd3 group was  $35.70 \pm 10.68$  years. This difference of mean age in both the groups was statistically non-significant and the groups were comparable ( $p = 0.139$ ). Maximum patients were in between 18 and 34 years of age group in both of groups. Duration of SCI in Tadalafil group was  $12.27 \pm 9.69$  and in calcium+vitD3 group was  $19.39 \pm 25.94$  months, and it was not significant ( $p = 0.144$ ) and both the

group were comparable and the level of injury in most of the patient was dorsal spine injury, followed by cervical spine and lumbar spine injury. Patients with complete spinal injury were more as compare to incomplete spinal cord injury in both the groups (Table 1).

In the present study after giving Tadalafil 20 mg, mean MDFP was improved to  $21.12 \pm 5.72$  cm H<sub>2</sub>O from  $24.42 \pm 6.75$  cm H<sub>2</sub>O, bladder capacity was improved to  $287.67 \pm 112.71$  mL from  $263.94 \pm 108.48$  mL and bladder compliance was improved to  $13.94 \pm 5.13$  mL/cm H<sub>2</sub>O from  $11.07 \pm 4.31$  mL/cm H<sub>2</sub>O at baseline. Tadalafil significantly decreased MDFP, increased maximal bladder capacity and compliance while control group had shown no significant improvement (Tables 2 and 3). When we compared difference of mean of MDFP, bladder capacity and bladder compliance between Tadalafil and calcium+vitD3 group, significant improvement ( $p < 0.001$ ) in Tadalafil group was noted as compared to calcium+vitD3 group (Table 4).

Neurogenic bladder is the most common and annihilative complication among SCI sequelae that results in reduced quality of life. It has varied presentation as flaccid bladder with low pressure and high compliance, spastic bladder with high pressures and low bladder compliance due to detrusor overactivity (DO) or mixed bladder pattern. The high bladder pressures when combined with detrusor sphincter dyssynergia can lead to upper tract deterioration [6]. Bladder-filling sensation is also lost in complete SCI individuals. UDS plays an important role in the assessment of the bladder, sphincters, and urethra work to store and release urine [7].

PDE5 gene and protein are expressed in the human bladder, where they represent more than 70% of all cyclic guanosine monophosphate metabolizing activity [8].

Nitric oxide activates the soluble Guanylyl cyclase that produces cGMP from GTP, cGMP is secondary messenger and it in downstream activates Protein Kinase G which phosphorylates the IP3 receptor thus inhibiting IP3-mediated release of calcium and inactivates voltage-gated calcium channels. The overall effect of this process is a decrease in the intracellular calcium producing smooth muscle relaxation.

Major mechanisms in SCI persons that contribute to LUTS include reduced nitric oxide/cGMP signaling, increased Rho A kinase pathway activity, autonomic over activity, increased bladder afferent activity, and pelvic ischemia [9].

Tadalafil causes smooth muscle relaxation, improved nerve activity, proliferation of endothelial cell, and increased tissue perfusion by improving lower urinary tract oxygenation, negative regulation of proliferation and trans-differentiation of lower urinary tract stroma, decrease in bladder afferent nerve activity and down-regulation of prostate inflammation.

We reviewed the literature and found only a few studies in support of clinical use of PDE5 inhibitors in improving LUTS on urodynamic parameters in SCI individuals. Furthermore, there are studies which support clinical use of PDE5 inhibitors in improving LUTS in benign prostatic hyperplasia.

Forgue *et al.* [4] reported that Tadalafil is absorbed rapidly with C max ( $378 \mu\text{g/L}$  for 20 mg) at 2 h independent of BMI, age, gender, or smoking. In the present study, we gave 20 mg single dose of Tadalafil and repeat UDS was done after 2 h assuming that it would reach to peak plasma concentration in 2 h.

We noticed significant improvement in mean MDFP from  $24.42 \pm 6.75$  to  $21.12 \pm 5.72$  cm H<sub>2</sub>O ( $p < 0.001$ ) 2 h after 20 mg oral Tadalafil and no significant improvement in MDFP among control group. On comparison of mean MDFP between case and control group we observed statistically significant improvement in the case group as compared to control

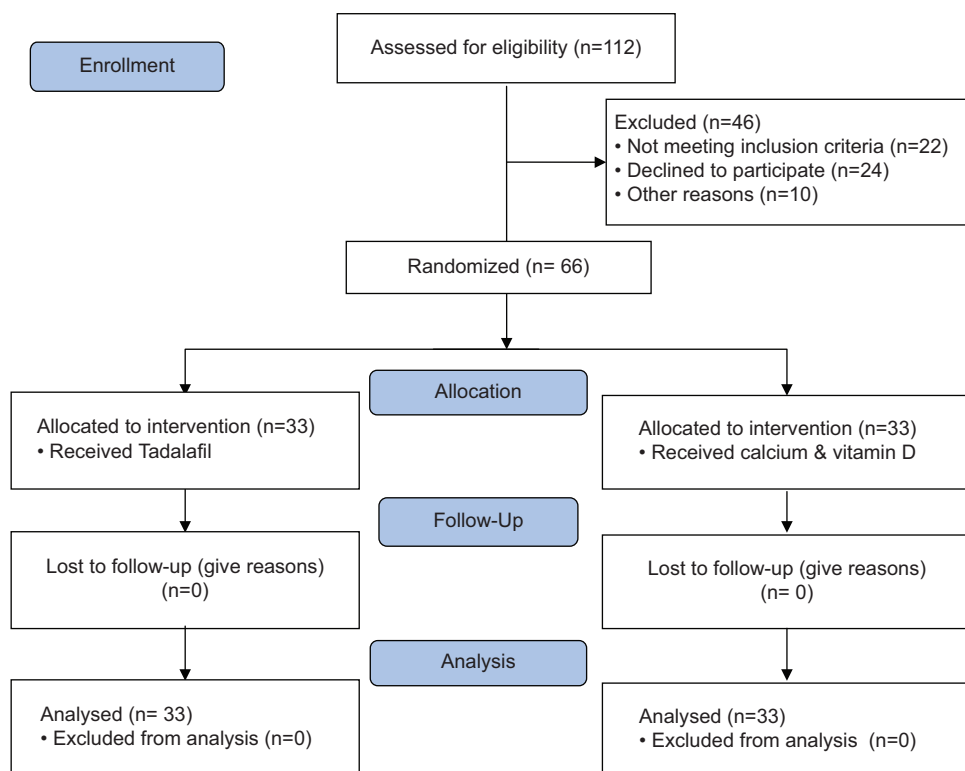


Fig. 1: CONSORT flow diagram

Table 1: Demographic and characteristics of the study population

Characteristics	Case (n=33)	Control (n=33)
Mean age (years)	36.48±12.36	35.70±10.68
Duration of injury (months)	12.27±9.69	19.39±25.94
Gender		
Male	26	29
Female	7	4
Mode of trauma		
Fall of heavy object	1	1
Fall from height	19	20
Road traffic accident	12	12
Slip and fall	1	0
Level of spine injury		
Cervical	11	7
Dorsal	20	18
Lumber	2	8
ASIA level		
ASIA-A	24	26
ASIA-B	8	7
ASIA-C	1	0

ASIA: American Spinal Injury Association

Table 2: Mean urodynamic parameters at baseline and follow-up for tadalafil

Variable (tadalafil group)	Pre (Mean±SD)	Post (Mean±SD)	p-value
MDFP (cm of H <sub>2</sub> O)	24.42±6.75	21.12±5.72	p<0.001
Maximum bladder capacity (mL)	263.94±108.48	287.67±112.71	p<0.001
Bladder compliance (mL/cm H <sub>2</sub> O)	11.07±4.31	13.94±5.13	p<0.001

MDFP: Maximum detrusor filling pressure

group. There was also a significant improvement in mean maximum bladder capacity from 263.94±108.48 to 287.67±112.71 mL (p<0.001)

Table 3: Mean urodynamic parameters at baseline and follow-up for control group

Variable (control group)	Pre (Mean±SD)	Post (Mean±SD)	P-value
MDFP (cm of H <sub>2</sub> O)	23.32±7.21	23.13±7.31	p=0.131
Maximum bladder capacity (mL)	302.58±124.59	300.33±123.02	p=0.100
Bladder compliance (mL/cm H <sub>2</sub> O)	12.88±3.47	12.96±3.62	p=0.245

MDFP: Maximum detrusor filling pressure

Table 4: Comparison of difference of urodynamic parameters at baseline and follow-up for both Tadalafil and control group

Variable (difference b/w pre- and post-drug)	Tadalafil group	Control group	p-value
MDFP difference (cm of H <sub>2</sub> O)	3.31±1.88	0.19±0.71	p<0.001
Maximum bladder capacity difference (mL)	23.73±10.97	-2.24±7.61	p<0.001
Bladder compliance difference (mL/cm H <sub>2</sub> O)	2.87±1.31	0.08±0.40	p<0.001

and mean bladder compliance from 11.07±4.31 to 13.94±5.13 mL/cm H<sub>2</sub>O (p<0.001) as compared to control group.

Iqbal et al. [10] performed a prospective hospital-based observational study of 31 suprasacral SCI individuals and illustrated statistically significant improvement in mean maximum bladder capacity from 268.39±130.0 to 298.55±112.0 mL (p<0.05) 2 h after Tadalafil 20 mg single dose. Bladder compliance improved from 18.68±6.4 to 20.25±7.5 mL/cm H<sub>2</sub>O (p>0.05) mean MDFP improved from 36.03±20.54 to 32.90±16.47 cm H<sub>2</sub>O (p>0.05).

Taie et al. [11] in pilot study among 20 suprasacral SCI individuals observed 1 h Following administration of 20 mg oral Tadalafil, there

was a significant increase in the bladder compliance (from 12.7 to 18.5 mL/cm H<sub>2</sub>O, p<0.001), bladder capacity (from 169.8 to 198.5 mL, p<0.001), and maximum voiding detrusor pressure (from 64.8 to 48.6 cm H<sub>2</sub>O, p<0.001).

Gacci *et al.* [12] in randomized, double-blind, and controlled trial among 25 male SCI individuals on oxybutynin treatment demonstrates that single 20 mg vardenafil administration achieved a significant decrease in MDFP (12%) and improvement in maximum cytometric capacity (17%).

Tewari *et al.* [13] in prospective hospital-based study assessed the urodynamic urinary bladder parameter improvements through 10000-fold effect after 2 h of 50 mg Intrathecal Sodium Nitroprusside (ITSNP) superfusion injection in 200 mL 5% dextrose, on 9 supra-SCI cases. NO generation at post-synaptic membrane by neuronal Nitric Oxide Synthetase through nitric oxide donor Sodium Nitroprusside causes 10,000-Fold effect at synapse at the injured portion of spinal cord. Thereafter the anterograde neurotransmission starts, and the autonomic connections of urinary bladder and various sphincters get the impulse. After ITSNP in all nine people, maximum bladder capacity 35.92%, bladder compliance 14.38%, and MDFP improved by 9.14%.

In the present study, we observed mild to moderate and tolerable adverse events in Tadalafil group and the participants did not require any pharmacological treatments or hospitalization for these adverse events. Reported adverse events in the Tadalafil group were as follows: 11 (33.3%) individuals complained of mild headache, 9 (27.3%) had muscle ache, 1 (3%) had vomiting, and 16 (48.5%) had nausea whereas six did not complain any side effect. Hence, we can conclude that treatment with Tadalafil 20 mg was well tolerated and safe. Very mild side effects in a few people were noted in the control group.

The study concluded that single-dose Tadalafil 20 mg is helpful in improving urodynamic parameters in SCI individuals with LUTS. Improvement in MDFP, maximum bladder capacity, and bladder compliance will permit the person to store additional amount of urine for extra period at same pressure; thus, it will decrease urinary frequency which will also decrease the chances of urinary tract infection. It will also decrease risk of urinary leakage which will help in maintaining hygiene, get rid of smell of urine and decreasing secondary infection in pressure ulcer and improving quality of life of SCI people. By decreasing detrusor contraction it can decrease risk of neurogenic DO and thus helpful in prevention of upper urinary tracts complications.

Limitations in our study include small sample size, single-dose effects of Tadalafil, and a smaller number of females.

Further studies are needed for taking into account different isoforms of PDE enzymes and combination of it with NO donor and other established drugs and evaluate mechanisms and target areas of its action in detail for generalizing this data to whole population.

## CONCLUSION

Hence, we finally concluded Tadalafil 20 mg single dose has beneficial role in improving urodynamic parameters such as MDFP, maximum bladder capacity and bladder compliance with minimal and tolerable adverse effect and improving quality of life.

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## AUTHORS CONTRIBUTION

All authors contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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