Improvement of Urodynamic Indices by Single Dose Oral Tadalafil in Men With Supra Sacral Spinal Cord Injury

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Purpose: To investigate the changes in urodynamic indices following a single dose of oral tadalafil in patients with supra sacral spinal cord injury (SCI).

Materials and Methods: Urodynamic study was accomplished on 20 patients with supra sacral SCI before and one hour after administration of 20 mg oral tadalafil as a single dose. Changes in the bladder capacity and compliance, maximum voiding detrusor pressure, and maximum detrusor filling pressure before and after tadalafil administration were recorded.

Results: Following administration of 20 mg oral tadalafil, there was a significant increase in the bladder compliance (from 12.7 to 18.5 mL/cmH_20, $P < .001$), bladder capacity (from 169.8 to 198.5 mL, $P < .001$), maximum voiding detrusor pressure (from 64.8 to 48.6 cmH_2O, $P < .001$), and maximum detrusor filling pressure (from 24.3 to 14.0 cmH_2O, $P < .001$).

Conclusion: Single dose of oral tadalafil has significant positive effects on urodynamic indices in patients with supra sacral SCI.

Keywords: urodynamic, spinal cord injury, phosphodiesterase inhibitors, drug therapy

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INTRODUCTION

Spinal cord injury (SCI) occurs most often in young population and results in negative psychosocial and physical consequences.[1,2] One of the most bothersome complaints of these patients is chronic and lifelong lower urinary tract symptoms (LUTS). It has been postulated that overactive bladder maybe the underlying cause for LUTS in these patients.[3]

Tadalafil is a potent phosphodiesterase-5 (PDE5) inhibitor that has been shown to be effective and safe for treatment of erectile dysfunction.[4] Phosphodiesterase-5 inhibitors are the first choice treatment for erectile dysfunction that can also significantly improve LUTS compared with placebo.[5] Therefore, it has been recommended for patients with concomitant erectile dysfunction and LUTS.[3,6] The probable mechanism by which these drugs decrease LUTS is that nitric oxide enters the smooth muscles and stimulates guanosine cyclase which converts cyclic guanosine three phosphates to cyclic guanosine mono phosphate. Cyclic guanosine mono phosphate decreases intracellular calcium concentration and consequently causes muscle relaxation.[7] It has been shown that receptors for PDE5 are also present in the detrusor muscle and with less frequency in the gastrointestinal, pulmonary, and vascular systems.[8]

It can be postulated that by

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inhibiting PDE5 in the bladder, we would be able to decrease overactivity of the detrusor muscle and increase the bladder capacity and compliance. It has been shown that 20mg tadalafil per day leads to clinically meaningful and statistically significant efficacy and is well tolerated in men with benign prostatic hyperplasia (BPH) and LUTS.

Urodynamic study is an extremely important part of the evaluation of patients with SCI.[9,10] It is "gold standard" for evaluation of the bladder and sphincter function as well as effectiveness of new drugs.[11] Our aim was to evaluate changes in urodynamic indices following administration of a single dose of oral tadalafil.

MATERIALS AND METHODS

This pilot study was carried out on 70 men with documented supra sacral SCI who referred to our clinic from February 2007 to February 2008.

Suffering from endocrinopathies (the thyroid, the pancreas, and the liver diseases) that interfere with the bladder function, renal failure, a history of previous bladder surgery, brain vascular disorders, recurrent urinary tract infection, and usage of drugs that have contraindication for PDE5 inhibitors administration were considered as exclusion criteria. Thus, 5 patients with diabetes mellitus, 3 with hypothyroidism, 4 with hyperthyroidism, 5 with renal failure, 7 with cardiac failure, 6 with cerebral vascular accident, 8 with previous bladder injury, and 4 patients with recurrent urinary tract infection were excluded from the study. Eight patients refused to participate in the study. Finally, 20 subjects fulfilled our criteria and were evaluated.

At baseline, all of the patients underwent urodynamic study. Thereafter, the patients were asked to take 20 mg tadalafil (Cialis; Lily ICOS. LLC, Indianapolis, IN, USA) as a single dose. After one hour, another urodynamic test was performed. Urodynamic indices before and after administration of tadalafil were compared. Normal bladder compliance of 20 mL/cmH_2O, normal bladder capacity of 200 mL, maximum detrusor voiding pressure of 50 cmH_2O, and maximum detrusor filling pressure of 5 to 10 cmH_2O were based on Gacci and colleagues' study.[12]

Urodynamic studies were performed in Urodynamic Center of Golestan Grand Hospital. After intramuscular injection of 80 mg of gentamicin as an antimicrobial prophylaxis, the patients were placed in the lithotomy position. First, the bladder was emptied by a 14F urethral catheter; then, a double lumen 9F catheter was inserted in the bladder. Abdominal pressure was checked with rectal catheter. Self-adhesive skin electrodes were placed to perform electromyography. After calibrating cystometry transducers to zero atmosphere, the bladder was filled with normal saline 10mL/min. The bladder pressure, detrusor pressure, abdominal pressure, filling rate, volume of infused normal saline, and electromyography data were recorded. When the patients were unable to retain the urine, they were asked to void, and voiding phase urodynamic study was done. We used MMS (Medication measurement system, Gladbeck, Germany) for urodynamic study. Data were analyzed by SPSS software (Statistical Package for the Social Science, version 16.0, SPSS Inc, Chicago, Illinois, USA) using paired sample *t* test.

RESULTS

The bladder compliance and capacity before the intervention were 12.7 mL/cmH_2O and 169.8 mL which increased to 18.5 mL/cmH_2O and 198.5 mL after a single dose of tadalafil, respectively ($P < .001$ and $P < .001$). Improvement in the bladder capacity with regard to normal bladder capacity in neurogenic bladders (200 mL) was statistically significant ($P < .001$) (Table 1 and Figure 1).

Maximum voiding detrusor pressure was 64.8 cmH_2O before the intervention which decreased to 48.6 cmH_2O after one dose of oral tadalafil ($P < .001$). The improvement of maximum voiding detrusor pressure based on normal maximum voiding detrusor pressure (50 cmH_2O) was also statistically significant ($P < .001$) (Table 2 and Figure 2).

Maximum detrusor filling pressure before the intervention was 24.3 cmH_2O which decreased

Table 1. Urodynamic indices before and after oral 20mg tadalafil

	Baseline urodynamic indices				Urodynamic indices after 20mg oral tadalafil			
	Maximum detrusor filling pressure	Maximum detrusor voiding pressure	Bladder capacity	Bladder compliance	Maximum detrusor filling pressure	Maximum detrusor voiding pressure	Bladder capacity	Bladder compliance
1	29	65	150	10	17	47	150	17
2	22	70	145	8	14	53	185	17
3	18	66	155	12	13	48	190	16
4	21	75	170	15	16	58	210	20
5	23	52	175	16	10	45	215	23
6	30	52	200	9	17	38	220	16
7	32	48	160	11	14	35	185	18
8	27	70	180	13	14	56	225	21
9	19	60	170	16	16	45	170	20
10	17	54	145	18	13	37	175	22
11	25	49	140	14	15	33	195	21
12	26	68	175	10	17	49	189	17
13	29	77	165	13	16	58	200	16
14	31	66	160	16	15	48	195	20
15	21	79	165	11	13	62	200	17
16	20	54	170	12	10	42	210	18
17	27	63	210	13	14	45	220	17
18	32	79	200	10	18	56	210	16
19	19	76	185	17	9	57	215	21
20	18	72	175	9	8	60	210	17

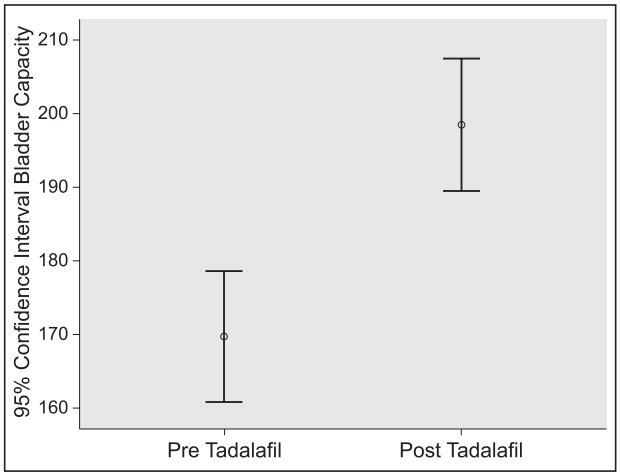

Figure 1. Bladder compliance before and after a single dose of tadalafil.

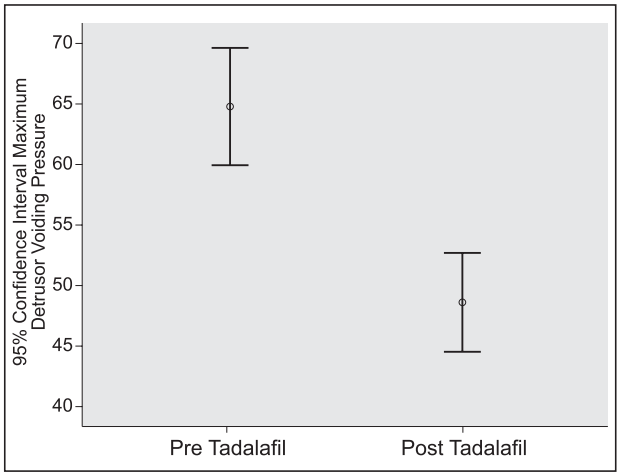

Figure 2. Maximum detrusor voiding pressure before and after a single dose of tadalafil.

Table 2. Urodynamic indices before and after a single dose of tadalafil in men with spinal cord injury

Outcome	Before Tadalafil Mean (± SD)	*P* *†	After Tadalafil Mean (± SD)	*P* *†	Mean Difference (95% Confidence Interval)	*P*‡
Bladder Compliance, mL/ cmH_2O	12.7 (± 2.9)	<.001	18.5 (± 2.3)	.008	5.9 (2.0 to 6.7)	<.001
Bladder Capacity, mL	169.8 (± 19.0)	<.001	198.5 (±19.2)	.721	28.7 (21.6 to 35.8)	<.001
Maximum Detrusor Voiding Pressure, cmH_2O	64.8 (± 10.3)	<.001	48.6 (± 8.7)	.482	16.2 (14.5 to 17.8)	<.001
Maximum Detrusor Filling Pressure, cmH_2O	24.3 (± 5.1)	<.001	14.0 (± 2.8)	<.001	10.4 (8.5 to 12.2)	<.001

*Compared to normal value.
†One sample *t* test.
‡Paired sample *t* test.

statistically significantly to 14.0 cmH_2O after a single dose of oral tadalafil ($P < .001$).

DISCUSSION

Efficacy of PDE5 inhibitors in amelioration of LUTS has gained attention in recent years. The mRNA expression of PDE5 has been demonstrated in lower urinary tract of rats and the highest expression is in the detrusor muscle followed by the urethra and the prostate. Phosphodiesterase-5 inhibitors can produce significant relaxation of the aforementioned tissues.[13] Sildenafil can prevent the bladder overactivity secondary to the bladder outlet obstruction in rats by preventing detrusor muscle hypertrophy and collagen deposition, which seems more effective than its effect on relaxation of the bladder outlet.[14]

Recent published randomized controlled trials of tadalafil versus placebo show significant clinical efficacy of tadalafil for treatment of LUTS in patients with BPH. The ability of tadalafil in treating both erectile dysfunction and BPH-induced LUTS is impressive.[15,16] However, in a recent study from Mayo clinic, Broderick and colleagues compared the safety and efficacy of tadalafil on BPH-induced LUTS in men with and without erectile dysfunction. They concluded that changes in BPH-induced LUTS after 12 weeks of treatment with placebo or various doses of once daily administered tadalafil were similar in men with and without erectile dysfunction.[17]

Since receptors of PDE5 are expressed in the detrusor muscle and the underlying pathophysiology of LUTS in supra sacral SCI patients is bladder overactivity, the impact of PDE5 inhibitors on amelioration of SCI-induced LUTS seems logical. To the best of our knowledge, Gacci and associates were the first ones who reported positive effects of vardenafil on improvement of urodynamic parameters in men with SCI.[12] Based on their randomized, double-blind, placebo controlled trial on 25 patients with supra sacral SCI, administration of a single dose of 20 mg vardenafil resulted in a 12% decrease in maximum detrusor pressure, a 17% improvement in maximum cystometric capacity, and a mean 25% increase in detrusor overactivity volume. Our results are consistent with Gacci and colleagues' investigation; however, we used single dose of oral tadalafil, as the state-of-the-art PDE5 inhibitor, and we found it beneficial in improvement of urodynamic parameters.

CONCLUSION

We conclude that tadalafil has beneficial effects on improvement of urodynamic parameters in patients with supra sacral SCI. However, larger studies with special attentions to clinical outcomes of tadalafil are needed before drawing final conclusion

CONFLICT OF INTERST

None declared.

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