

Original Research Article

Efficacy and safety of tadalafil in ureteric stent related symptoms: a double blind, prospective, randomised study

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ABSTRACT

Background: Is tadalafil effective and safe in ureteric stent related symptoms? The objective of this trial is to study the efficacy and safety of tadalafil and compare it with tamsulosin in relieving ureteric stent related symptoms by using ureteral stent symptom questionnaire.

Methods: Total 144 patients with dj stent symptoms were randomized into two groups with 72 patients in each. Group A patients were given tadalafil 5mg and Group B, tamsulosin 0.4mg for 2 weeks. Ureteral stent symptom questionnaire was filled on 7th day and on 21st day after stent insertion. Statistically significant difference between groups was determined by the t-test, Mann-Whitney U-test, Pearson Chi-square test or Fisher's exact test. Comparison between quantitative time related variables was done by Wilcoxon Signed Rank test. All the statistical tests were two-sided and were performed at a significance level of $\alpha=0.05$.

Results: Tamsulosin was found more effective than tadalafil in decreasing mean urinary index ($p=0.004$). Tadalafil caused significant decrease in body pain ($p=0.006$) and improvement in general health index score, work performance and sex score (P value= 0.041, <0.001 and <0.015 respectively) as compared to tamsulosin. Additional problems score improvement and analgesic use were found comparable in 2 groups (p value =0.193, 0.070 respectively). Adverse effect with both the drugs were minimal, mild to moderate and self-limiting.

Conclusions: Tadalafil found more effective than Tamsulosin in relieving body pain, sexual symptoms and improving general health and work performance but less effective in improvement of urinary symptoms.

Keywords: Tadalafil, Tamsulosin, Ureteral stent symptom questionnaire

INTRODUCTION

Ureteral stent is a tool of paramount utility in present endourological practice. Zimskind et al, described ureteral stent in 1967 and later on development of Dj stent by Finney and Hepperlen (1978) helped in reducing the problems of stent migration and expulsion.^{1,2} Since then, it has been used as a simple and effective method of

ureteral drainage in various urinary tract problems both in routine practice and in emergency.^{3,4}

Contrary to the ureteric stent advantages, ureteral stents may lead to several untoward symptoms in >80% of the patients such as frequency (50-60%), urgency (57-60%), dysuria (40%), flank pain (19-32%), suprapubic pain (30%), and haematuria (25%). These symptoms

negatively influence sexual life, work performance and overall general health of the patient.^{5,6} Exact pathophysiology of stent symptoms is unknown and various mechanisms have been proposed.⁷⁻¹⁰

Joshi et al, developed and validated Ureteral Stent Symptom Questionnaire (USSQ), a self-administered tool for evaluating stent related symptoms and to know their frequency, severity, daily variations, associated bothersomeness and their impact on quality of life.¹¹

Several modifications in stent materials and composition, designs, shapes diameters and coating to reduce the stent symptoms have been tried. Optimum stent length and proper positioning of distal curl has been found to be very important in preventing stent related symptoms.¹²⁻²⁰

Pharmacological agents commonly used in stent related symptoms are antimuscarinic agents, α -1adrenoregic blockers and their combinations. α -1adrenoreceptors are present in distal ureter, bladder trigone and neck, prostate and proximal urethra. They inhibit contraction of the smooth muscles in these organs. Tamsulosin, acts as a selective α -1a/1d blocker, decreases ureteric spasm, bladder outlet resistance and voiding pressure, hence decreases voiding symptoms and urinary reflux.²¹⁻³²

Phosphodiesterase-5 (PDE-5) receptors are present in urinary bladder, prostate, proximal urethra, ureter and PDE-5 inhibitors lead to smooth muscles relaxation in these organs. Tadalafil, a PDE-5 inhibitor, has proven its efficacy in erectile dysfunction and relieving BPH related lower urinary tract symptoms (LUTS).^{33,34}

Recently, tadalafil has been tried in lower ureteric stone expulsion and to relieve symptoms related to Dj stent.³⁵⁻³⁷ The present study intends to find out the efficacy of tadalafil (5mg) in alleviation of stent related symptoms and comparing it with tamsulosin (0.4mg), which is a widely used drug in stent symptoms, based on ureteral stent symptom questionnaire. Also, safety profile of both the drugs will be studied and compared.

METHODS

After Institutional Ethical Committee approval, A prospective, randomised, double blind, single centre, comparative study was conducted. After applying inclusion and exclusion criteria's total 144 patients (Age 18-50yrs) who underwent URSL (Ureteroscopic lithotripsy) /RIRS (Retrograde Intra Renal Surgery) and Dj stenting between March 2016 to June 2017 with stent related symptoms and willing to participate were included in the study. Exclusion criteria's were Incomplete stone clearance, staged procedure, long-term stenting (on regular change), urinary bladder/prostate pathology, prior lower urinary tract surgery, chronic uses of α -1 blocker and/or anticholinergic agents, pregnancy, urinary tract infection, severe cardiovascular

diseases and left ventricular outflow obstruction and patients taking nitrates.

After history and examination of all the probable patients for URSL/RIRS visiting hospital, routine blood and urine investigations, urine culture was done, with imaging studies including plain X ray KUB, ultra-sonography, plain CT KUB or CT IVP, for the size of calculus, its characteristics and location. Patients then planned for RIRS/URSL based on investigation results.

Ureteroscopic lithotripsy (6/7.5 F semirigid ureteroscope, Wolf make)/ Retrograde Intra Renal Surgery (Karl Storz flexible ureterorenoscope, 7.5/8.5 F) was done using Holmium LASER and DJ stent was introduced where needed. 6 Fr and 26cm long DJ stent composed of polyurethane material (Cook Medical) used in all the cases. Patients were prescribed antibiotics (levofloxacin 500/750mg) at the time of discharge as per hospital protocol for 3 days and advised to visit hospital after a week. X ray KUB and R/E urine were done after 1 week.

Patients with stent symptoms, fulfilling eligibility criteria's were explained about the stent related symptoms, study and the expected benefits and side effects of the drugs. All the patients were provided patient information sheet in their preferred language of communication and patients willing to participate were enrolled in the study.

USS questionnaire and its components were explained to the enrolled patients and their queries were solved. Patients filled up the consent form and USSQ questionnaire.

Eligible candidates were randomised into 2 groups and were sent to pharmacist with a sealed envelope with allotted group mentioned inside. 2 boxes were provided to the pharmacist, A and B containing 72 similar, non-transparent bottles each. Box A contained tadalafil 5mg and box B tamsulosin 0.4mg. Pharmacist gave the drug bottle to the patient as per the group in the sealed envelope and maintained the record. Pharmacist was unaware of the contents of the bottles. Patients were advised to take medication at the same time every day with or without meal.

Group A received phosphodiesterase 5 inhibitor, tadalafil 5mg once daily and Group B α -1 blocker, tamsulosin 0.4mg once daily for the stent related symptoms. It was a double blind study as the investigator and patients were blinded, till the analysis stage.

In tadalafil group, one patient was lost to follow up and in 1 patient Dj stent was removed early and exchanged because of stent migration. In tamsulosin group, one patient had urinary tract infection and 1 patient did not take medication regularly. Data of these 4 patients was not analysed (Figure 1).

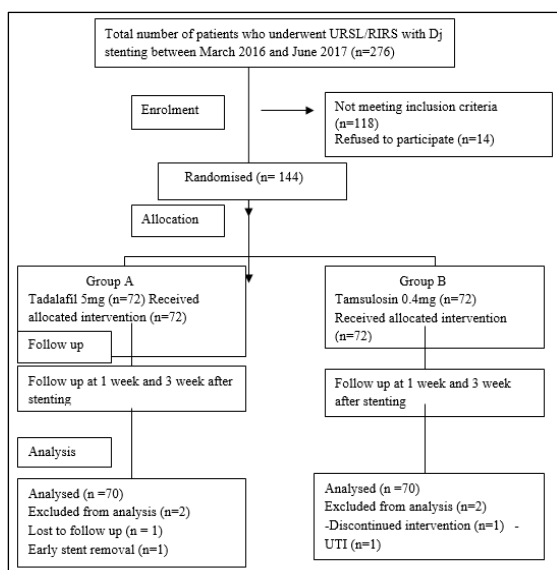


Figure 1: Study design.

For normally distributed data t-test and for skewed data or ordered categorical data Non parametric Mann-Whitney U-test was used for statistical analysis of 2 groups. Comparison between quantitative time related variables was done by Wilcoxon Signed Rank test.

For categorical data, comparisons were made by Pearson Chi-square test or Fisher's exact test as appropriate (%). All the statistical tests were two-sided and were performed at a significance level of $\alpha=0.05$. Data was entered into a password protected computerised database for analysis. Analysis was conducted using IBM SPSS Statistics (version 22.0).

RESULTS

Out of total 276 patients who underwent Dj stenting after RIRS/URSL 189 (68%) patients developed stent related symptoms. 31 patients did not meet the eligibility criteria's and 14 patients refused to participate in the study. Total 144 patients were randomized into two groups i.e. Group A (tadalafil 5mg), and Group B (tamsulosin 0.4mg). Data of 140 patients analysed.

There was no statistical difference in mean Age, Height and Sex distribution between 2 groups. No difference in calculus related parameters and type of surgery found between 2 groups (Table 1).

Both tadalafil and tamsulosin decreased urinary symptoms and pain. They also improved general health, work performance and sexual health. The mean urinary index score was found to be decreased significantly in Tamsulosin group at week 3 (p=0.004).

Tamsulosin decreased mean urinary index by 5% more than the tadalafil. Significant decrease in the number of patients with pain, Visual Analogue Scale (VAS) Score

and mean pain index score was noticed in tadalafil group at week 3 as compared to group B (p=0.006, p= 0.001, p=<0.001) respectively). Tadalafil caused significant improvement in general health index score, work performance and sex score (P value= 0.041, <0.001 and <0.015 respectively) as compared to tamsulosin.

Additional problems score improvement and analgesic uses were found comparable in 2 groups (P value =0.193, 0.070 respectively).

Table 1: Patient characteristics.

Characteristic	Tadalafil	Tamsulosin	P Value
No. of patients	70	70	
Mean Age in years	38.6 (19-50)	40.1(20-50)	0.417#
Gender (%)			0.693*
Male	54 (77%)	52(74.2%)	
Female	16 (23%)	18(25.8%)	
Mean height in cms	165.6 (150-186)	166.7 (151-184)	0.489#
Employed (%)			0.431*
Full time	48 (68.6%)	54 (77%)	
Part time	0	0	
Retired on health ground	0	0	
Students	6 (8.6%)	2 (2.9%)	
Unemployed	6 (8.6%)	4 (5.7%)	
Retired for other Reason (in age)	10 (14.3%)	10 (14.3%)	
Calculus			
Mean Size in cms	11(8-15)	11.6(9-15)	0.052+
Side (%)			0.290*
Right	42(60%)	48(68.6%)	
Left	28(40%)	22(31.4%)	
Location (%)			0.831*
Lower calyx	6 (8.6 %)	8 (11.4 %)	
Mid- calyx	7(10 %)	9 (12.9 %)	
Upper-calyx	4 (5.7 %)	8 (11.4 %)	
Renal Pelvis	5 (7.1 %)	4 (5.7 %)	
Lower Ureter	23 (32.9%)	22 (31.4 %)	
Mid Ureter	13 (18.6 %)	10 (14.3 %)	
Upper Ureter	12 (17.1 %)	9 (12.9 %)	
Surgery (%)			0.392*
RIRS	27(38.6%)	32 (45.7%)	
URSL	43(61.4%)	38 (54.3%)	

#t-Test, *Pearson Chi-square test/Fisher's exact test, +Mann-Whitney U-test, URSL (Ureteroscopy Lithotripsy), RIRS (Retrograde Intra Renal Surgery)

Total 9 patents in group A (tadalafil) and 10 patients in group B experienced adverse effects such as headache, dizziness, general weakness, flushing and abnormal ejaculation. These symptoms were mild to moderate and gradually improved with time. No patient left study because of these adverse effects (Table 2 Table 3).

Table 2: Study results.

Variable	Tadalafil	Tamsulosin	P Value
Mean Urinary Index Score			
First week	34.7±7.3	33.8±7.31	0.308+
Third week	22.65±4.64	20.11±3.13	0.004
Patients with pain (%)			
First week	56 (80)	58 (82.9)	0.664*
Third week	32 (45.7)	48 (68.6)	0.006
Mean sum of VAS scores for all sites of pain			
First week	5.47±2.96	5.79±2.8	0.491+
Third week	3.88±1.13	5.17±1.22	<0.001
Mean Pain Index Score			
First week	18.17±3.66	18.17±2.03	0.882+
Third week	13±2.12	14.7±2.23	<0.001
Mean general health index score			
First week	19.7±4.91	18.8±4.71	0.320+
Third week	15±4.17	13.7±3.73	0.041

VAS, visual analogue scale, #t-test, *Pearson Chi-square test/Fisher's exact test, +Mann-Whitney U-test

Table 3: Study results.

Variable	Tadalafil	Tamsulosin	P Value
Work performance score			
Mean days in bed	2.13±1.26	1.94±1.78	0.1+
Mean days with lost activity	3.2±1.16	3.17±2.22	0.98
Mean quality of work score			
First week	11.77±1.94	12.18 ±2.03	0.241+
Third week	8.77±1.71	10.4±1.79	<0.001
Sexually active (%)			
First week	16 (23)	18 (25.7)	0.693*
Third week	46 (65.7)	30 (43)	0.007
Stent-related sexual abstinence (%)			
First week	42 (60)	40 (57)	0.73*
Third week	10 (14.3)	26 (37)	0.002
Mean Quality of sex score			
First week	6.75±2.32	6.22±2.18	0.33+
Third week	4.65±1.22	5.3±1.67	0.015
Mean Additional problems score with stent in situ			
First week	11.97±2.43	12.2±1.9	0.516+
Third week	10.1±1.96	10.4±1.39	0.193
Mean analgesic use in mg	703.6±319.6	817.2±364.2	0.070+

#t-test, *Pearson Chi-square test/Fisher's exact test, +Mann-Whitney U-test

DISCUSSION

Zimskind et al, described ureteral stent and later on Finney and Hepperlen developed Dj stent.^{1,2} Dj stent is commonly used stent and utilised in various endourological, laparoscopic and open procedures, in routine and emergency conditions. Obstructive pyelonephritis, intolerable acute renal colic, ureteral

edema or perforation, procedure on solitary and transplant kidney, passive ureteral dilatation, reconstructive surgeries (as a support), steinstrasse etc. are some important indications.^{3,4} Despite their great utility, ureteral stents lead to several untoward symptoms in >80% of the patients such as frequency, urgency, dysuria, flank pain, suprapubic pain, and haematuria. Ureteral stent symptoms reduce quality of life and are associated with negative functional capacity. >80% experience pain severe enough to reduce their daily activities, 58% report decreased work capacity and about one third experience sexual dysfunction.^{5,6}

Exact pathophysiology of stent symptoms is unknown. It could be related to lower ureteral spasms, local trigonal sensitivity to the ureteral stent and reflux of urine back into kidney. Irritative voiding symptoms are probably caused by local irritation of bladder trigone by distal end of the stent especially when it crosses midline. Flank pain is most likely caused by urine reflux and rise in intrapelvic pressure. Suprapubic pain is caused by irritation by distal coil and because of complications like infection and stent encrustation. Haematuria may be due to stent insertion procedure itself or because of surgical management of primary pathology. Urinary incontinence is either due to trigonal irritation by stent or migration of stent into urethra bypassing the sphincter.⁷⁻¹⁰

Joshi et al, developed and validated Ureteral Stent Symptom Questionnaire (USSQ) for evaluating stent related symptoms which consists of 38 items examining 6 sections: voiding symptoms (11 questions), body pain (visual analog scale, site of pain and six questions), work performance (7 questions), sexual matters (4 questions), general health (6 questions) and additional problems (5 questions). Each question has a score giving a total score for each section, with a high score means the symptom is more bothersome. It is a self-administered tool which can be used in clinical and research settings.¹¹

Judicial use of Dj stent, optimum stent length and proper positioning of distal curl of stent may help in preventing stent related symptoms. HoCH et al, in their study found that longer stent was significantly associated with a higher incidence of urinary frequency and urgency.¹²

There have been several modifications in stent materials and composition, designs, shapes, diameters and coating to achieve the ideal characteristics, but search for an ideal stent is still going on.¹³⁻²⁰

Various pharmacological agents have been tried in stent related symptoms. Stent coils irritate bladder trigone leading to overactive bladder like symptoms caused by involuntary urinary bladder contraction. Anticholinergic drugs like solifenacin and tolterodine have been found to be effective in relieving stent related symptoms.^{21,22} Their combination with α-blockers were found more efficacious than monotherapy.^{23,24}

Alpha-blockers are widely accepted for their beneficial effects in patients with BPH associated LUTS. Tamsulosin has also been found effective in distal ureter stone expulsion.²⁵ The α -1A-adrenergic receptors regulates contraction of the smooth muscle in the prostate tissue, bladder base and neck, urethra, seminal vesicles, vas deferens and ureter.²⁶⁻²⁸

Deliveliotis et al, for the first time used alfuzosin(α -blocker) for stent-related pain and urinary symptoms. Results showed a decrease in mean urinary symptom index, frequency of stent-related pain and an improvement in the general health index score.²⁹

Singh I et al, in their study found that tamsulosin group had significant decrease in urinary index score, pain index score, work performance score, average VAS score.³⁰ Similarly, Wang CJ et al, and Dellis AE et al, in their studies found significant improvement in stent related symptoms with tamsulosin.^{31,32}

In our study, tamsulosin was found to be very effective in reducing Mean urinary symptoms index. Pain index score, work performance, general health index score and sexual function were also improved.

Tamsulosin, acts as a selective α -1a/1d blocker, decreases ureteric spasm, bladder outlet resistance and voiding pressure. Hence decreases voiding symptoms and urinary reflux related pain. Decreased urinary symptoms and pain possibly caused improved work performance, general health index score and sexual function.

Phosphodiesterase-5 (PDE-5) receptors are present in urinary bladder, prostate, proximal urethra, ureter and PDE-5 inhibitors lead to smooth muscles relaxation in these organs.^{33,34} Tadalafil (a PDE-5 inhibitor) has been approved by FDA for the treatment of erectile dysfunction and BPH/LUTS. Because of its smooth muscle relaxing activity tadalafil has also been used in lower ureteric calculi with promising results.³⁵

Recently, tadalafil has been tried in symptoms related to Dj stent. Hajebrahimi et al, in their study found that stent related symptoms respond well to tadalafil in comparison with placebo. Mean urinary symptom score decrease, body pain relief, and improvement in sexual function were significantly high in tadalafil group.³⁶

Aggarwal SP et al, in their study of 161 patients with Dj stent compared tadalafil, tamsulosin and placebo for stent related symptoms. They found tadalafil to be more effective than placebo. It was found comparable to tamsulosin in relieving urinary symptoms and better than tamsulosin in improving sexual health and body pain.³⁷

In our study, tadalafil reduced urinary symptoms (urinary index score) and body pain. Tadalafil was found to be very effective in improving sexual health. It improved

work performance and general health scores. Smooth muscle relaxation in lower ureter, bladder trigone possibly caused decrease in urinary symptoms and pain. Sexual health improvement with tadalafil can be attributed to decreased pain, urinary symptoms and positive effect on underlying erectile dysfunction.

Present study is a single centre randomised control trial comparing efficacy and safety of tadalafil (5mg) with tamsulosin (0.4mg). Only limited studies have been done using tadalafil in ureteric stent symptoms. Previous studies also compared placebo with tadalafil and placebo was found to have no improvement in stent related symptoms. So, in order to reduce stent symptoms associated morbidity, placebo group was not included in this study. Tadalafil 5mg is compared with tamsulosin 0.4mg, a widely used drug in stent related symptoms. All 6 sections and subsections in USSQ were studied in detail and compared. Tadalafil reduced urinary symptoms (urinary index score) significantly but found to be less effective than tamsulosin. Tadalafil was found to be more effective in relieving body pain and improving sexual health. Also found better than tamsulosin in improving work performance and general health scores. Adverse effects with both the drugs were minimal (<15%), mild to moderate and improved with time and no patient left study because of these adverse effects.

Dj stent of same length, diameter and material used irrespective of the height of the patient. Although, mean height difference between 2 groups was statistically insignificant, so, it can be assumed that inappropriate stent length would have affected both the groups equally. To detect small differences between these two groups, probably same size is statistically small.

CONCLUSION

Tadalafil 5mg is an effective and safe drug and can be used as first choice in relieving ureteric stent related symptoms and associated problems especially in sexually active patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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