

COMPARISON OF SOLIFENACIN VERSUS COMBINATION OF SOLIFENACIN AND TAMSULOSIN IN IMPROVING UNILATERAL DOUBLE-J STENT RELATED LOWER URINARY TRACT SYMPTOMS

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ABSTRACT

Objective: To compare Solifenacin versus solifenacin plus tamsulosin in terms of international prostate symptom score (IPSS) for lower urinary tract symptoms (LUTS) in patients with unilateral double-J (DJ) ureteric stents.

Study Design: Comparative cross sectional study.

Place and Duration of Study: Armed Forces Institute of Urology, Rawalpindi from Sep 2018 to Feb 2019.

Methodology: A total of two hundred (n=200) patients of either gender aged 20-50 years, who underwent unilateral DJ stenting for different endourological procedures, were enrolled after satisfying inclusion/exclusion criteria and then randomly allocated to group A (Solifenacin 5mg once daily (OD) ± placebo for 2 weeks) or group B (Solifenacin 5mg OD ± Tamsulosin 0.4 mg OD for 2 weeks) respectively. Baseline (1st post-operative day) and Post 02 weeks treatment IPSS was recorded and analyzed.

Results: Mean age of presentation in group A and group B was 41.11 ± 6.45 vs 39.86 ± 5.34 years with *p*-value 0.14. Majority of patients in both groups were male (34% female in group A while 31% in group B, difference being statistically insignificant *p* 0.65). Baseline IPSS in group A and group B was 10.33 ± 2.72 vs 10.46 ± 3.12 with *p*-value 0.76 (statistically insignificant) while post 02 weeks treatment IPSS in group A and B was 9.20 ± 2.67 vs 7.88 ± 2.63 respectively with *p*-value <0.001, the difference being statistically significant.

Conclusions: Current study revealed significant advantage of combination therapy (solifenacin ± tamsulosin) compared with solifenacin monotherapy in lowering LUTS based on IPSS in patients having unilateral DJ stent.

Keywords: Lower urinary tract symptoms, Solifenacin, Tamsulosin, Ureteral calculi, Ureteroscopy.

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INTRODUCTION

Ureteral stent placement is a routine urological procedure performed post ureteroscopy for various etiologies¹, helping assist passage of ureteral stone, reduction in renal pelvic pressure after pyeloplasty or pyleo-or nephrolithotomy, relieving obstruction, acceleration of ureteric injury recovery and auxiliary for shockwave lithotripsy². Procedure introduced almost five decades ago by Zimskind *et al*³, was popularized by Finney *et al*, in 1978, currently being one of the most commonly carried endourological intervention worldwide⁴.

Despite usefulness, stent related symptoms (SRS) are cause of well documented significant morbidity with estimated incidence of 19-76%.

The reported bothersome urinary morbidities encountered are voiding / storage symptoms (LUTS), flank or suprapubic pain, hematuria and urinary tract infection (UTI) obviously affecting general health and work performance in as many as 80% cases⁵.

Various theories have been proposed although exact pathophysiology of SRS remains unclear⁶. Spasm of ureteral smooth muscle secondary to foreign body in situ, irritation of trigone by intravesical lower coil leading to bladder spasm and increase retrograde pressure transmission during voiding are few such proposed mechanisms augmented by nature of material and size of the stent⁷.

Tamsulosin, a selective inhibitor of a 1A/1D-adrenoceptors expressed amongst smooth muscles of ureter, trigone, prostate and bladder neck, relaxes these smooth muscles leading to reduced

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bladder outlet resistance and voiding pressure thus effectively decreasing incidence of dysuria, frequency, and pain compared to placebo⁸. Solifenacin inhibits acetylcholine binding on all five subtypes of G-protein-coupled muscarinic receptors, M2/3 being most frequently found detrusor smooth muscle, interstitial and nerve cells of bladder, effectively reducing spontaneous myocyte activity leading to decreased frequency as well as intensity of bladder contractions. Solifenacin 5mg OD was selected due to least adverse events in clinical practice, tolerability and good efficacy⁹. IPSS is a self-administered validated psychometric tool allowing objective assessment of LUTS. Questionnaire allows quantification of the symptoms and has been validated by numerous researchers in different languages¹⁰.

Several treatment strategies have been proposed to deal with SRS. Oral NSAIDs or opioids were commonly prescribed with moderate efficacy. Alpha-1 adrenergic blockers and antimuscarinic agents have revolutionized pharmacologic management of these symptoms. However international literature review revealed inconsistent, fluctuating results and to our knowledge very limited local data was found addressing this aspect¹¹. We aimed to evaluate whether combination of tamsulosin and solifenacin is more effective in reducing symptoms associated with indwelling double-J ureteral stents in our target population.

METHODOLOGY

This comparative cross sectional study was conducted at Armed Forces Institute of Urology, Rawalpindi from September 2018 to February 2019. The study protocol was approved by the hospital ethics review Committee (certificate no Uro-06/ERC-104585/TRG/19). Non probability consecutive sampling technique utilized at outpatient department to enroll 100 patients in each group (WHO calculator, confidence interval 95%, power of test 80%, mean IPSS population A 11.04 & B 7.16)¹², after satisfying inclusion criteria (unilateral DJ stenting, age 20-50 years & of either gender) while patients having bleeding disorders,

lactating/pregnant, bilateral ureteric stents, anticholinergics or α -blockers use in past, bladder outlet obstruction or prostatitis were excluded. Randomization into two groups was done by computer generated random number table and written informed consent was obtained. Both investigators and patients were blinded to the randomization scheme and medications. Sequentially numbered containers having solifenacin \pm placebo or solifenacin \pm Tamsulosin were administered by duty nurse knowing allocation sequence and patient grouping.

Demographic information including name, age and gender were taken from all patients. Pre-operative assessment included routine investigations for the planned procedures to be carried out under general or regional anesthesia. A Soft Percuflex™ Stent with Hydro Plus™ (Contour™ Ureteral Stent, Boston Scientific Corporation, Natick, MA 01760-1537, USA) was used, adjusting the length and caliber for each patient. Procedure was performed by two consultant urologists without knowing group of the patient to eliminate bias. A plain radiograph of the kidneys, ureters and bladder confirmed the position of the DJ stent in all patients before discharge. Patients in group A and B received Solifenacin (5mg) \pm placebo and Solifenacin (5mg) \pm Tamsulosin (0.4 mg) OD respectively for 2 weeks. IPSS was recorded at 1st post-operative day and after 2 weeks on a pre-designed proforma.

Statistical analysis was done using SPSS-24. Descriptive statistics were used to calculate means \pm standard deviation for quantitative variables. Frequencies with percentage were calculated for qualitative variables. Independent sample t-test was applied to compare mean of IPSS after 14 days in both groups. Post stratification t-test was applied. *p*-value ≤ 0.05 was considered significant.

RESULTS

A total of two hundred patients were enrolled and randomly allocated. Baseline characteristics were similar in both groups. Mean age of presentation in group A and group B was 41.11 \pm

6.45 vs 39.86 ± 5.34 years with *p*-value 0.14. Majority of patients in both groups were male (34 (34%) female in group A while 31 (31%) in group

Table-I: Demographic variables of the patients included in the study (n=200).

Demographic Variable	Group A (n=100) (Solifenacin)	Group B (n=100) (Solifenacin ± Tamsulosin)	<i>p</i> -value
Age (years)			
Mean ± SD	41.11 ± 6.45	39.86 ± 5.34	0.14
Gender Ratio			
M:F	1.9:1	2.2:1	0.65
Male	66 (66%)	69 (69%)	
Female	34 (34%)	31 (31%)	
Age Groups, n (%)			
20-35 Years	21 (21.0%)	25 (25.0%)	0.50
36-50 Years	79 (79.0%)	75 (75%)	
Body Mass Index (BMI)			
Mean ± SD	27.10 ± 4.13	27.40 ± 3.84	0.59
ASA Status			
I	51 (51%)	37 (37%)	0.20
II	41 (41%)	49 (49%)	
III	06 (6%)	10 (10%)	
IV	02 (2%)	04 (4%)	
Operation Time (Minutes)			
Mean ± SD	32.54 ± 8.57	32.48 ± 7.73	0.95

Table-II: IPSS in both groups baseline, baseline stratified and at 02 weeks post treatment.

Variable	Group A (n=100) (Solifenacin)	Group B (n=100) (Solifenacin ± Tamsulosin)	<i>p</i> -value
Baseline IPSS			
Mean ± SD	10.33 ± 2.87	10.46 ± 3.12	0.76
Stratified Baseline IPSS, n (%)			
IPSS 1-7	21 (21%)	20 (20%)	0.861
IPSS 8-19	79 (79%)	80 (80%)	
IPSS at 02 Weeks			
Mean ± SD	9.20 ± 2.67	7.88 ± 2.63	0.001

B, difference being statistically insignificant (*p* 0.65) (table-I). Baseline IPSS in group A and group B was 10.33 ± 2.72 vs 10.46 ± 3.12 with *p*-value 0.76 (statistically insignificant) while post 02 weeks treatment IPSS in group A and B was 9.20 ± 2.67 vs 7.88 ± 2.63 respectively with *p*-value <0.001, the difference being statistically significant. Similar trend was noted when data was stratified with respect to gender, age and baseline

IPSS. *p*-value was <0.05 in all cases, except for younger age group where no significant difference was noted (*p* 0.26) (table-III).

Table-III: Data stratification of mean IPSS at 02 weeks with respect to age, gender and baseline IPSS in both groups.

Variable	IPSS at 2 Weeks Post Treatment		<i>p</i> -value
	Group A (n=100) (Solifenacin) (Mean ± SD)	Group B (n=100) (Solifenacin ± Tamsulosin) (Mean ± SD)	
Age Groups (Years)			
20-35	8.95 ± 2.38	8.08 ± 2.78	0.018
36-50	9.27 ± 2.75	7.81 ± 2.60	<0.01
Gender			
Male	9.14 ± 2.65	8.00 ± 2.73	0.003
Female	9.32 ± 2.74	7.61 ± 2.42	<0.001
Baseline IPSS			
IPSS 1-7	6.62 ± 0.87	4.50 ± 0.52	<0.001
IPSS 8-19	9.89 ± 2.57	8.73 ± 2.24	<0.01

DISCUSSION

Both α-blockers and anti-muscarinic drugs are effective for ureteral SRS whether used alone or in combination¹⁰, the combination being better option^{11,13}. However; clinical trials have combined tamsulosin with different doses of solifenacin with conflicting results^{14,15}. Present study was designed to compare solifenacin versus solifenacin plus tamsulosin for the management of SRS in local population. A total of two hundred (n=200) patients of either gender were enrolled and randomly allocated to group A (Solifenacin) and group B (Solifenacin ± Tamsulosin) for 2 weeks respectively to compare SRS in terms of IPSS. Our results revealed comparable baseline characteristics in both groups. Post 02 weeks treatment IPSS in group A and B was 9.20 ± 2.67 vs 7.88 ± 2.63 respectively with *p*-value <0.001 (students t-test), the difference being statistically significant supporting better efficacy of combination therapy.

These results are comparable to data quoted worldwide^{16,17}. Abdelaal *et al*¹⁶, reported their findings in 260 patients divided into four groups (no treatment, tamsulosin alone, solifenacin alone or combination). A highly significant lower ureteral

stent symptom questionnaire (USSQ) score were observed in combination group (16.6 ± 2.5 vs 37.1 ± 3.1 vs 22.9 ± 2.4 vs 22 ± 2.8 respectively, $p < 0.001$) while another trial carried out by Avila *et al*¹⁷, found combination of tamsulosin \pm oxybutynin to perform significantly better in terms of irritative symptoms, work performance and sexual score as compared to tamsulosin or oxybutynin alone (15.5 ± 5 vs 21.5 ± 6.27 vs 17.8 ± 5.5 , $p < 0.001$). Similarly Lim *et al*¹², evaluated tamsulosin, solifenacin and their combination in improving LUTS in 168 patients having indwelling ureteral stents in terms of International Prostate Symptom Score/quality of life (IPSS/QoL) and visual analogue pain scale (VAPS). They found significant different IPSS total score between groups (13.77 ± 4.5 tamsulosin vs 11.04 ± 5.29 solifenacin vs 7.16 ± 3.37 combination respectively, p -value < 0.001). Authors concluded that combination therapy should be strongly considered for patients who complain of SRS as proved by our study as well.

Yan *et al*¹⁸, in their meta-analysis involving 710 patients aimed to evaluate the efficacy of antimuscarinics alone or in combination with alpha-blockers for the treatment of SRS. Authors found significantly improved total IPSS, QoL, body pain and work performance score of USSQ in the combination group compared with antimuscarinics alone ($p < 0.001$). They concluded that alpha-blockers enhance efficacy of antimuscarinics leading to additive favorable effects in tackling SRS compared with antimuscarinics monotherapy.

In another meta-analysis, Zhang *et al*¹⁹, systematically evaluated efficacy of combination therapy for SRS in 545 patients. Their analysis revealed that compared with α -blockers, the combination group achieved significant improvements in total IPSS ($p < 0.00001$), obstructive sub score ($p < 0.00001$), irritative sub score ($p < 0.00001$) and QoL score ($p < 0.001$). Their findings strongly supported significant advantages of combination therapy based on IPSS as depicted by our study.

Dellis *et al*²⁰, studied the effect of tamsulosin, solifenacin, and their combination in improving symptoms and quality of life in patients with

indwelling ureteral stents in a RCT involving 260 patients. The validated USSQ was completed 1 and 4 weeks after stent insertion and 4 weeks after stent removal. Their results highlighted that patients on combination therapy expressed significantly less LUTS ($p < 0.001$), pain ($p < 0.001$) and work performance ($p < 0.001$) scores in the fourth week with stent in situ and after stent removal ($p = 0.005$). No patients had to discontinue medication due to side effects. They concluded that simple medication, such as tamsulosin and solifenacin alone or in combination, improves stent-related symptoms and has a positive impact on quality of life.

In another meta-analysis involving 1408 patients Zhou *et al*²¹, evaluated the effects of α -blockers, antimuscarinics, or a combination of both in reducing ureteral SRS. They found that compared with α -blockers monotherapy, combination therapy has significant lower total IPSS ($p < 0.00001$), VAPS (p -value 0.01), and QoL ($p < 0.00001$). They concluded that combination therapy has significant advantages compared with α -blocker monotherapy supporting our results.

El-Nahas *et al*²², in their randomized controlled trial involving patients who underwent temporary unilateral ureteral stent for drainage of calculi upper tract obstruction aimed to compare the effectiveness of tamsulosin and solifenacin in relieving ureteral SRS. Patients in group 1 received placebo, group 2 received tamsulosin 0.4 mg once daily while those in group 3 received solifenacin 5 mg once daily. They found the total USSQ scores in all domains, except sexual index, were significantly better in solifenacin than in tamsulosin group ($p < 0.05$). They did not use combination therapy in their study.

Although all above mentioned literature favors our results, a meta-analysis by Wang *et al*²³, revealed safety and efficacy of solifenacin in reducing SRS but no significant advantage was found over tamsulosin. In addition, combination of solifenacin and tamsulosin did not show beneficial effects over solifenacin monotherapy. However a recent RCT performed in 2018 revealed

significant efficacy of combination therapy with silodosin and Solifenacin as compared to monotherapy for relieving SRS with improved QoL and less requirement of analgesia supporting our findings²⁴.

The results of present study should be interpreted with care as efficacy was measured after 2 weeks only and IPSS was used as measuring tool. Moreover, the study was carried out in a single center. There was no comparison of side effects as well as cost of the treatment. Large multicenter RCTs are required to further clarify the role of combination therapy adopting more validated USSQ²⁵. Various aspects of drug therapy, like cost analysis, patient satisfaction and side effect profile, need to be studied to make this combination modality part of effective SRS care program.

CONCLUSIONS

Significant advantage of combination therapy of α -blocker and antimuscarinic compared with antimuscarinic mono therapy was observed in the present study in terms of improvement in mean IPSS at day 14. Further large scale RCTs adopting more validated USSQ as outcome measures are warranted to support the recommendation of combination therapy for routine clinical use.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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