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Original Article

Comparison of safety and efficacy of silodosin, solifenacin, tadalafil and their combinations in the treatment of double-J stent- related lower urinary system symptoms: A prospective randomized trial

Çift J stentine ilişkin alt üriner sistem semptomlarının tedavisinde silodosin, solfenasin, tadalafil ve kombinasyonlarının güvenlilik ve etkinliğinin karşılaştırılması: bir prospektif randomize çalışma

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ABSTRACT

Objective: To evaluate the efficacy and safety of silodosin, solifenacin, tadalafil and their combinations in reducing double J (DJ) stent-related symptoms (SRS).

Material and methods: A total of 335 patients who underwent DJ stenting and develop SRS at 1st week were randomized into eight groups. Ureteral stent symptom questionnaire (USSQ) and Quality of life (QOL) scores were noted in each group: Group A-Silodosin (8 mg OD)+ Solifenacin (10 mg OD)+ Tadalafil (5 mg OD), B - Silodosin 8 mg OD, C - Solifenacin 10 mg OD, D- Tadalafil 5 mg OD, E- Silodosin (8 mg OD) + Solifenacin (10 mg OD), F- Silodosin (8 mg 0D)+ Tadalafil (5 mg OD), G- Solifenacin (10 mg OD)+ Tadalafil (5 mg OD) and H-placebo. Analgesic (diclofenac 50 mg) was given as per requirement. All groups received the drugs for 14 days and again USSQ, QOL score with analgesic requirement were noted in each group.

Results: USSQ score was similar in all groups at 1st week but all groups (Groups A-G) led to significant decrease in USSQ score at 3rd week as compared to Group H with less requirement of analgesic. However when we compared groups with each other we found that mean USSQ score and analgesic requirement was favoring Group E as compared to other groups. Quality of life score was also best in Group E (mean 1.5) ($p<0.05$).

Conclusion: Combination therapy with silodosin and solifenacin (group E) was effective for relieving SRS with improved quality of life and less requirement of analgesic than any other groups and should be considered in patients who develop SRS.

Keywords: Double J stent; quality of life; urinary symptom.

ÖZ

Amaç: Çift J stentine ilişkin alt üriner sistem semptomlarının azaltılmasında silodosin, solfenasin, tadalafil ve kombinasyonlarının güvenlilik ve etkinliğinin değerlendirilmesi.

Gereç ve yöntemler: DJ stenti yerleştirilen ve 1. haftada stent ilişkili semptomlar (SİS) gelişen 335 hasta sekiz gruba randomize edildi. Group A-Silodosin (8 mg GTD)+ Solifenasin (10 mg GTD)+ Tadalafil (5 mg GTD), B - Silodosin 8 mg OD, C - Solifenasin 10 mg GTD, D- Tadalafil 5 mg GTD, E- Silodosin (8 mg GTD) + Solifenasin (10 mg OD), F- Silodosin (8 mg GTD)+ Tadalafil (5 mg GTD), G- Solifenasin (10 mg GTD)+ Tadalafil (5 mg GTD) ve H-plasebo. Her grubun üreter stent semptom anketi (ÜSSA) ve Yaşam kalitesi (YŞK) skorları kaydedildi. Gerektiğnde analjezik (diklofenak 50 mg) verildi. Her grup ilaçları 14 gün boyunca aldı ve yine her bir grupta ÜSSA, YŞK ve analjezik gereksinmesi kaydedildi.

Bulgular: ÜSSA 1. haftada her grupta benzerdi. Ancak Grup H ile karşılaştırıldığında 3. haftada A-G gruplarında ÜSSA skoru anlamlı derecede azalmış, analjeziğe daha az gerek duyulmuştur. Grupları birbirleriyle karşılaştırdığımızda, diğer gruplara göre ortalama ÜSSA skoru ve analjezik gereksinmesinin E grubu lehine olduğunu saptadık. En iyi yaşam kalitesi skoruna Grup E de elde edilmiştir (median 1,5) ($p<0,05$).

Sonuç: Silodosin ve solifenasin ile kombinasyon tedavisi (Grup E), diğer gruplara göre daha yüksek YŞK ve daha düşük oranda analjezik gereksinmesiyle SİS'leri gidermede etkiliydi. SİS gelişen hastalarda bu kombinasyon düşünülmelidir.

Anahtar Kelimeler: Çift J stent; yaşam kalitesi; üriner semptom.

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Introduction

Although Simon was credited as the first person who stented the ureter during open bladder surgery, Zimskind was the first who used it endoscopically.[1] Since then, many modifications have been made in stent design to prevent complications like stent migration or expulsion but this problem was solved by Finney and Hepperlen double J (DJ) or double pigtail stent.[2-4] Despite its usefulness, morbidity associated with these stents has been considered as a potential health problem. These problems can vary from commonly experienced stent symptoms to serious issues like forgotten stent.[5] DJ stent- related symptoms are frequency (50-60%), sexual dysfunction (male, 42-82% and female, 30-86%), reduced work capacity (58%), urgency (57-60%), dysuria (40%), flank pain (19-32%), incomplete emptying (76%), suprapubic pain (30%) hematuria (25%) and reduced quality of life (QOL) in approximately 80% of the patients.[4,6-8] Although nonspecific, still the International Prostate Symptom Score (IPSS) was widely used for the assessment of stent-related symptoms (SRSs). Later on Joshi et al. had developed a self-administered validated Ureteral Stent Symptom Questionnaire (USSQ) to objectively evaluate SRS and associated impact on QOL.[9-11] Pathophysiology of these SRS are still not clear and various theories had been proposed like ureteral smooth muscle spasm or distal curl of the stent that may lead to bladder mucosal/trigonal irritation and urinary reflux which can be responsible for these symptoms.[11,12] Various attempts had been made to minimize these symptoms but pharmacological treatment is the simplest and a noninvasive option. Numerous drugs had been tried to relieve these symptoms like alpha blockers, anticholinergics, phosphodiesterase inhibitors (PDE5Is) and analgesics.[6,7,13-26] Silodosin is a highly selective alpha-1 adrenergic receptor antagonist which is used in the treatment of lower urinary tract symptoms (LUTS). Alpha-1 adrenergic receptors are densely found in the smooth muscle cells of the lower urinary tract, and silodosin relaxes them and improves the SRS, and various studies had also shown similar effect.[13-21] Anticholinergics can also improve SRS by reducing the involuntary bladder contraction that occurs due to trigone irritation.[18-25] PDE5Is increase levels of cGMP that will lead to relaxation of the smooth muscle of ureter and reduces SRS.[6,26] The aim of our study was to evaluate the efficacy and safety of silodosin, solifenacin, tadalafil, and their combinations in reducing DJ stent-related LUTS.

Material and methods

After taking institutional review board approval (2431/MC/EC/2016), this prospective, randomized double-blind placebo controlled study was conducted in our department of urology from Januray 2016 to June 2017. Informed written consent was taken from all the study participants. History and physical examination was done in all the patients. General characteristics of all patients were recorded like age, height, weight and body mass index. Investigations like serum creatinine analysis, urinalysis with urine culture, ultrasonography, plain X-ray of the kidneys, ureters, and bladder (KUB) and contrast enhanced computed tomography (CECT) KUB were performed in every patient before surgery. The greatest dimension of the stone was taken into consideration as the stone size.

All patients undergoing routine DJ stenting after an endourological surgery [either unilateral percutaneous nephrolithotomy (PCNL) or ureteroscopic lithotripsy (URSL)] were enrolled in the study for evaluation. A 6 Fr polyurethane DJ stent was used in all the study participants and the length of DJ stent was adjusted according to patient's height. Patients with 18 to 40 years of age group who were sexually active and not having any contraindication for the drugs used in this study were included for evaluation. Patients having previous or present history of prostatic or bladder surgery, lower urinary tract surgery, malignancy, neurological disorder, pelvic irradiation, diabetes, acute or chronic renal insufficiency, solitary kidney or congenital urinary abnormality, medical treatment (α blockers, beta-blockers, calcium antagonists, 5 alfa reductase inhibitors, PDE5 inhibitors, anticholinergics and cholinergics, nitrates), cardiac disease, postoperative residual stone fragments, multiple or bilateral ureteral stones, patients with bilateral stents or long-term stenting with frequent change of stents, history of interstitial cystitis, chronic cystitis or prostatitis, pregnant and lactating women, and patients not available for follow up were excluded from this study.

Postoperative X-ray KUB and urinary ultrasonography were done in all patients to identify residual stone fragment(s). Foleys catheter was removed on 1st post-operative day in both PCNL and URSL patients. On 2nd post-op day, nephrostograms were obtained before removal of nephrostomy tubes in all PCNL patients. Patients were discharged on the third postoperative day with 7 day course of oral antibiotic. USSQ forms were given to all patients at the time of discharge and they were told to come 7 days later with completed survey forms, on the off chance that they experience symptoms. Scoring at first week was carried out to see the severity of DJ stent- related symptoms.

After applying inclusion and exclusion criteria, 361 patients reported DJ-related symptoms at 1st week and out of these, 9 patients were not willing to participate in the study so a total of 352 patients were equally randomized into 8 groups (A, B, C, D, E, F, G and H). Groups receive oral doses of the drugs as follows: Group A Silodosin (8 mg OD)+ Solifenacin (10 mg OD)+ Tadalafil (5 mg OD), B - Silodosin 8 mg OD, C - Solifenacin 10 mg OD, D- Tadalafil 5 mg OD, E- Silodosin (8 mg OD) + Solifenacin (10 mg OD), F- Silodosin (8 mg 0D)+

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Table 1. Basic parameters of all groups

Features	Group A (Silod+Soli+ Tada)	Group B (Silod)	Group C (Soli)	Group D (Tada)	Group E (Silod+Soli)	Group F (Silod+Tada)	Group G (Soli+Tada)	Group H (Placebo)	p
Number	40	43	43	42	42	41	42	42	0.95
Age (years) (mean±SD)	30.7±8.8	30.7±9.1	29.9±8.5	30.1±8.8	31.1±7.9	28.9±8.7	30±8.5	29.5±8.5	1.0
Male: Female	30:10	32:11	33:10	30:12	29:13	28:13	31:11	33:9	1.0
BMI (kg/m^2) (mean±SD)	20.3±3.8	21.4±3.7	21.8±3.3	22±4	21.1±4.1	19.9±3.9	20.1±4.2	20.7±3.3	0.086
Procedure PCNL: URSL	28:12	30:13	29:14	29:13	28:14	31:10	32:10	29:13	1.0

BMI: body mass index; PCNL: percutaneous nephrolithotomy; SD: standard deviation; URSL: ureteroscopic lithotripsy; Silod; silodosin; Soli: solifenacin; Tada: tadalafil

Tadalafil (5 mg OD), G- Solifenacin (10 mg OD)+ Tadalafil (5 mg OD) and group H- were given multivitamin OD (placebo). Patients were advised to take analgesics (diclofenac sodium 50 mg) as per requirement. To minimize bias, double blinding was done. All of these drugs were put in 8 identical boxes and chit-pull method was used to allot the boxes to each group. These boxes were allotted by nursing staff and neither the patient nor the researcher was aware of allocation of drugs to groups. All patients were informed of the side effects of the drugs. Patients were asked to come after 14 days of taking these drugs (at 3rd week) with complete USSQ and QOL items were responded before removal of DJ stents. Items related to urinary symptoms (11), body pain (9), sexual health (4), general health (6), work performance (7), and additional problems (4) contained respective number of questions, respectively. The body pain domain questioned pain experience, visual analog scale, and contained six questions. QOL scores ranged between 1, and 7 points. In every domain a final score was found by adding the scores obtained from each question and higher score was considered as representing more bothersome symptoms. Side effects of the drugs and analgesic requirement were also noted in each group.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA), Trial version 23 for Windows statistical software package and Primer. The quantitative data were presented as mean and standard deviation and compared using Student t-test and the categorical data were presented as numbers (percent) and compared among groups using Chi square test. ANOVA Test and post Hoc Test Tukey Test applied to find out the most significant groups among all the groups. P value <0.05 was considered as statistically significant.

Results

Figure 1 shows the study design. Out of 514 patients, 361 patients complained about SRS (70.23%). 9 patients were not ready to participate in the study so a total of 352 eligible patients based on inclusion criteria were randomly assigned into eight groups. Out of these, some patients lost to follow up and some had early removal of DJ stent because of hematuria and urinary tract infection (UTI) so finally 335 patients were left for final analysis. Out of these 335 patients, groups A (40), B (43), C (43), D (42), E (42), F (41), G (42) and H (42) contained indicated number of patients. All patients tolerated drug well and none of them were excluded from the study because of drug related side effects.

Table 1 shows the basic characteristics of all the study participants. No statistically significant differences were observed regarding patient's age, gender, body mass index and procedure done (PCNL/URSL) in all the groups.

Table 2 and 3 show the USSQ of all groups at 1st and 3rd week respectively and requirement of analgesic in all groups at 3rd week. Table 4 shows variations in USSQ variables among the groups between 1st, and 3rd week. USSQ was similar in all groups at 1st week but Groups A-G led to significant decrease in USSQ scores at 3rd week as compared to Group H with less requirement of analgesic. Table 5 shows results of statistical analysis (p value) performed in all groups regarding USSQ and analgesic used at 3rd week. Although we didn't find significant difference between Groups A-G in terms of frequency of urinary symptoms, it was lowest in Group E (median 19.05). Body pain score was <10 in Groups B, C and E (median values, 7.53, 8.02 and 7.14 respectively). Patients in Group E had statistical sig-

Table 2. Ureteral stent symptom questionnaire scores of all groups at 1st weeks

	Groups	A	B	C	D	E	F	G	H		
Features	**No**	**40**	**43**	**43**	**42**	**42**	**41**	**42**	**42**	**F**	**p**
Urinary symptoms	Mean	41.83	40.3	39.84	39.76	39.12	39.78	38.81	41.26	1.131	0.343
	SD	5.363	6.151	6.384	6.404	6.329	6.342	6.564	5.539		
	Minimum	30	28	28	28	28	28	27	28		
	Maximum	30	28	28	28	28	28	27	28		
Body pain	Mean	19.48	19.4	19.56	19.5	19.33	19.71	19.71	19.86	0.163	0.992
	SD	2.708	2.977	2.881	3.022	3.034	2.9	2.865	2.485		
	Minimum	14	11	13	12	12	12	12	14		
	Maximum	26	26	26	26	26	26	26	26		
Sexual health	Mean	7.45	7.3	7.07	6.98	6.93	7.15	7.14	7.05	0.401	0.901
	SD	1.679	1.846	1.791	1.774	1.745	1.621	1.571	1.886		
	Minimum	4	3	3	3	3	3	3	3		
	Maximum	10	10	10	10	10	10	10	10		
General health	Mean	19.79	20.47	20.65	20.6	20.17	20.98	20.14	19.6	0.73	0.646
	SD	4.1	3.383	3.116	3.313	3.435	3.004	3.017	4.168		
	Minimum	12	14	14	13	13	13	13	10		
	Maximum	25	25	25	25	25	25	25	25		
Work performance	Mean	16.98	17.84	17.93	17.83	17.6	17.34	16.81	17.21	1.451	0.184
	SD	2.348	2.081	2.086	2.152	2.187	2.265	2.422	2.609		
	Minimum	12	14	14	14	13	13	13	12		
	Maximum	22	22	22	22	22	22	22	22		
Additional health	Mean	12.78	13.12	12.88	12.88	12.79	12.46	13.26	13.76	1.338	.232
	SD	2.154	2.174	2.174	2.308	2.343	2.388	1.901	2.01		
	Minimum	8	8	8	6	6	6	10	9		
	Maximum	16	17	17	17	17	17	17	17		
Quality of life	Mean	5.78	5.6	5.49	5.45	5.36	5.49	5.71	5.9	1.594	0.136
	SD	0.891	0.955	0.935	0.942	0.983	0.978	0.995	0.932		
	Minimum	4	4	4	4	4	4	4	4		
	Maximum	7	7	7	7	7	7	7	7		

SD: standard deviation

nificantly less body pain with respect to all other groups except Group C. We also didn't find significant difference between Groups B and C in terms of body pain. Median sexual health score was >4 in Groups B, C and H (median values, 6.74, 6.84 and 7.05, respectively). We found increased number of sexual problems in Groups B, C and H as compared to Groups A, D, E, F and G, which were statistically significant. Median scores for general health was <10 in Groups A and E, (6.20 and 6.43 respectively) which was statistically significant as compared to other groups (B, C, D, F, G and H). Mean work performance

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Table 3. Ureteral stent symptom questionnaire scores and analgesic requirements in all groups at 3rd weeks

	Groups	A	B	C	D	E	F	G	H	
Features	**No**	**40**	**43**	**43**	**42**	**42**	**41**	**42**	**42**	**p**
Urinary symptoms	Mean	20	20.4	20.6	21.69	19.05	21.39	21	39.88	<0.001
	SD	4.8	4.76	4.87	4.72	4.77	4.21	4.56	6.64	
	Minimum	12	12	12	12	12	12	12	28	
	Maximum	29	29	29	31	28	29	29	50	
Body pain	Mean	11.05	7.53	8.02	15.67	7.14	14.41	11.12	18.55	<0.001
	SD	4.83	0.96	2.11	5.29	1.34	5.83	4.9	3.26	
	Minimum	6	6	5	7	4	5	6	11	
	Maximum	18	10	15	26	10	26	19	24	
Sexual health	Mean	2.63	6.74	6.84	2.76	3.14	3.24	3.26	7.05	<0.001
	SD	0.95	2.34	2.11	1.25	1.63	1.84	1.82	1.72	
	Minimum	2	2	2	2	2	2	2	3	
	Maximum	7	10	10	8	8	8	8	10	
General health	Mean	6.2	12.3	11.6	14.4	6.43	12.49	12.19	19.57	<0.001
	SD	2.65	4.41	4.06	4.13	2.7	4.87	4.28	3.86	
	Minimum	4	6	6	9	4	5	6	10	
	Maximum	15	24	24	24	15	22	24	25	
Work performance	Mean	6.9	7	6.74	9.6	6.81	9.39	7.62	16.48	<0.001
	SD	2.11	2.42	2.27	4.74	2.32	4.47	3.03	3.68	
	Minimum	4	4	4	4	4	1	4	6	
	Maximum	13	15	15	18	15	17	16	22	
Additional health	Mean	8.6	9.79	7.53	11.19	7.38	11.07	7.76	12.81	<0.001
	SD	2.59	2.72	2.98	2.32	2.48	3.03	2.99	2.39	
	Minimum	4	4	4	7	4	7	4	8	
	Maximum	15	16	16	16	15	17	16	17	
Quality of life	Mean	2.3	2.7	2.65	3.29	1.5	3	3.1	5.05	<0.001
	SD	0.79	1.17	1.07	1.25	0.74	1.28	1.1	0.94	
	Minimum	1	1	1	2	1	2	2	3	
	Maximum	5	6	5	6	4	6	6	7	
Analgesic used (Tab dilcofenac in mg)	Mean	326.25	339.53	453.49	548.81	255.95	384.15	417.86	1246.43	<0.001
	SD	132.04	96.09	164.17	112.34	78.24	116.43	144.75	162.07	
	Minimum	150	200	150	400	100	200	300	550	
	Maximum	600	550	700	750	350	600	650	1550	

SD: standard deviation

Table 4. Intergroups differences in variables between 1st and 3rd weeks

	Groups	A	B	C	D	E	F	G	H	
Features	**No**	**40**	**43**	**43**	**42**	**42**	**41**	**42**	**42**	**p**
Urinary symptoms	Mean	21.83	19.91	19.23	18.07	20.07	18.39	17.81	1.38	<0.001
	SD	7.243	8.283	7.955	8.101	7.728	8.249	8.918	3.575	
	Minimum	8	0	0	0	6	0	0	-2	
	Maximum	33	33	33	33	33	33	33	10	
Body pain	Mean	8.43	11.86	11.53	3.83	12.19	5.29	8.6	1.31	<0.001
	SD	6.172	2.989	3.165	4.963	3.038	5.076	6.137	2.892	
	Minimum	-3	4	2	-2	5	-2	-5	-2	
	Maximum	17	17	17	13	17	14	17	10	
Sexual health	Mean	4.83	0.56	0.23	4.21	3.79	3.9	3.88	0	<0.001
	SD	2.086	2.594	2.496	2.312	2.628	2.557	2.539	1.126	
	Minimum	0	-5	-5	-2	-2	-2	-2	-3	
	Maximum	8	6	6	8	8	8	8	4	
General health	Mean	13.4	8.16	9.05	6.19	13.74	8.49	7.95	0.21	<0.001
	SD	5.247	4.86	4.551	4.718	3.832	5.573	4.417	3.892	
	Minimum	3	-1	-1	-2	4	-8	-2	-11	
	Maximum	21	17	17	14	21	20	17	10	
Work performance	Mean	10.08	10.84	11.19	8.24	10.79	7.95	9.19	0.74	<0.001
	SD	2.965	3.124	2.978	5.23	3.143	4.99	3.395	2.44	
	Minimum	3	2	3	-2	3	-1	1	-4	
	Maximum	17	17	17	17	17	20	14	10	
Additional health	Mean	4.18	3.33	5.35	1.69	5.4	1.39	5.5	0.95	<0.001
	SD	3.637	3.503	3.401	3.166	3.163	3.767	3.344	2.603	
	Minimum	-2	-4	-4	-4	0	-5	-4	-4	
	Maximum	11	11	11	9	10	9	11	9	
Quality of life	Mean	3.48	2.91	2.84	2.17	3.86	2.49	2.62	0.86	<0.001
	SD	1.198	1.525	1.446	1.591	1.26	1.63	1.396	1.138	
	Minimum	1	0	0	0	0	-1	0	0	
	Maximum	6	5	5	5	6	5	5	4	

SD: standard deviation

scores were 9.60, 9.39 and 16.48 in Groups D, F and H, respectively and which were statistically significant as compared to other groups (A, B, C, E and G), however Groups D and F, had statistically significantly better scores than Group H in terms of work performance. Additional health score was >10 in Groups D, F and H (median values; 11.19, 11.07 and 12.81 respectively) which was statistical significant as compared to Groups A, C, E and G. This score was 9.79 in Group B which was significant as compared to Groups C, E, G and H. QOL was best in Group E (median, 1.5) which was statistically significant as compared

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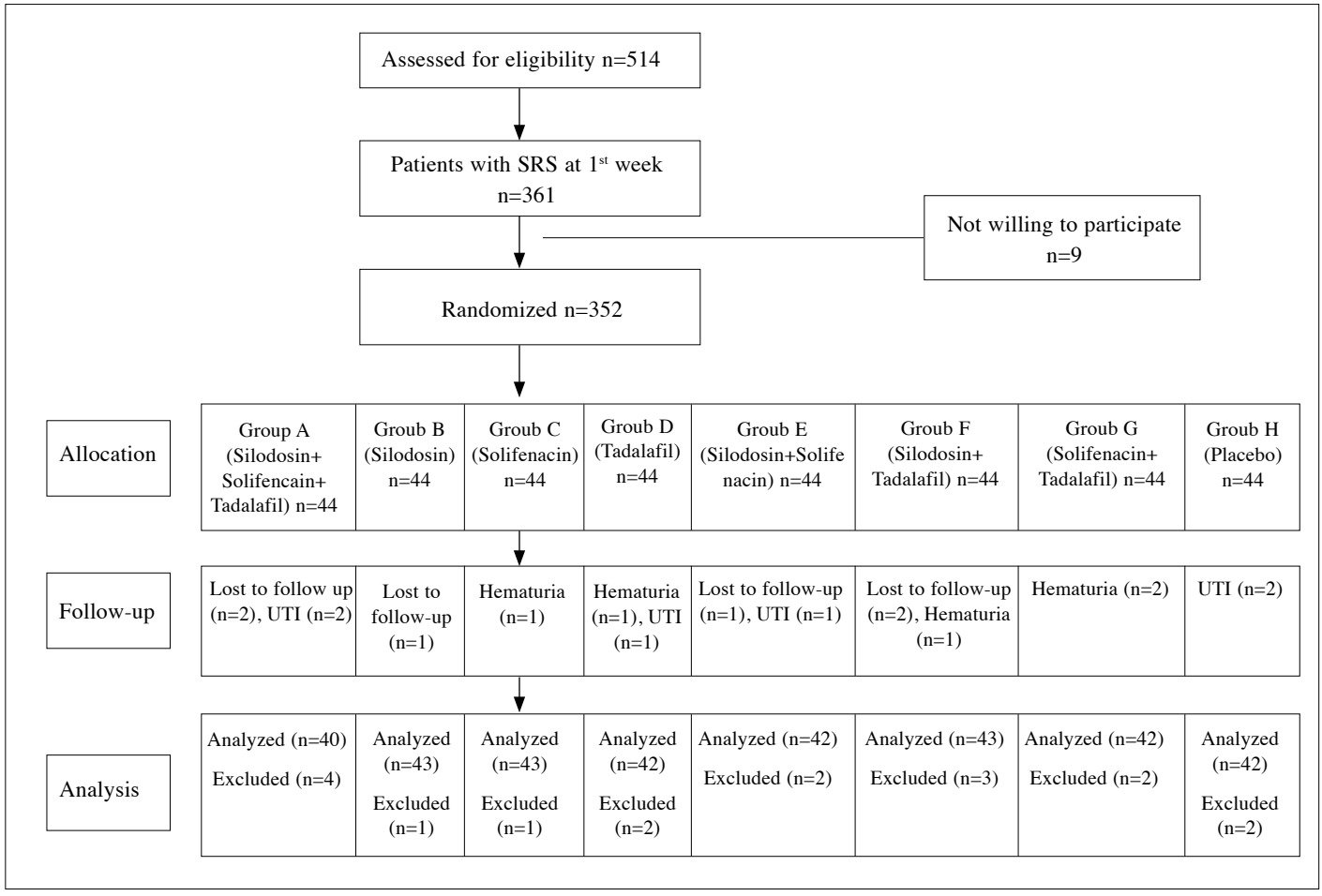

Figure 1. A CONSORT flow diagram depicting patients' randomization and recruitment

to all other groups. However all other groups (A-G) did better than Group H in terms of QOL ($p<0.05$). Analgesic requirement was lowest in Group E (median 250 mg) as compared to other groups with statistical significance.

Table 6 shows results of statistical analysis (p value) of mean difference in USSQ between 3rd and 1st weeks among all groups. We found that Groups A and E did better than Group H in all components of USSQ ($p<0.05$). However Group E was better than Group A in terms of body pain ($p=0.004$). Group E was better than Groups B and C in terms of sexual health, general health and QOL ($p<0.05$). Group E was better than Groups D and F in all components of USSQ except urinary symptoms and sexual health ($p<0.05$). Group G was found to be inferior than Group E in terms of body pain, general health and QOL ($p<0.05$).

Discussion

Indwelling double J (DJ) stents are routinely used for resolution/prevention of ureteral obstruction caused by different etiologies and they are in use for more than three decades.[1] However SRS is an important issue with the use of these stents and can present in majority of patients with a significant negative impact on patients' QOL.[5,8,9] Many theories have been suggested to understand the pathophysiology of these symptoms but still the exact mechanism is not completely understood.[11,12] To understand these symptoms in a better way, Joshi et al.[10] had developed USSQ scores that consist six domains-urinary symptoms, body pain, sexual health, general health, work performance and additional problems which assess impact on QOL of patients.

Various strategies have been applied for better compatibility of these stents based on preventive and pharmaceutical methods. Preventive strategies include minimum use of stents, stent length adjusted according to patients' height, proper positioning of stents, changes in stent design like biodegradable stents, hydrophilic material coating tapered distal end of these stents, stent coating, drug-eluting stents and proper patient counseling regarding symptoms.[27-29] It had been sug-

Table 5. Results of statistical analysis (p values) among all groups regarding ureteral stent symptom questionnaire scores and analgesic used at 3rd weeks

Dependent variable (3rd week)		Urinary symptoms	Body pain	Sexual health	General health	Work performance	Additional health	Quality of life	Analgesic (diclofenac)
Group A	B	1.000	0.002	0.000	0.000	1.000	0.479	0.683	1.000
	C	0.999	0.013	0.000	0.000	1.000	0.624	0.803	0.000
	D	0.785	0.000	1.000	0.000	0.006	0.000	0.001	0.000
	E	0.989	0.000	0.888	1.000	1.000	0.454	0.016	0.214
	F	0.913	0.004	0.764	0.000	0.016	0.001	0.063	0.471
	G	0.985	1.000	0.730	0.000	0.975	0.855	0.017	0.031
	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Group B	C	1.000	0.999	1.000	0.992	1.000	0.003	1.000	0.001
	D	0.931	0.000	0.000	0.219	0.007	0.250	0.176	0.000
	E	0.916	1.000	0.000	0.000	1.000	0.001	0.000	0.060
	F	0.984	0.000	0.000	1.000	0.021	0.369	0.896	0.760
	G	0.999	0.001	0.000	1.000	0.988	0.014	0.669	0.099
	H	0.000	0.000	0.993	0.000	0.000	0.000	0.000	0.000
Group C	D	0.973	0.999	0.000	0.026	0.002	0.000	0.110	0.017
	E	0.835	0.000	0.000	0.000	1.000	1.000	0.000	0.000
	F	0.996	0.971	0.000	0.970	0.006	0.000	0.803	0.216
	G	1.000	0.000	0.000	0.997	0.922	1.000	0.531	0.908
	H	0.000	0.000	0.999	0.000	0.000	0.000	0.000	0.000
Group D	E	0.226	0.000	0.976	0.000	0.003	0.000	0.000	0.000
	F	1.000	0.838	0.918	0.347	1.000	1.000	0.923	0.000
	G	0.998	0.000	0.899	0.170	0.108	0.000	0.992	0.000
	H	0.000	0.021	0.000	0.000	0.000	0.112	0.000	0.000
Group E	F	0.386	0.000	1.000	0.000	0.009	0.000	0.000	0.000
	G	0.620	0.000	1.000	0.000	0.949	0.998	0.000	0.000
	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Group F	G	1.000	0.004	1.000	1.000	0.216	0.000	1.000	0.934
	H	0.000	0.000	0.000	0.000	0.000	0.070	0.000	0.000
Group G	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

gested that drugs like alpha-blockers and anticholinergics decrease the pressure transmitted toward the renal pelvis during micturition, reduce the peak contraction pressure leading to ureteral dilation and decrease the bladder irritation with the intravesical portion of the stent that will lead to less discomfort related to stents.[30]

Alpha-blockers, anticholinergics and their combinations can be used for the management of SRSs with good results.[13-26,30] Recently some studies have also shown the role of PDE5Is in SRS.[6,26] But most of these studies haven't used the most validated score (USSQ) with QOL score for the assessment of SRSs. None of these study have used tadalafil in combination with an

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Table 6. Results of statistical analysis (p value) regarding mean differences between ureteral stent symptom questionnaire scores at 1st and 3rd weeks between all groups

Dependent variable (3rd week)		Urinary symptoms	Body pain	Sexual health	General health	Work performance	Additional health	Quality of life
Group A	B	0.948	0.013	0.000	0.000	0.981	0.943	0.597
	C	0.786	0.037	0.000	0.001	0.864	0.749	0.443
	D	0.345	0.000	0.937	0.000	0.310	0.019	0.001
	E	0.969	0.004	0.478	1.000	0.988	0.708	0.923
	F	0.473	0.039	0.639	0.000	0.154	0.005	0.037
	G	0.260	1.000	0.604	0.000	0.957	0.623	0.112
	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Group B	C	1.000	1.000	0.998	0.988	1.000	0.096	1.000
	D	0.956	0.000	0.000	0.518	0.025	0.320	0.235
	E	1.000	1.000	0.000	0.000	1.000	0.082	0.042
	F	0.985	0.000	0.000	1.000	0.008	0.140	0.874
	G	0.912	0.020	0.000	1.000	0.432	0.057	0.982
	H	0.000	0.000	0.957	0.000	0.000	0.025	0.000
Group C	D	0.997	0.000	0.000	0.093	0.006	0.000	0.359
	E	1.000	0.998	0.000	0.000	1.000	1.000	0.021
	F	1.000	0.000	0.000	0.999	0.002	0.000	0.949
	G	0.990	0.055	0.000	0.960	0.192	1.000	0.997
	H	0.000	0.000	1.000	0.000	0.000	0.000	0.000
Group D	E	0.933	0.000	0.991	0.000	0.033	0.000	0.000
	F	1.000	0.817	0.999	0.329	1.000	1.000	0.968
	G	1.000	0.000	0.998	0.667	0.933	0.000	0.823
	H	0.000	0.168	0.000	0.000	0.000	0.972	0.001
Group E	F	0.974	0.000	1.000	0.000	0.011	0.000	0.000
	G	0.878	0.007	1.000	0.000	0.483	1.000	0.002
	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Group F	G	1.000	0.020	1.000	1.000	0.782	0.000	1.000
	H	0.000	0.002	0.000	0.000	0.000	0.999	0.000
Group G	H	0.000	0.000	0.000	0.000	0.000	0.000	0.000

alpha-blocker or anticholinergic to assess the impact on SRS. Our study showed that combination of silodosin with solifenacin improved SRS and better QOL with less requirement for analgesics as compared to any other group. Psai et al.[13] and Kim et al.[14] had also shown the benefit of silodosin in patients with SRS. Alpha-blockers are commonly used drugs for SRS and various other researchers have also found that these drugs are effective in reducing SRSs.[13-17] Similarly in our study, silodosin alone was effective in reducing SRS as compared to placebo.

Anticholinergics alone and in combination with alpha-blockers have been found to be effective in patients with SRS but com-

bination therapy is more effective than monotherapy.[18-25,30] PDE-5 inhibitors are FDA approved drugs for erectile dysfunction, LUTS due to prostatic hyperplasia, and pulmonary hypertension.[6] PDE5i receptors are present at lower ureter, bladder neck and trigone. Antagonism of these receptors reduces ureteral spasm, relaxes the ureteric smooth muscle, and promotes expulsion of calculi and improvement of irritative urinary symptoms.[6,26] Hajebrahimi et al.[29] evaluated the effect of tadalafil on SRS in his placebo-controlled randomized trial. In their study, tadalafil improved stent-related urinary symptoms, body pain and sexual functions with good QOL. Aggarwal et al.[6] had also compared tadalafil, tamsulosin and placebo in patients with SRS and found that tadalafil was more effective than tamsulosin in relieving body pain, improving general, and sexual health states with similar improvements in rest of the domain of USSQ in both groups (tamsulosin and tadalafil), however both groups were found to be effective when compared to placebo in patients with SRS. In contrast to this study, we found that addition of tadalafil (Group A) to silodosin with solifenacin group (Group E) didn't lead to any advantage but in fact this combination was associated with more body pain and negative impact on QOL.

However our study was also not free from limitations like use of single stent design and material and being a single center study. Although the sample size was adequately calculated, it was still small in each group.

In conclusion, SRS has major impact on patient's daily life and combination of silodosin and solifenacin (Group E) was an effective drug treatment for relieving these symptoms with improved QOL and less requirement of analgesic than all other groups. However, study with multicentre design can be more helpful to validate our results.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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