Trends in Medicine

Research Article ISSN: 1594-2848

Effect of two different doses of solifenacin succinate therapy (5 mg, 10 mg) for the treatment of ureteral stent (Double J) related symptoms in comparison to placebo

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Abstract

Background and objectives: Double-J ureteral stent is widely used in the endourologic surgery. However, it might cause some annoying side effects. This study aimed to evaluate the effect of two different doses of solifenacin (5 mg, 10 mg) on double-J stent-related symptoms after uncomplicated ureteroscopic lithotripsy.

Methods: This study involved 120 patients. A total of 80 patients undergoing double-J ureteral stent insertion after ureteroscopic lithotripsy were recruited and provided with solifenacin postoperatively (40 patients received 5 mg and another 40 patients received 10 mg). Another 40 age-and sex-matched patients without solifenacin therapy (received placebo) were enrolled as a placebo group. All patients completed the modified-form Ureteral Symptom Score Questionnaire to evaluate the lower urinary tract symptoms, hematuria and stent-related body pain two weeks following the operation. The severity of stent-related symptoms was compared between the three groups.

Results: The mean age was 45.4 years in 5 mg solifenacin group, 48.2 years in the 10 mg solifenacin group and 46.8 years in the placebo group. Compared to the placebo group, both solifenacin groups had significantly lower total symptom score, urgency and urge incontinence scores. Solifenacin groups had significantly less urethral, abdominal and flank pain and hematuria scores. There was no statistically significant difference between the two solifenacin groups of 5 mg and 10 mg. The solifenacin groups versus placebo group showed significant benefits in lower urinary tract symptoms, hematuria and stent-related pain in both genders. Ten subjects encountered minor adverse events in solifenacin groups (8 in the 10 mg group and 2 in the 5 mg group) which was mostly dry mouth and constipation.

Conclusion: Postoperative solifenacin was effective and well-tolerated in patients undergoing ureteroscopic lithotripsy and double-J stent indwelling irrespective of genders, particularly for the treatment of stent-related body pain, hematuria and the lower urinary tract symptoms.

Introduction

The double-J ureteral stent is widely used in the endourologic surgery to treat or prevent ureteral obstruction [1]. Some of the patients might suffer from stent-related morbidities, such as lower urinary tract symptoms (LUTS), stent-related body pain and hematuria. These side effects are annoying and might have an adverse effect on quality of life (QoL) and sexual performance for both genders [2-4]. The pathophysiology of stent-related symptoms is not wee understood. However, the pain and LUTS caused by stent placement could be attributed to lower ureter and bladder spasm resulting from local irritation of the stent [5]. Previous research has revealed that oral agents such as tolterodine ER (antimuscarinics), tamsulosin and alfuzosin (alpha-1 antagonists) can relieve the stent-related symptoms [6-9]. Solifenacin is a new antimuscarinic, which is used for treating patients with overactive bladder [10,11]. The drug might also be useful for stent-related symptoms. However, the currently existing evidence is scarce [12]. This study aimed to assess the effectiveness and safety of solifenacin in treating double-J stent-related symptoms after uncomplicated ureteroscopic lithotripsy (URSL).

Materials and methods

This prospective comparative study was carried out in Rizgary Teaching Hospital, Erbil, Iraqi Kurdistan Region between April and October 2017. We prospectively collected 80 consecutive adult patients with ureteral stone who received URSL and double-J stent indwelling after obtaining verbal informed consent. The first half of them received 5 mg solifenacin and the second half received 10 mg solifenacin each day postoperatively. Another 40 age-and sex-matched patients given a placebo postoperatively were enrolled as the placebo group. All the procedures were done under general anesthesia. The calculi were disintegrated by Pneumatic lithotripser. A double-J ureteral stent was indwelled at the end of the URSL and the size and length of the stent were the same for all (4.7 Fr. width, 28 cm length & of the same manufacturer -ENDOVASIVE). All procedures were completed with no complications (no significant residual fragments, no ureteral injury, and no migration to renal pelvis).

The patients were discharged after 6 hours. Gentamycin Ampule (80 mg t.i.d.) for three days and diclofenac tablet (50 mg t.i.d.) were prescribed postoperatively. A number of exclusion criteria were applied

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Key words: *solifenacin, double j ureteral stent, lower urinary tract symptoms*

Received: September 07, 2018; **Accepted:** September 20, 2018; **Published:** September 24, 2018

in this study. Firstly, patients with concomitant renal calculi or residual calculi on the postoperative Kidney–Ureter–Bladder (KUB) film were excluded. Secondly, patients with other diseases which can result in LUTS or bladder pain, including prostate disease (benign prostate hypertrophy, chronic prostatitis, and prostate cancer), overactive bladder, interstitial cystitis, painful bladder syndrome and urinary tract infection were also excluded. Thirdly, patients with long-term medications with alpha-blockers or analgesics were excluded. Lastly, patients with procedure-associated complications such as fragments migration to the kidney, ureteral injury or stent malposition were also excluded from the study. A KUB film was taken to all the patients to confirm the position of the stent and exclude the presence of residual stones.

Ureteral stent Symptom Score Questionnaire (USSQ) is a validated and broadly used questionnaire for stent-related symptoms [13]. We utilized a modified version, brief-form questionnaire, which included urinary symptoms score and body pain score, the two main sections of USSQ. The first section of the questionnaire included four items to evaluate the severity of urinary frequency, urgency, urgent incontinence and nocturia. This part is adapted from the validated questionnaire of International Prostate Symptoms Score (IPSS). The second section of the questionnaire included four items to evaluate the severity of body flank pain, abdominal pain, urethral pain and the presence or absence of gross hematuria. The scoring ranged from 0 to 5; 0 being no pain and 5 being the worst pain ever experienced. Two weeks after the operation, the stent-related symptoms of the studied subjects were assessed. The study protocol was approved by the scientific and ethics committees of the Kurdistan Board of Medical Specialties.

Statistical analysis

Data were collected using a specially designed questionnaire. The statistical package for the social sciences (version 22) was used for data analysis. The results were compared between patients with different variables. The results were presented as rates, ratio, frequencies, percentages in tables and analyzed using ANVOA and Chi square test. The statistical significance level was set at <0.05.

Results

The demographic and clinical data are listed in Tables 1 and 2. The mean age was similar between three groups (placebo; 46.8±11.9 years, 5 mg solifenacin 45.4±12.3 years and 10 mg solifenacin; 48.2±10.6 years, p<0.71). There were no significant differences in stone position, laterality, body height and weight of the subjects in all the three groups.

Table 3 shows the comparison in double-J stent-related symptoms score for all three groups, the total mean±SD for frequency (2.56±0.93, p<0.88) which is not significant between all three groups, the same thing is right for Nocturia (mean±SD, 1.84±0.74, p<0.36).the mean±SD for Urgency (1.05±1.04, p<0.001) and for incontinence (0.32±0.62, p<0.001) show significant differences between them with no significant

Table 1. The demographic and clinical characteristic in all subjects (age, body height and body weight)

Variables	5 mg Solifenacin (n=40)	10 mg Solifenacin (n=40)	Placebo (n=40)	P (ANOVA)
Age (mean±SD)	45.4±12.3	48.2±10.6	46.8±11.9	0.71
Body height (mean±SD)	163±9.1	161±9.8	164±9.3	0.12
Body weight (mean±SD)	70.2±9.8	68.6±10.1	71.1±8.6	0.23

Table 2. The demographic and clinical characteristic in all subjects (gender, stone position and laterality)

Varivables	Categories	5 mg Solifenacin	10 mg Solifenacin	Placebo	P
		No. (%)	No. (%)	No. (%)	
Gender	Male	20 (50.0)	20 (50.0)	20 (50.0)	1.00
	Female	20 (50.0)	20 (50.0)	20 (50.0)	
Stone position	Upper 1/3	8 (20.0)	10 (25.0)	8 (20.0)	0.07
	Middle 1/3	12 (30.0)	14 (35.0)	10 (25.0)	
	Lower 1/3	20 (50.0)	16 (40.0)	22 (55.0)	
Stone laterality	Right side	23 (57.5)	19 (47.5)	24 (60.0)	0.09
	Left side	17 (42.5)	21 (52.5)	16 (40.0)	

difference between 5 mg solifenacin group and 10 mg solifenacin group (p<0.641 for urgency and p<0.833 for incontenece). In stent related pain and gross hematuria all parameter shows significant differences between placebo group and the two solifenacin groups (total mean±SD for flank pain 1.37±0.95, p<0.001, for abdominal pain 1.25±1.26, p<0.001, for urethral pain 1.45±1.20, p<0.001, and for Gross hematuria 1.46±1.21, p<0.001) but with no significant differences between the two solifenacin groups.

Discussion

Research has revealed that there is no need for ureteral stenting after uncomplicated URSL [14,15]. In the present study, we routinely placed the double-J stent in all subjects following URSL to prevent postoperative morbidities such as hydronephrosis and colic during the process of ureteral edema resolution after URSL.

Undoubtedly, ureteral stents might assist in ensuring the patency of the involved ureter with adequate drainage. However, associated morbidities such as LUTS, body pain and hematuria might cause significant adverse effects on patient's Quality of Life (QoL) [2]. This study evaluated the effect of two different doses of solifenacin for the prevention of stent-related symptoms following URSL using a structured questionnaire as compared with the age-and gender-matched placebo group. In the present study, we found that solifenacin was effective for stent-related urgency, urgent incontinence, body pain and hematuria for both genders with no significant difference in between daily 5 mg and 10 mg doses.

The pathophysiology of stent-related symptoms is still unclear. Bladder and lower ureter spasm due to irritation of intravesical portion of the stent is a probable mechanism for stent-related LUTS. The involuntary contraction of the bladder is mediated by muscarinic receptors [6,16]. The irritation, spasm and high-pressure transmission to renal collecting system through stent might be responsible for the urethra, abdomen or flank pain [5]. It has been suggested that gross hematuria is closely related to stent friction in the collecting system due to physical activity and low urine amount. However, intense and constant spasm and retrograde pressure transmission through stent are also associated with hematuria [17].

Several oral agents have been reported to relieve the stent-related symptoms, including tamsulosin, alfuzosin and tolterodine ER, and the results were encouraging [6-8]. Oral medication alone was most effective in patients with short-term indwelling stent following URSL. Solifenacin is an effective and safe drug for treating overactive bladder with limited side effects [10,11,18-22]. The present study also shows that the side effects of solifenacin in the study participants were limited. Moreover, most of the side effects such as headache, dry mouth and constipation were minor and self-limited (Table 4).

Table 3. The comparison in double-J stent-related symptoms score for all three groups

Variables	Groups	N	Mean	S.D.	P (ANOVA)	Groups	P value
Frequency	Solifenacin (5 mg)	40	2.55	0.98	0.88	Solifenacin (5 mg) Solifenacin (10 mg)	0.905
	Solifenacin (10 mg)	40	2.52	0.87		Solifenacin (5 mg) Placebo	0.722
	Placebo	40	2.62	0.95		Solifenacin (10 mg) Placebo	0.635
	Total	120	2.56	0.93			
Urgency	Solifenacin (5 mg)	40	0.55	0.63	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.641
	Solifenacin (10 mg)	40	0.47	0.64		Solifenacin (5 mg) Placebo	0.001
	Placebo	40	2.12	0.85		Solifenacin (10 mg) Placebo	0.001
	Total	120	1.05	1.04			
Incontinence	Solifenacin (5 mg)	40	0.10	0.30	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.833
	Solifenacin (10 mg)	40	0.07	0.26		Solifenacin (5 mg) Placebo	0.001
	Placebo	40	0.80	0.82		Solifenacin (10 mg) Placebo	0.001
	Total	120	0.32	0.62			
Nocturia	Solifenacin (5 mg)	40	1.80	0.72	0.36	Solifenacin (5 mg) Solifenacin (10 mg)	0.764
	Solifenacin (10 mg)	40	1.75	0.74		Solifenacin (5 mg) Placebo	0.295
	Placebo	40	1.97	0.76		Solifenacin (10 mg) Placebo	0.179
	Total	120	1.84	0.74			
Flank pain	Solifenacin (5 mg)	40	1.02	0.69	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.780
	Solifenacin (10 mg)	40	0.97	0.80		Solifenacin (5 mg) Placebo	.668
	Placebo	40	2.12	0.88		Solifenacin (10 mg) Placebo	0.001
	Total	120	1.37	0.95			
Abdominal pain	Solifenacin (5 mg)	40	0.80	1.04	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.668
	Solifenacin (10 mg)	40	0.70	1.01		Solifenacin (5 mg) Placebo	0.001
	Placebo	40	2.27	1.06		Solifenacin (10 mg) Placebo	0.001
	Total	120	1.25	1.26			
Urethral pain	Solifenacin (5 mg)	40	1.07	1.02	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.918
	Solifenacin (10 mg)	40	1.05	1.08		Solifenacin (5 mg) Placebo	0.001
	Placebo	40	2.22	1.14		Solifenacin (10 mg) Placebo	0.001
	Total	120	1.45	1.20			
Gross hematuria	Solifenacin (5 mg)	40	1.18	1.15	0.001	Solifenacin (5 mg) Solifenacin (10 mg)	0.619
	Solifenacin (10 mg)	40	1.05	1.10		Solifenacin (5 mg) Placebo	0.001
	Placebo	40	2.15	1.09		Solifenacin (10 mg) Placebo	0.001
	Total	120	1.46	1.21			

In our study, Frequency and Nocturia scores were not significantly decreased in the solifenacin groups (5 mg &10 mg) as compared to placebo group. Since water intake was encouraged for patients undergoing URSL and double-J stent indwelling, polyuria may explain the persistence of these symptoms.

Male and female patients may suffer from different grades of stent-related symptoms. The present study reveals that male patients suffered more severe LUTS than female patients in the placebo group, although not statistically significant.

It was noteworthy that solifenacin (both doses 5 mg and 10 mg) has been shown to be effective in treating stent-related symptoms for both genders in our study.

Table 4. Side effects encountered in all the three groups

	5 mg Solifenacin (n=40)	10 mg Solifenacin (n=40)	Placebo (n=40)
Dry mouth	1	3	1
Constipation	1	2	0
Headache	0	3	1

Our study has some limitations. First, we did not collect preoperative (baseline) voiding and pain scores for all three groups to compare it postoperatively. Second, the determination of stone-free status by KUB in the present study may not be sufficient, since non-contrast CT is a better imaging modality for the detection of residual stones [23,24]. Third, all the URSLs in the study were uncomplicated. Nevertheless, the ureteroscopic procedure has specific traumatic consequences on ureter,

which might be responsible for the lower urinary tract symptoms. This may confound the evaluation of solifenacin effect on the treatment of stent-related symptoms which are directly induced by the stent itself.

Conclusions

For patients with ureteral calculi following URSL, postoperative 5 mg solifenacin or 10 mg Solifenacin are effective and well tolerated for the treatment of stent-related symptoms, mainly urgency and urgent incontinence, stent-related body pain and hematuria among both genders with no significant differences between 5 and 10 mg.

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