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Original Research Article

Effects of silodosin, darifenacin, and combination therapy for the treatment of ureteral stent related discomforts

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ABSTRACT

Background: To evaluate the effect of silodosin, darifenacin and combination therapy of two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.
Methods: A total of 150 patients underwent placement of a double-J ureteral stent after retrograde ureteroscopy for urinary stone disease. All patients received polyurethane double-J ureteral stents (4 Fr and length 26 cm), which were removed at a mean of around 14 days postoperatively. A total of 40 patients were given no medication (group 1), 39 patients were given silodosin 4 mg once daily (group 2), 40 patients were given darifenacin 7.5 mg once daily (group 3), and 31 patients were given a combination of two agents postoperatively (group 4). International prostate symptom score (IPSS) and visual analogue pain scale (VAPS) questionnaires were completed by each patient at 1st day postoperatively and on the day of stent removal.
Results: In the total group of patients, the mean age was 50.24±12.90 years. There was a significant difference in the IPSS total score between group 1 and groups 3 and 4. Group 4 also differed significantly from group 1 in the irritative subscore. The obstructive subscore differed between groups 2 and 4 and group 1. There was a statistically significant difference between group 1 and group 4 in the quality of life (QoL) score.
Conclusions: Combination therapy with silodosin and darifenacin improved both irritative and obstructive symptoms more than in the other groups. Combination therapy should be strongly considered for patients who complain of stent-related symptoms.

Keywords: Pain, Stents, Ureter

INTRODUCTION

Ureteral stents, which were introduced by Zimskind et al in 1967, are widely used for urinary tract disease.[1] The double-J stent, which is the most common form of ureteral stent, is used in obstructive pyelonephritis, intolerable acute renal colic, ureteral edema, ureter perforation following endoscopic procedures, and diseases such as stein- strasse.[2,3] Despite the usefulness of stents, however, patients experience various stent-related symptoms, such as pain, frequency and urgency, which cause a significant decrease in patient health-related quality of life (HRQoL).[4]

The etiology of these symptoms is unknown. Thomas reported that an important factor of stent-related symptoms is the pressure transmitted to the renal pelvis during urination and trigonal irritation by the intravesicular part of the stent.[5] For this reason, several attempts to minimize stent-related symptoms have recently been reported. Pharmacologic management is one such trial, especially the prescription of selective alpha-1-blockers and antimuscarinic agents.

We believe that pharmacologic management is simpler and less invasive than other ways.

The objective of this article was therefore to analyze and assess the effectiveness of a selective alpha-1-blocker (silodosin) and antimuscarinic (darifenacin) in improving the lower urinary tract symptoms of patients with indwelling ureteral stents after a successful clearance of ureteric stones via ureteroscopy and lithotripsy.

METHODS

Materials

Between January 2020 and December 2020, 150 patients (98 men and 52 women) underwent double-J stenting retrogradely after retrograde ureteroscopy for urinary stones via the same technique. Patient data were obtained retrospectively through chart review. Patients who were previously diagnosed with benign prostatic hyperplasia or overactive bladder and who were prescribed a selective alpha-1-blocker or antimuscarinic agent were excluded from this study. In addition, patients who were using analgesics before surgery were also excluded. The ureteral stent was composed of polyurethane material and its diameter was 4 Fr; the length was 26 cm.

Methods

Our study is a randomized controlled trial conducted in Aarupadai Veedu Medical College, Puducherry, during the period of January 2020 to December 2020.

Inclusion criteria

The inclusion criteria for patients to be enrolled into the study are those patients: between age group 20 and 50 years, who have radiologically confirmed single ureteric stone of size 5 mm to 15 mm, and with first episode of stone formation.

Exclusion criteria

The exclusion criteria were: those patients with lower urinary tract symptoms prior to surgery, patients with prostatomegaly more than 30 cc in pre-operative imaging, those who had previous stone episodes, those who had prior urological instrumentation, those where the intraoperative stone fragmentation were inadequate, those who had complications like hematuria, infections and those with comorbidities.

The university ethical committee approval was obtained prior to the conduction of the study after appropriate scrutiny and all the participants signed a written informed consent before enrolment into the study. The randomization of the patient was done with the help of our statistician in a systematic manner and the patients were enrolled into the study.

Surgery was performed under spinal anesthesia using 6-7.5 Fr semi-rigid URS and the position of the stent was confirmed by plain X-ray. The stents were removed 14 days after surgery. The patients were divided into four groups. Group 1 (n=40) was the control group and did not take any drugs. Group 2 (n=39) received silodosin 4 mg once a day every day. Group 3 (n=40) received darifenacin 7.5 mg once a day every day. Group 4 (n=31) received silodosin 4 mg and darifenacin 7.5 mg daily. The day before surgery, on postoperative day 1, and on the day of stent removal, each patient completed written international prostate symptom score (IPSS) and visual analogue pain scale (VAPS) questionnaires. The IPSS was divided into the total score, obstructive symptom score, and irritative symptom score, and each was compared. Each group's preoperative day, postoperative day, and stent removal day scores were compared. Chi-square test, one-way analysis of variance (ANOVA), and one-way repeated-measures ANOVA were used for comparisons between each of four groups. Values of $p<0.05$ were considered statistically significant. Statistical analyses were performed with statistical package for the social sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 50.24±12.90 years, and there were no significant differences between the groups. A total of 97 patients had lower ureter stones, whereas 12 patients had mid ureter stones and 41 patients had upper ureteric stones. The stone distribution was significantly different in each group ($p<0.001$) (Table 1). There were statistically significant differences in the IPSS total score and the obstructive subscore by one-way repeated-measures ANOVA ($p=0.013$, 0.006). There were significant differences between group 1 and group 4 ($p=0.015$), and between group 2 and group 4 ($p=0.031$), in the IPSS total score. For the obstructive subscore, group 4 differed significantly from group 1 ($p=0.003$). There were no statistically significant differences in the irritative sub-score, QoL, or VAPS ($p=0.075$, 0.068, and 0.088, respectively). However, the p-value of interaction was statistically significant for the IPSS total score, irritative subscore, obstructive subscore, and QoL ($p<0.001$, <0.001, 0.015, and 0.012, respectively). We therefore compared each group by one-way ANOVA at each time point. On the day of stent removal, all scores were significantly different in each group except the VAPS ($p<0.001$, <0.001, <0.001, and <0.001). In particular, all scores were significantly lower in group 4 except for VAPS. In group 2, only the obstructive score was significantly lower. The total and irritative subscore were significantly lower in group 3. Preoperatively and 1 day postoperatively, there were no significant differences in any group. The VAPS did not appear to significantly change in any groups (Table 2). According to the multiple comparison test on the day of stent removal, there was a significant decrease only in group 4. This suggests that that stent-related symptoms improved more in group 4 than in group 1. Symptoms did not significantly improve in the other groups. The side effects of silodosin and darifenacin were minimal. No patients discontinued the medication because of side effects.

Table 1: The characteristics of 150 patients.

Characteristics	Group 1	Group 2	Group 3	Group 4	P value[a]
Patient (n)	40	39	40	31	
Age[b] (years)	50.08±11.47	49.91±15.23	48.87±13.29	50.72±11.46	0.986
Gender					
Male	27	22	28	21	
Female	13	17	12	10	
Stone location					
Upper ureter	5	9	14	13	
Mid ureter	2	3	3	4	
Lower ureter	33	27	23	14	

[a]: Chi-square test, [b]: mean±SD

Table 2: Comparisons of IPSS/QoL and VAPS in group 1, 2, 3 and 4.

Parameters	Group 1	Group 2	Group 3	Group 4	P value[a]	P value[b]
IPSS total score						
Pre-operative	8.94±4,13	8.60±4.12	9.04±3.94	8.72±4.2		0.958
On one day postoperatively	11.65±4.3	12.53±4.8	11.16±5.1	11.5±3.9	0.013	0.552
On the day of stent removal	13.77±4.5	12.77±5.2	11.04±5.29	7.16±3.37	(<0.001)[c]	<0.001
T[d]	1	1, 2	2	3		
IPSS irritative subscore						
Preoperative	4.15±2.59	4.30±2.84	4.49±3.09	4.84±2.71		0.735
On one day postoperatively	6.44±3.46	7.79±3.69	6.27±4.00	7.09±3.52	0.075	0.201
On the day of stent removal	7.48±3.50	8.05±3.88	5.73±4.00	4.22±2.70	(<0.001)[c]	<0.001
T[d]	1, 2	1	2, 3	3		
IPSS obstructive subscore						
Preoperative	4.79±3.16	4.30±2.95	4.56±2.78	3.88±2.9		0.572
On one day postoperatively	5.21±2.57	4.74±2.91	4.89±2.73	4.38±2.5	0.006	0.592
On the day of stent removal	6.29±2.63	4.72±3.24	5.31±2.91	2.94±2.06	(0.015)[c]	<0.001
T[d]	1	2	1, 2	3		
QoL						
Preoperative	2.52±1.79	2.19±1.80	2.42±1.62	1.88±1.8		0.385
On one day postoperatively	2.21±1.76	2.44±1.71	2.51±1.74	2.34±1.5	0.068	0.844
On the day of stent removal	2.83±1.72	3.07±1.67	2.87±1.77	1.47±1.44	(0.012)[c]	<0.001
T[d]	1	1	1	2		
VAPS						
Preoperative	6.42±1.71	6.60±1.59	6.18±1.70	6.28±1.65		
On one day postoperatively	2.56±1.47	2.88±1.50	2.69±1.46	2.44±1.37	0.088 (0.634)[c]	
On the day of stent removal	2.90±1.65	3.67±1.94	2.87±1.87	2.69±1.3		

IPSS/QoL: International Prostate Symptom Score and Quality of Life, VAPS: Visual analogue pain scale, a: one-way repeated measures ANOVA, b: one-way ANOVA, c: p-value of interaction, d: the same letters indicate non-significant difference between groups based on Tukey's multiple comparison test.

DISCUSSION

Stents placed in the ureter are used in the treatment of urinary tract diseases. The prevention of obstruction of the ureter and enhancement of recovery of the traumatized ureteral tissue, expansion of the ureteral lumen to aid in the expulsion of the stones being few examples.[2] After ureterorenoscopy, especially after ureteroscopic surgery for the ureteral stones, we often make use of ureteral stents.[6]

These stents in the ureter help in the recovery from urinary tract disease, whereas those patients with double J stents in their ureters often complain of various stent-related disturbances. In fact, flank pain, lower abdominal pain or loin pain, increased frequency, urinary urgency, urinary tract infection and hematuria are known symptoms of indwelling ureteral stents.[7] Joshi et al reported that, 80% of patients have a reduction in their HRQoL due to indwelling stents and need continued recognition and interest about those symptoms.[8]

In order to clarify these problems, studies have been done. Initially changes in the stent material were done to decrease the symptoms. For instance, double-J stents were introduced with a tapered distal end made with a hydrophilic material.[9] Furthermore, studies about the morbidity associated with the stent length were reported. If a stent in the ureter is needed after any surgery, length of the ureter should be calculated so that a stent of optimum dimensions is used in those patients, which will definitely decrease the migration of the stent and associated symptoms.[10] Injection of botulinum toxin type A after the placement of the stent is shown to reduce the pain and narcotic requirement.[11] We tend to believe that manufacture of a new stent is difficult. Furthermore, the cost effectiveness of using botulinum toxin is considered to be a problem.

Thus we went after safe and convenient ways of improving the stent-related symptoms and we have researched pharmacologic manipulation as one of those methods. Stent-related symptoms are not too dissimilar to the benign hyperplasia of prostate symptoms which is caused due urethral and bladder outlet obstruction and bladder instability.[12] For this purpose, some researches have reported that use of selective alpha-1-blockers that improved the stent-related symptoms. Beddingfield et al reported that patients taking alfuzosin 10 mg everyday had improved frequency and flank pain.[13] In addition, improvement of sleep disorders and daily life were also reported. Deliveliotis et al reported that alfuzosin reduced the stent-related symptoms and pain along with sexual function and general health.[14] Wang et al showed that the selective alpha-1 receptor-blocker tamsulosin reduced urinary symptoms, flank pain, and dysuria.[15] Furthermore, Damiano et al revealed that the addition of tamsulosin improved urinary symptoms, VAPS, and also the QoL.[12] In our research, the IPSS total score, irritative subscore, QoL, and pain score did not reveal any statistically significant difference. But, the difference in the obstructive subscore was statistically significant.

Symptoms related to the placement of indwelling ureteral stents are similar to the symptoms of overactive bladder (urinary frequency, urgency, and urge incontinence) caused by involuntary bladder contraction mediated by cholinergic receptors.[16] Antimuscarinic agents were used to treat overactive bladder. Norris et al reported that there were no significant differences between groups treated by oxybutynin and a placebo.[17] But they suggested that further ongoing research is required. Agarwal et al reported that bladder disturbances were improved in an Oxybutynin or tolterodine administration group compared with a placebo group before surgery.[18] In our study, the dalifenacin 7.5 mg daily group had statistically significant differences in the total score and irritative subscore. The other scores were not significantly different.

Lee et al analysed the combination treatment with tamsulosin and tolterodine and compared with a placebo group.[19] Each group does not show significant differences in the IPSS or VAPS. They reported that proper location was more efficacious in the improvement of stent-related symptoms. In the current research, however, IPSS and QoL showed statistically significant improvement in the silodosin and darifenacin combination treatment group. However, there was no significant difference in the VAPS.

The limitations of this study are as follows. Few patients were not able to completely answer the ureteral stent symptom questionnaire on the preoperative day. Thus, we were not able to use this questionnaire. The small sample size of each group made it difficult to assess the statistical significance. Therefore, further large-scale, randomized, prospective study is needed to get more accurate information.

CONCLUSION

Combination therapy with silodosin and darifenacin reduced the obstructive and irritative symptoms and QoL more than that in the control group. Thus, combination therapy with silodosin and darifenacin should be considered for patients who complain of stent-related symptoms. In the future, large-scale, prospective, and randomized study will be needed.

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