

Prospective Randomized Controlled Study Evaluating Efficacy of Alpha-Blockers, Antimuscarinics or Combination Therapy in Relieving Ureteral Stent-Related Symptoms

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Abstract

Background: Double-J ureteral stent placement is a routine urologic procedure after most of urological interventions. Great efforts are being done to decrease stent symptoms including; improving stent materials, physical properties, and design. Also the application of a combination of alpha-blockers and antimuscarinics are used in our study.

Aim of Study: We evaluated the effectiveness and safety of tamsulosin, solifenacin, and combination of both in reducing double-J stent-related lower urinary symptoms.

Patients and Methods: A total of 120 patients with double-J ureteral stenting were randomly divided, post-operatively, into 4 groups. In Group A (n=30), tamsulosin 0.4mg was given, Group B (n=30) received solifenacin 10mg daily, Group C (n=30) received solifenacin 10mg and tamsulosin 0.4mg daily, and Group D (n=30) received placebo (control group). Two weeks after discharge was the first time of evaluation (pre-treatment assessment), using an arabic validated version of USSQ. The second visit was after 4 weeks from surgery just before stent removal (post-treatment assessment).

Results: There were statistical significance in urinary symptoms, pain, general health and work performance scores in favour of Group III as compared to the tamsulosin group, the solifenacin group, and the control group (p -value <0.001).

Conclusion: Combined therapy of tamsulosin and solifenacin significantly alleviated symptoms associated with double-J stents as compared to either medication alone.

Key Words: Alpha blockers – Antimuscarinics – Combination – Double-J symptoms.

Introduction

DOUBLE-J ureteral stent placement is a routine urologic procedure after most of urological interventions. D-J stent helps to control many complications as ureteral edema, extravasation, and perforation to avoid later stricture. We report the

incidence Urinary symptoms and pain (flank and suprapubic) associated with stenting. Also there are deterioration in general health and work performance and affection of the sexual performance. The discomfort from placement of the stent, however, occurs significantly in some patients. The studies reported the incidence of frequency (50%-60%), urgency (57%-60%), dysuria (40%), incomplete emptying (76%), flank (19%-32%) and suprapubic pain (30%), and hematuria (25%) [1].

Great efforts are being done to decrease stent symptoms including; improving stent materials, physical properties, and design. Also the application of a combination of alpha-blockers and antimuscarinics are used in our study [2].

Tamsulosin acts as a selective inhibitor of α -1 adrenergic mediated contraction of the smooth muscles in distal ureter, bladder trigone, and bladder neck. It is thought that relaxing these smooth muscles decreases bladder outlet resistance and voiding pressure, with beneficial effect on stent [3].

Solifenacin acts as a muscarinic receptor antagonist used for treatment of patients with Overactive Bladder (OAB) and might be effective as well for stent related symptoms [4].

In this prospective study we evaluated the effectiveness and safety of alpha-1-blocker (tamsulosin), antimuscarinic (solifenacin), and combination of both medications in reducing double-J stent-related LUTS, using the Arabic version of USSQ [5].

Patients and Methods

This study was carried out in Tanta University Hospitals during the period from January 2017 to

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January 2018. After hospital Ethical Committee approval and written informed consent, 120 patients were included in the study according to exclusion and inclusion criteria with ureteral stent insertion after ureteral surgeries for a variety of reasons. There was a code number for every patient's file. Complete history taking, physical examination and routine laboratory and radiological investigations for the patient were done.

Inclusion criteria: All adult patient who underwent ureteral stent insertion after ureteral surgeries for a variety of reasons.

Exclusion criteria:

- 1- Pediatric patients less than 18 years old.
- 2- Patient with bleeding tendency.
- 3- Patient with neurogenic bladder.
- 4- Patient with bladder outlet obstruction.

All patients were randomly assigned into four treatment groups by the block randomization method which is designed to randomize subjects into groups that result in equal sample sizes. The resulted group assignment were;

Group A: Included code numbers from 1 through 30 whom took alpha blocker in the form of (tamsulosin 0.4mg, tablet as a single dose at bed time).

Group B: Included code numbers from 31 through 60 whom took antimuscarinic in the form of (solifenacin 10mg, tablet once daily).

Group C: Included code numbers from 61 through 90 whom took alpha blocker (tamsulosin) and antimuscarinic (solifenacin).

Group D: Included code numbers from 91 through 120 whom took placebo (in the form of starch tablet once daily).

All the stents were placed by senior staff, stent introduced with an appropriate length according to mathematic formula; $\text{length} = 0.125 \times \text{body height in cm} + 0.5\text{cm}$, positioning verified at the completion of surgery. 16 Fr urethral catheter was fixed for 1 to 2 days postoperatively. In the first post-operative day a KUB film was done to confirm position of the DJ stent. Injection antibiotics used according to urine culture and antibiotic sensitivity besides NSAIDs for analgesia. After discharge suitable antibiotic and analgesic were prescribed in oral forms taken for 7 days.

Two weeks after discharge was the first time of evaluation (pre-treatment assessment), all patients asked to come again into the hospital to

assess stent related symptoms using an Arabic validated version of USSQ, which evaluates stent-related morbidity in six sections, including urinary symptoms, body pain, general health, work performance, sexual matters, and additional problems. Each section comprises several questions the answers of which are summed to allocate a score. The calculation of the score for each section provides the urinary index score, pain index score, general health score, work performance score, and sexual matters score. The second visit was after 4 weeks from surgery just before stent removal and after 2 weeks of treatment with the tested drugs, the same USSQ items of the first visit were evaluated according to patient experience in the 2 weeks of treatment with tested drugs (post-treatment assessment).

Statistical analysis:

Chi-square test: For categorical variables, to compare between different groups.

F-test (ANOVA): For normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons.

Kruskal Wallis test: For abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.

Mean/average: Sum of all values divided by the number of values.

Standard deviation (SD): Indicates how much a set of values is spread around the average.

The p (probability) value: Gives the probability of any observed difference having happened by chance. The lower the *p*-value, the less likely it is that the difference happened by chance and so the higher the significance of the finding. $p=0.01$ is often considered to be "highly significant".

Ethical considerations:

There are adequate provisions to maintain privacy of participants and confidentiality of the data as every patient had a code number, the name and the address were kept in a special private file linked to the research, the results of the study were used only for scientific purpose and not for any other purposes. The ethical committee approval was taken under the number () also an informed consent was obtained from all participants in this research after full explanation of benefits and risks of the study.

Results

A total of 120 patients were enrolled in the study, and 107 patients completed the study (3 patients from Group A, 4 patients from Group B, 2 patients from Group C, and 4 patient from Group D dropped out). Group A (27 patients) consisted of 14 men and 13 women (mean age: 49.44 ± 12.59 SD), Group B (26 patients) consisted of 13 men and 13 women (mean age: 46.65 ± 13.05 SD years), Group C (28 patients) consisted of 15 men and 13 women (mean age: 45.96 ± 9.43 SD years), and Group D (26 patients) consisted of 16 men and 8 women (mean age: 48.81 ± 10.73 SD years). The main indication of ureteral double-J stent placement was URS and ESWL. All patients completed the necessary questionnaires. There were no statistically significant differences between groups regarding patient's demographics and treatment indications (Table 1). Therapies were well tolerated, and no

patients discontinued the treatments because of side effects. When comparing the pretreatment and post treatment scores, we found that there were a statistically significant differences in Group D for all evaluated scores, in Group A for the urinary symptoms, pain and general health scores, and in Group B for the urinary symptoms, pain and sexual matters (Table 2).

There were statistical significances when we compared the percentage of improvement between Group C and the control group as regard to urinary symptoms, pain, general health and work performance (p 2-values were <0.001), aslo there were significances between Group A and the control group according to urinary symptoms and pain (p 2-value were 0.047 and 0.001 respectively), and there were values when comparing Group B with the control group in the urinary symptoms and pain scores (p 2-value were <0.001 and 0.005) (Table 2).

Table (1): Comparison between the characteristics of studied patients.

Variables	Group A	Group B	Group C	Group D	<i>p</i> -value
Number of patients	27	26	28	26	
Mean age (years)	49.44 ± 12.59	46.65 ± 13.05	45.96 ± 9.43	48.81 ± 10.73	0.636
Sex (Male: Female)	14:13	13:13	15:13	13:8	0.478
<i>Indications of stent placement:</i>					
URS	12	13	11	13	0.992
PCNL	4	3	4	5	
ESWL	7	6	7	5	
Ureterolithotomy	4	4	6	3	

Table (2): Comparison between different studied groups according to percentage of improvement and *p*-values.

Score	Group A	Group B	Group C	Group D
<i>Urinary symptoms:</i>				
% of improvement	11.52 ± 14.38	29.32 ± 14.39	45.0 ± 14.50	0.60 ± 1.70
<i>p</i> ₁ value	<0.001	<0.001	<0.001	0.083
<i>p</i> ₂ value	0.047	<0.001	<0.001	
<i>Pain:</i>				
% of improvement	13.52 ± 15.19	7.30 ± 7.72	47.56 ± 11.35	0.16 ± 2.60
<i>p</i> ₁ value	<0.001	<0.001	<0.001	0.782
<i>p</i> ₂ value	0.001	0.005	<0.001	
<i>General health:</i>				
% of improvement	7.77 ± 10.33	2.18 ± 6.67	38.98 ± 16.03	2.58 ± 6.81
<i>p</i> ₁ value	<0.001	0.106	<0.001	0.057
<i>p</i> ₂ value	0.100	0.841	<0.001	
<i>Work performance:</i>				
% of improvement	9.52 ± 17.22	5.79 ± 13.18	47.31 ± 19.11	0.89 ± 8.94
<i>p</i> ₁ value	0.007	0.026	<0.001	0.502
<i>p</i> ₂ value	0.148	0.357	<0.001	
<i>Sexual matters:</i>				
% of improvement	2.26 ± 45.23	8.25 ± 13.50	8.10 ± 12.30	0.77 ± 7.20
<i>P</i> ₁	0.307	0.005	0.003	0.480

Discussion

The double-J or pigtail stent is a tube placed within the ureteral lumen in a retrograde or antegrade fashion in order to maintain its patency. Placement of indwelling ureteral stents has become routine in the management of a variety of urinary tract diseases. Stents prevent upper urinary tract obstruction, divert urine, allowing for faster tissue healing, and dilate the ureter, assisting in stone passage [6].

Leibovici and colleagues suggested that use of double-J stents can lead to several side effects and cause negative effects on quality of life. These authors found common symptoms such as urgency, frequency and dysuria (55%, 50% and 40% respectively) [7].

In their study of 146 cases, Damiano and colleagues showed that discomfort due to stent (37.6%) and irritative urinary symptoms (18.8%) were the most common complications in cases with a ureteral stent [8].

Joshi and colleagues in a study on 62 patients found that irritative urinary symptoms, incontinence and hematuria were present in 78% of the patients in whom the double-J stent was applied. In more than 80% of these patients, pain related to the stent affects their daily lives. Sexual dysfunction was seen in 38% and deterioration in work performance was seen in 58% [9].

This was corresponding with our findings. We reported that the urinary symptoms post-operative were found in 80% of our cases, discomfort was 85% of the cases, pain associated with stenting was in 76% of our cases, affection of work performance was in 50 of our cases, decline in general health was 46%, and sexual performance deterioration was in 44% of patients.

Wang and his colleagues suggested that relaxation of bladder neck/prostatic smooth muscle setting a rationale behind using alpha blockers in overcoming ureteral stent symptoms [10].

Another mechanism was thought to be related to stent itself which may unmask or exacerbate preexisting subclinical detrusor overactivity setting a rationale behind using antimuscarinic agents to improve stent-related symptoms [11,12].

There are multiple strategies for managing stent complications include accurate stent indications, stenting maneuvers, stent design and use of medications. Many medical therapies have been tested, such as analgesics, anticholinergics and α -blockers,

to deal with the irritative symptoms and pain related with ureteral stents [13].

In the present study, we found that tamsulosin monotherapy controlled ureteral stent related symptoms. We recorded only significance with urinary symptoms and pain. Yakoubi et al., performed a meta-analysis showed that alpha-blockers were associated with a significant decrease in urinary symptoms (p -value 0.005) Also similar result was a significant decrease in pain score (p -value 0.0004) [14].

Wang, et al., in a prospective randomized study comparing tamsulosin to placebo in 145 patients using (USSQ) reported that tamsulosin improved stent related urinary symptoms (p -value <0.0001) and significant decrease in pain using VAPS (p -value <0.0001) as compared to placebo, and they recommended its routine use [15].

Also Damiano et al., reported that administration of tamsulosin has a positive effect on stent related urinary irritative symptoms although this study was not double-blinded or placebo-controlled [16].

Along with the above mentioned α -blockers studies, similar trials were performed with regimens such as anticholinergics in the treatment of stent related symptoms. In the present study, solifenacin monotherapy controlled stent-related symptoms and pain and these results were of statistical significant value. Similarly, Lee et al., reported in a prospective, randomized, and placebo-controlled study that post-operative solifenacin use was effective and well tolerated for the treatment of LUTS, stent-related body pain, and hematuria [17].

Also we recorded in our study that the patients received anticholinergic showed no statistical significant differences in the general health score, the work performance score, and the sexual matters score. Many researchers studied the effect of others antimuscrinic agents in reducing the negative symptoms associated with double-J ureteral stent. Park et al. In a prospective randomized controlled study reported that tolterodine was significantly able to improve pain and urinary symptom index scores when compared with alfuzosin and placebo [18].

Our study showed that the combination therapy gave the best results in improvement of urinary symptoms in the form of (frequency, urgency, dysuria, urge incontinence, and post voiding dribbling), pain associated with double-J stents, general health of the patients during the period of stenting, and work performance states of the patients, the

p-values of improvement in these scores were of statistical significances except for sexual matter, and when we compared the combination therapy with the placebo group and the mono therapy groups (tamsulosin or solifenacin), there were statistical significant values as regard to urinary symptoms, pain, general health, and work performance. Yan H et al., in a randomized controlled trials that referred to the use of a combination of antimuscarinics and alpha-blockers for the treatment of ureteral stent-related symptoms, a systematic review and meta-analysis was conducted. The conclusion of meta-analysis showed the beneficial effect of the combined use of antimuscarinics and alpha-blockers. The alpha-blockers may enhance the efficacy of the antimuscarinics, which is beneficial for the treatment of ureteral stent related symptoms [19].

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تأثير مضادات ألفا والمضادات المسكارينية أو الإثنين معا على الأعراض الناتجة من تركيب دعامات الحالب

دعامة الحالب هي عبارة عن قسطرة يتم وضعها في الحالب للمحافظة على بقاء إتساع الحالب بعد جراحات المسالك البولية. وقد أصبح وضعها مهم جدا في كثير من عمليات جراحة المسالك فهي تقوم بمنع إنسداد الحالب وتحويل مسار البول وسرعة إلتئام أنسجة الحالب وطرده الحصوات وتوسيع الحالب. ومن الأعراض التي تسببها الدعامات: الإلحاح للتبول والحرقان عند التبول وعدم الراحة والسلس البولي والنزيف البولي والألم المصاحب لتركيب الدعامات بالإضافة إلى تدهور الحالة الجنسية والأداء في العمل وتأثر في جودة المعيشة. تم عمل دراستنا في مستشفى جامعة طنطا على ١٢٠ مريض لمعرفة تأثير مضادات ألفا والمضادات المسكارينية وإستخدام الإثنين معا على الأعراض المصاحبة لتركيب دعامات الحالب. تم إختيار المرضى على حسب مواصفات خاصة حيث تم إختيار المرضى الخاضعين لعمليات في الحالب لأسباب متعددة وتم إستبعاد الأطفال أقل من ١٨ سنة والمرضى المصابين بسيولة في الدم والمصابين بمثانة عصبية أو إنسداد في مجرى البول على مستوى ما بعد المثانة. تم تقييم المرضى بإستخدام إستبيان معين معروف عالميا وكانت النتيجة التي توصلنا إليها بعد عمل الإحصاءات أنه عند إستخدام دواء التامسولين وهو نوع من مضادات ألفا مع دواء السوليفناسين وهو نوع من المضادات المسكارينية تم الوصول لأفضل محصلة من إستخدامها على حدى من حيث إنخفاض الأعراض المصاحبة لتركيب الدعامات والشعور بالآم والصحة العامة والأداء الجنسي والأداء في العمل ومستوى المعيشة.