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Effects of Tamsulosin and Tolterodine on double J stent–related symptoms: A double-blind, randomized, placebo-controlled trial

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Abstract

Background: Ureteral double J stent are routinely applied for urologic patients although stent-related symptoms are common. Several attempts have been reported to minimize these symptoms.

Objective: To compare Tolterodine, Tamsulosin, and placebo effects on double J stent–related symptoms.

Material and method: In all, 125 patients (82 males and 43 females) with double J stent were randomly divided into three groups (group 1, n: 42, group2, n: 40 and group 3, n: 43). Each patient randomly received one pack of drug in different colors by a nurse unaware of the content to take Tamsulosin 0.4 mg before sleep (MODALUSINE), Tolterodine 2 mg twice a day or placebo once daily (capsules filled with starch): group 1 received placebo, group 2 Tamsulosin and group 3 Tolterodine for 1 month in a double-blind manner. Ureteral stent-related morbidity indices which analyzed include urinary symptom, pain, general health, quality of work and sex scores. All of indices measured by Ureteral Symptom Score Questionnaire for first and fourth weeks after drug consumption and the first week after double J stent removal (labeled as w1, w4, and w5, respectively).

Result: The mean age was 44.8 years (range: 15–83 years). There was no statistically significant difference in background characteristics between groups (p value > 0.05). The most important and statistically significant results were Tolterodine-reduced urinary symptom score (p value = 0.001) and improved general health score (p value = 0.007) of the fourth week. The pain score in groups of Tamsulosin and Tolterodine significantly reduced between weeks 4 and 1 and 5 and 1 (both with the p value < 0.05), but in other indices, there was no significant difference between them.

Conclusion: According to our results, we suggest Tolterodine to minimize stent-related urinary symptom and improve general health in patients with double J stent.

Keywords

Tamsulosin, tolterodine, double J stent–related symptom, Ureteral Symptom Score Questionnaire

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Introduction

Zimskind et al.[1] were the first group who cystoscopically placed an endoluminal stent in 1967. Nowadays, ureteral stent is routinely applied to bypass ureteral obstruction due to various etiologies. However, stent-related symptoms have a high prevalence, up to 80%,[2] and cause a lot of complications and problems which affect the quality of life (QoL).[3,4] The most common complication is "stent syndrome" that patients have irritative urinary symptoms, flank pain, suprapubic discomfort and hematuria.[5]

Several attempts reported to minimize stent-related symptoms including stent material changes, application of appropriate stent length, periureteral injection of botulinum toxin A after stent placement, and pharmacological managements. In some

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study, alpha-1 antagonists had positive effects on stent-related symptoms and improving the QoL of patients.[6,7] But in other study have not.[8] Recent systematic review and meta-analysis supported the hypothesis that α1-blockers beneficially influence pain, urinary symptoms and the QoL of patients with an indwelling ureteral stent.[9] However, the efficacy of anticholinergic agents has been shown to other reports.[10,11] One recent meta-analysis suggested significant advantages of combination therapy of α-blocker and antimuscarinic compared with α-blocker monotherapy.[10] The effects of combination therapy were significant in other studies,[12,13] but in one study combination therapy was not effective.[14]

In a randomized controlled trial, Tadalafil was as effective as Tamsulosin in relieving urinary symptoms but more effective in relieving sexual symptoms and body pain.[15] Many of these studies were not placebo controlled and have not evaluated these side effects in a systematized way by a validated questionnaire.

Therefore, we performed a double-blind, randomized, placebo-controlled trial to evaluate and compare the effect of the anticholinergic agent, Tolterodine and selective alpha-1 antagonist, Tamsulosin in alleviation of stent-related symptoms and improvement of the QoL in patients with double J stent (DJS) by a validated questionnaire.

Materials and methods

Between April 2011 and June 2015, after consulting with expert in statistics and applying the mentioned formula (Figure 1) to estimate the number of participants who must be allocated in all three arms, 150 cases were assigned. The study was conducted in Imam Reza Hospital of Kermanshah University of Medical Sciences. All the patients we involved in study during the mentioned time were 145 who were selected based on the inclusion and exclusion criteria and underwent unilateral ureteral stenting for relieving upper urinary tract obstruction due to stone. Patients with lower urinary tract symptoms, history of benign prostatic hyperplasia (BPH; International Prostate Symptom Score (IPSS) > 7), urinary tract surgery or recent stent insertion, pregnant women, advanced cardiac or hepatic disease and consumers of selective alpha-1 blocker, anticholinergic or analgesics were excluded from the study. Out of 145 patients, 20 were excluded due to spontaneous stent passage (2 patients), drug cessation and incomplete or incorrect consumption (15 patients) or side effects (3 patients, discontinued the study due to Tamsulosin side effects; Figure 2).

After history taking, physical examination and routine laboratory exam, male patients answered IPSS questionnaire (International Prostatic Symptom Score) to evaluate infravesical obstruction and 5-item version of International Index of Erectile Function (IIEF-5) questionnaire for erectile function status. Then, under general anesthesia, DJSs (4.8 F, 28–32 cm; BIOTEQ) were inserted by rigid cystoscope or semi-rigid ureteroscope with or without transureteral

$$n_A = \kappa n_B \text{ and } n_B = \left(1 + \frac{1}{\kappa}\right)\left(\sigma \frac{z_{1-\alpha} + z_{1-\beta}}{\mu_A - \mu_B - \delta}\right)^2$$

$$1 - \beta = \Phi\left(z - z_{1-\alpha}\right) + \Phi\left(-z - z_{1-\alpha}\right) \quad , \quad z = \frac{\mu_A - \mu_B - \delta}{\sigma\sqrt{\frac{1}{n_A} + \frac{1}{n_B}}}$$

$\kappa = nA/nB$ is the matching ratio
- σ is standard deviation
- Φ is the standard Normal distribution function
- Φ^{-1} is the standard Normal quantile function
- α is Type I error
- β is Type II error
- $1-\beta$ is power
- δ is the testing margin

Figure 1. Formula applied for sample size estimation.

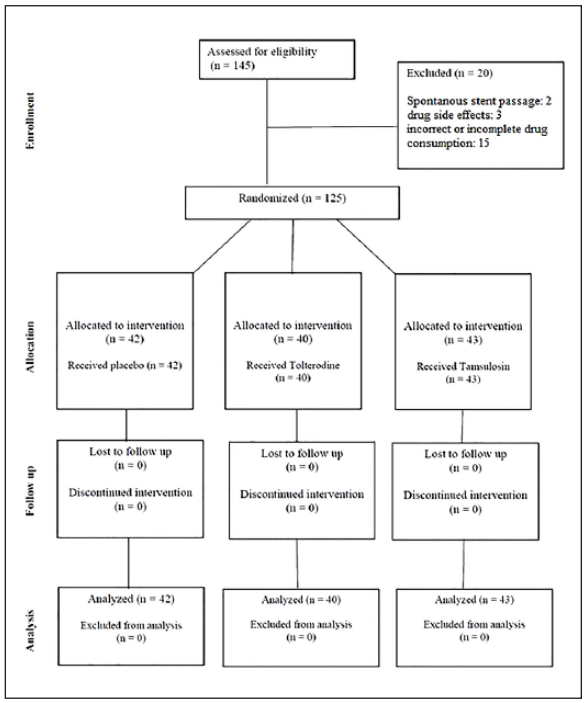

Figure 2. CONSORT flow diagram of present trial.

lithotripsy (TUL). Then, the position of stent was confirmed by kidney, ureter and bladder (KUB) radiograph. After performing all of these, the patients were randomly divided into three groups (group 1 (placebo), n: 42, group 2 (Tolterodine), n: 40 and group 3 (Tamsulosin), n: 43) to receive 4 weeks of medication; a pharmacist provided three different colors of same size drug packs, each containing one of the drugs or placebo, its prescription and an simple brochure in Persian language. Each patient randomly received one pack of the drug by a nurse unaware of the content, by picking up a pack through a basket in order to take Tamsulosin 0.4 mg before sleep (nightly) (MODALUSINE), Tolterodine 2 mg twice a day or placebo once daily (capsules filled with starch). Ureteral stent-related morbidity indices include the following: urinary symptom, pain, general health, quality of work, quality of sex and QoL scores which was assessed by Ureteral

Symptom Score Questionnaire (USSQ) in first and fourth weeks (labeled as w1 and w4, respectively) after drug consumption and 1 week after DJS removal (w5). Every patient completed an informed consent. The patients were told not to take another medicine and should be visited in situations such as fever, severe pain and discomfort. Consumption of any other drugs, significant complications or drug cessation were recorded in each visit. They were reminded by a physician the day before each visit by the phone call. We compared scores of groups in week 1, week 4 and week 5 with independent samples t-test and analysis of variance (ANOVA). However, comparisons between w1, w4 and w5 in each group were done by paired samples t-test.

Results

The study was performed with 125 patients (82 males and 43 females), with a mean age of 44.8 years (range: 15–83 years). None of the patients encountered any complication during the endoscopic procedure. There was no statistically significant difference in background characteristics between groups ($p > 0.05$) (Tables 1 and 2). (See supplementary file for all results: evidence for more information about the report of USSQ parts.)

In urinary symptoms, although not significant ($p > 0.05$), the mean scores of drug groups (especially Tolterodine) were less than the placebo group in w1, w4 and w5. While Tolterodine group had a significantly lower score in comparison to the placebo group in the fourth week ($p = 0.001$). Indeed, there was a significant reduction in the symptoms from the first to fourth week in the drug groups (Tamsulosin: $p = 0.000$; Tolterodine: $p = 0.000$).

In stent-related pain, no significant difference between the groups in w1, w4 and w5 was found. But by comparing the pain scores of the subgroups who had pain (eliminating the patients without pain), mean pain index score in the placebo group was 7.093 greater than Tolterodine group and 3.167 greater than Tamsulosin group in W4. The difference in pain index score between placebo and Tolterodine groups was significant ($p = 0.027$), though the difference between placebo and Tamsulosin groups ($p = 0.349$) or Tamsulosin and Tolterodine ($p = 0.091$) was not significant in this subgroup. Overall, drug groups showed a significant reduction in pain score from the first to fourth week ($p < 0.05$), but there was no difference between the subgroup who had pain ($p > 0.05$); however, according to the estimated number of participants for this study, the number of patients in each arm is not enough to compare them in stent-related pain index.

There was no difference in visual analogue scale (VAS) score between the groups ($p > 0.05$), but by comparing the subgroup who had pain, Tolterodine was more effective than placebo in w4 ($p = 0.011$).

In general health score, Tolterodine group had less score in comparison with Tamsulosin ($p = 0.010$) and placebo ($p = 0.006$) groups in the fourth week.

Table 1. Patients' characteristics.

Variables		Groups						p value
		Placebo		Tamsulosin		Tolterodine		
		N	%	N	%	N	%	
Gender	Male	29	69	31	72.1	22	55	0.221
	Female	13	31	12	27.9	18	45	
Surgery	UR + DJ	13	30.9	7	16.2	7	17.5	0.485
	TUL + DJ	23	54.7	30	69.7	27	67.5	
	DJ only	6	14.2	6	13.9	6	15	
Side	Right	21	50	19	44.1	19	47.5	0.865
	Left	21	50	24	55.8	21	52.5	
ESWL	Yes	11	26.1	15	34.8	5	12.5	0.060
	No	31	73.8	28	65.1	35	87.5	
Other drugs	NO	39	92.8	38	88.3	35	87.5	0.563
	AB	2	4.7	3	6.9	5	12.5	
	NSAID	1	2.3	2	4.6	1	2.5	

TUL: transureteral lithotripsy; UR: ureteroscopy; DJ: double J; ESWL: extracorporial shockwave lithotripsy; NO: none other drugs; AB: antibiotics; NSAID: nonsteroidal anti-inflammatory drugs.

Table 2. Patients' various baseline characteristics before the trial.

Variables	Groups						p value
	Placebo		Tamsulosin		Tolterodine		
	Mean	SD	Mean	SD	Mean	SD	
Days in situ	37.71	17.294	35.05	11.723	43.52	20.657	0.070
QoL	4.64	1.722	4.60	1.692	5.22	1.776	0.196
IPSS	2.21	2.445	1.77	2.010	1.50	1.974	0.319
IIEF	14.81	11.381	16.74	10.887	12.78	12.012	0.290

IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; QoL: quality of life; SD: standard deviation.

In work performance, Tamsulosin impaired work quality in first week even worse than placebo ($p = 0.00$), but there was no significant difference in other parts of work performance status (mean days in bed and loss of activity).

In quality of sex, there was no difference between the groups, but all of them had higher score in quality of sex in the fourth week in comparison to first week ($p = 0.00$).

In QoL, by comparing the groups in week1, week4 and week5, no significant difference was found ($p > 0.05$). In stent related comorbidities such as urinary tract infection (UTI), antibiotic consumption and seeking medication by visiting a doctor or emergency wards, no significant difference between groups found ($p > 0.05$).

Discussion

The ureteral stent has been introduced nearly three decades ago. During this period, it has been popularized as a useful

device to relieve the obstruction, divert urine, dilate ureter and allow faster tissue healing.[1] But patients have experienced a variety of stent-related morbidities.[3,4] The most common complication is "stent syndrome," for which patients experience symptoms like irritative urinary symptoms, flank pain, suprapubic discomfort and hematuria.[5] To assess these symptoms in a systematized manner, for the first time, Joshi et al. developed and validated the USSQ and evaluated stent-related morbidity. They reported 80% urinary symptoms and pain and 40% sexual dysfunction in patients with a DJ ureteral stent.[3]

Several attempts have been reported to minimize stent-related symptoms including changing stent material, application of appropriate stent length, periureteral injection of botulinum toxin A after stent insertion and pharmacological managements. A great effort has been made to improve ureteral stent characteristics in order to minimize morbidities. However, the ideal stent is not yet available.

There are few data about pharmaceutical treatment of these symptoms. Among the medications, alpha-1 antagonists have been the most valuable for the relief of stent-related symptoms and improving the QoL of these patients. However, anticholinergic agents have been prescribed anecdotally. The mechanism of alpha-1 adrenergic receptor antagonist involves the reduction of ureter and trigon smooth muscle activity and the mechanism of the anticholinergic drug involves relief of involuntary bladder contraction that is mediated with muscarinic receptors. Mokhtari et al. evaluated the effect of Terazosin for relief of urinary tract and flank pain in patients with DJS in comparison with placebo. They used IPSS questionnaire and VAS for evaluation and concluded that administration of Terazosin improves urinary tract symptoms and pain but has no effect on hematuria.[16] Dellis et al. in a prospective randomized control study compared Tamsulosin 0.4 mg and Alfuzosin 10 mg with placebo in 150 patients with a double-J ureteral stent. They used validated USSQ and concluded that simple medication, such as α-blockers, reduces stent-related symptoms and the negative impact of it on QoL and stent-related symptom improvement was independent of the type of α-blocker.[6] In other systematic review and network meta-analysis for Alfuzosin versus Tamsulosin versus placebo for ureteral stent-related discomfort, Kwon et al.[7] observed that alpha-blockers significantly decrease urinary symptom score (USS) and body pain score (BPS) in comparison with placebo and Tamsulosin was more effective than Alfuzosin.[7]

In another similar study, Valiere Vialeix et al.[8] evaluated Tamsulosin versus placebo for management of ureteral stent discomfort. Their study did not show the superiority of Tamsulosin versus placebo in the improvement of the ureteral stent tolerance.[8]

Recently, Zhang et al.[9] in a systematic review and meta-analysis supported the hypothesis that α1-blockers beneficially influence pain, urinary symptoms and the QoL of patients with an indwelling ureteral stent. A meta-analysis of 13 articles including 1408 patients from January 2000 to May 2014 showed the beneficial effect of α-blockers and antimuscarinics in reducing stent-related symptoms. Furthermore, it also showed the significant advantages of combination therapy of α-blocker and antimuscarinics compared with α-blocker monotherapy.[10] El-Nahas et al. compared the effectiveness of Tamsulosin and Solifenacin in relieving ureteral stent–related symptoms. The study included 131 patients. All baseline characteristics (age, sex, side, indication, length and duration of stent placement) were compared for all groups. Total USSQ score was 61 in Solifenacin group, 76 in Tamsulosin group and 83 in the control group ($p < 0.001$). The total and domains of USSQ scores, except sexual index, were significantly better in Solifenacin than in Tamsulosin group.[11] Shalaby et al. evaluated the effectiveness and safety of Tamsulosin, Solifenacin and the combination in reducing double-J stent-related lower urinary symptoms. A total of 338 patients with double-J ureteral stenting were randomly divided, postoperatively, into four groups and received Tamsulosin 0.4 mg daily, Solifenacin 10 mg daily, placebo and combination of both medications. They concluded that combined therapy of Tamsulosin and Solifenacin significantly alleviated lower urinary symptoms associated with DJSs in comparison to each medication alone.[12] Tehranchi et al.[13] evaluated the effects of Terazosin and Tolterodine on ureteral stent discomfort in the double-blind placebo-controlled randomized clinical trial. They observed that Terazosin with Tolterodine improves ureteral stent-related complications, including irritative symptoms, number of analgesics use, QoL, flank pain and micturition pain, but does not decrease obstructive symptoms or suprapubic pain.[13]

In contrast to the above-mentioned studies in randomized trial, neither Tamsulosin nor Solifenacin provided beneficial effects on relieving various SRSs, and the combination therapy was not effective too.[14] In a comparative study of Tadalafil and Tamsulosin in DJS-related symptoms, Tadalafil was as effective as Tamsulosin in relieving urinary symptom but more effective in relieving sexual symptoms and body pain.[15]

We designed this study as a randomized, double-blinded, placebo-controlled study, with same stent and placement technique for all patients to minimize trial variability. Our patients experienced less urinary symptoms with Tolterodine, and both Tolterodine and Tamsulosin made a significant reduction in the symptoms in a chronological manner from the first week to the fourth week. All the patients in three groups had fewer pain scores in the fourth week than the first week. These effects in drug groups were more significant than placebo. Although this can be concluded as the placebo effect, the drugs made a really greater reduction in pain as time passed. Patients had better general health in the fourth week of Tolterodine consumption. This effect was not only better than placebo but also better than Tamsulosin. No other group made a significant difference even by time passage. Tamsulosin group had a worse quality of work in the first

week than the two other groups. Although, only three patients reported significant side effects of Tamsulosin. Asthenia is a known side effect of it and can be responsible for the impairment of "rest", job efficacy and regular hours of work.

Patients who had sex during the stent in situ did not experience significant improvement by drug consumption, but all groups had better sex after 4 weeks. Although this can be interpreted as a placebo effect, drug groups had really greater improvement compared to placebo.

Neither drugs nor placebo resulted in any difference in QoL. Although time passage made some symptoms better, the patients did not experience prospered or deteriorated sense about having a stent again in the future. If they are not benefited from drugs or even placebo effect, they should have had a worse feeling about repeating this procedure. Overall, positive effects of Tolterodine were remarkable in the fourth week, and indeed, time passage itself had positive effect in some symptoms.

In the subgroup who had pain, there were some significant differences between drug groups and placebo: first, Tolterodine was more effective in pain index score in comparison with placebo, and second, Tolterodine improved symptoms in five-part USSQ questionnaire in the fourth week. The variations in these five parts have a logical correlation to each other; for example, the patients who had stent-related urinary symptoms have more chance for sexual dysfunction, and the patients who had urinary symptoms, pain and inappropriate general health had bad quality and quantity of job. Our study showed that anticholinergic and α-blockers are effective in improving stent-related urinary symptoms, body pain and general health; also, these drugs, especially Tolterodine, are effective in sexual function quality. The limitations of our study are small sample size specially for pain score index, and the 25 patients reduction in comparison to primary estimated sample size because of mentioned reasons in 'Results' section maybe is a big bias, and it might be better to assess the effect of Tamsulosin and Tolterodine as combination so as to evaluate the prosperity of prescription.

Conclusion

In some stent-related symptoms between the groups, there was no significant difference, but in the case of drug groups, Tolterodine had higher general health score in the fourth week and less mean pain index score; the difference was significant in the subgroup who had pain, albeit our sample size must be large for such a precise result. All in mind we suggest Tolterodine to minimize stent-related symptoms however we need further studies with larger sample size to determine superior medicines.

Author contribution

M.M. helped in project development and data collection; H.A. contributed by taking part in data collection, data analysis and manuscript writing; S.E. helped in data collection; H.R. helped in data analysis and manuscript editing and writing; K.K. contributed by helping in data analysis and manuscript editing and writing.

Consent to publish

Consent to publish has been obtained from all the participants.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

Our research has been approved by Ethics Committee of Kermanshah University of Medical Sciences (approval number: 54122).

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Informed consent

Written informed consent was obtained from all participants before the study.

Trial registration

IRCT: IRCT138812173509N1.

Supplemental Material

Supplementary material for this paper can be found at http://journals.sagepub.com/doi/suppl/10.1177/2050312117696436

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