Does Combination Therapy with Tamsulosin and Tolterodine Improve Ureteral Stent Discomfort Compared with Tamsulosin Alone? A Double-Blind, Randomized, Controlled Trial

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Purpose: Ureteral stent discomfort is a significant postoperative problem for many patients. Despite the use of narcotics and α-blockers patients often experience bothersome lower urinary tract symptoms and pain, which impair daily activities. We compared combination therapy with an α-blocker and an anticholinergic to monotherapy with an α-blocker.

Materials and Methods: A double-blind, randomized, controlled trial was performed from December 2012 to April 2014. A total of 80 patients were randomized, including 44 to the combination group (tamsulosin 0.4 mg and tolterodine early release 4 mg) and 36 to the monotherapy group (tamsulosin 0.4 mg and placebo). Patients with preexisting ureteral stent placement or current anticholinergic therapy were excluded from study. Patients completed USSQ (Urinary Stent Symptom Questionnaire) before stent placement on the day of surgery, the day after stent placement, the morning of stent removal and the day after stent removal. The questionnaire included questions regarding urinary symptoms, general health, body pain, and work and sexual history.

Results: A total of 80 patients (40 males and 40 females) were studied. Mean age was 51.5 vs 51.3 years ($p = 0.95$) and mean body mass index was 33.6 vs 31.9 kg/m^2 ($p = 0.44$) in monotherapy group 1 vs combination therapy group 2. Between the 2 groups there was no significant difference in urinary symptoms, body pain and activities of daily living from baseline to just before stent removal ($p = 0.95$, 0.40 and 0.95, respectively). Although there was no difference between the groups, both showed improvement in urinary symptoms from the time of initial stent insertion to just prior to stent removal (difference −0.50 for combination therapy and −0.40 for monotherapy). The mean stent indwelling time of 9.6 and 8.7 days in the combination and monotherapy groups, respectively, did not differ ($p = 0.67$). On ANOVA it had no significant impact on results ($p = 0.64$).

Conclusions: Combination therapy with tamsulosin and tolterodine does not appear to improve urinary symptoms, bodily pain or quality of life in patients after ureteral stent placement for nephrolithiasis compared to tamsulosin alone. Both groups experienced worse urinary symptoms, pain and quality of life with a stent, suggesting that further research is necessary to improve stent discomfort.

Key Words: ureter, nephrolithiasis, stents, tamsulosin, tolterodine

Abbreviations and Acronyms

ADL = daily living activities
BMI = body mass index
ER = early release
QOL = quality of life
RCT = randomized, controlled trial
T0 = prior to stent placement
T1 = morning after stent placement
T2 = 7 days after stent insertion/ morning of stent removal
T3 = day after stent removal
UTI = urinary tract infection

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WHILE urinary stents are frequently used in endoscopic urological practice, they continue to be a significant source of patient morbidity due to stent induced symptoms. The reported QOL impairment from ureteral stents ranges from 45% to 80%.[1] A number of unsatisfactory strategies have been used in an effort to mitigate these symptoms, including pharmacotherapy, stent design changes and drug eluting stents.[2,3]

USSQ is a validated questionnaire that has been an effective tool to facilitate studies measuring stent symptoms.[1] Of the different pharmacological agents studied one with demonstrable benefit compared to placebo is the uroselective α-blocker tamsulosin.[4,5] Despite common use few RCTs have been done to investigate the effects of anticholinergics on mitigating stent symptoms and results have not been consistent.[6] However, a recent study evaluated tolterodine ER and showed symptom improvement over placebo.[7] In clinical practice urologists often prescribe a multidrug regimen but its superiority to a single agent therapy is unclear. Data on combination therapy with anticholinergic and α-antagonist agents is limited and show conflicting results.[8,9]

To this end the purpose of our randomized, placebo controlled study was to assess whether adding tolterodine ER to tamsulosin would improve stent related symptoms. We hypothesized that combination therapy with tamsulosin and tolterodine ER would yield a greater decrease in stent related symptoms and improved QOL compared to tamsulosin monotherapy.

METHODS

A prospective, double-blind RCT was performed with patient enrollment from December 2012 to April 2014 after obtaining full institutional research ethics board approval. All patients who might require stent placement following ureteroscopic procedures to manage renal/ureteral stones or other conditions such as upper tract transitional cell carcinoma were prospectively identified and recruited for randomization into the combination or monotherapy arm based on a computer generated randomization scheme (see figure). Patients with preexisting stents, active UTI, current anticholinergic therapy, contraindications to any study drug, chronic pelvic pain syndrome or pregnancy, patients younger than 18 years and patients with cognitive impairment were excluded from study. Patients were also not randomized if stent placement was deemed clinically unnecessary at the end of ureteroscopy.

The C-Flex® Double Pigtail ureteral stent was placed in all patients who received a stent and stent length was approximated based on body height. The stent tether string was removed prior to stent placement in all patients. Of the patients 80% were randomized, including 44 to the combination group (tamsulosin 0.4 mg and tolterodine ER 4 mg) and 36 to the monotherapy group (tamsulosin 0.4 mg and placebo). All patients received similar perioperative antibiotic prophylaxis. A ureteral access sheath was not used in any of the procedures included in this study.

The validated USSQ was administered to assess stent related symptoms. The scoring system for the questionnaire consists of a simple sum of the scores on the individual questions for each section. The patients completed USSQ prior to stent placement on T0, T1, T2 and T3.

Study participants were provided with prefilled deidentified vials based on group assignment with tamsulosin plus placebo or tamsulosin plus tolterodine ER for 7 days. The placebo capsule was designed to be similar in color and appearance to the tolterodine ER capsule. Stent removal was scheduled for T2, which concluded the study period. However, if circumstances delayed stent removal, patients were instructed to complete the third questionnaire on T2. Patients were excluded from analysis if the questionnaire was not completed at T2. Intragroup and intergroup scores were compared, specifically at T1 and T2, to assess any differences in symptom improvement between monotherapy group 1 and combination therapy group 2.

Study Drug Details

The selective α_{1a}-blocker tamsulosin (Flomax®) has been generic since 2009. It is an antagonist of α1 mediated contraction of prostate, bladder and proximal urethral smooth muscle. As such it reduces urethral pressure and resistance, bladder outlet resistance and bladder hyperactivity, and consequently lowers urinary tract symptoms.[10] Its adverse effects include headache, dizziness, asthenia, nasal congestion, retrograde ejaculation and a rare reversible condition known as floppy iris syndrome, which is only relevant if patients are undergoing cataract surgery.

Tolterodine ER is an anticholinergic (antimuscarinic) agent used as one of the first line agents for detrusor overactivity. It is given as a once daily dose for overactive bladder symptoms. Side effects include xerostomia, xerophthalmia, gastroparesis, constipation, drowsiness and acute urinary retention. However, unlike other drugs of this class, eg oxybutynin, tolterodine ER causes little to no cognitive impairment due to its larger molecular weight, which precludes crossing of the brain-blood barrier.[11]

Statistical Analysis and Power Calculation

Our sample size calculation was based on the recommended sample size calculations by Joshi et al, the original developers of USSQ.[1] Their calculations were based on the results of their validation studies that compared mean domain score and SD differences between stented and control patients using the 2-tailed test ($p < 0.05$). The 15% change translates to an absolute change in score by 4 points. Additionally we extrapolated data from a recent meta-analysis evaluating the efficacy of tamsulosin to relieve stent related symptoms, which showed a mean SD of 6.5 points between the tamsulosin and placebo arms[12] to confirm the sample size in the study by Joshi et al.[1] To detect a 15% reduction in symptom scores